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Highly chemo- and regioselective phosphitylation of unprotected 2′-deoxyribonucleosides

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Abstract—We have developed the chemo- and regioselective phosphitylation of unprotected 2′-deoxyribonucleosides by the use of di-*tert*-butyl *N*,*N*-diethylphosphoramidite, a sterically hindered phosphoramidite. Both N/O- and primary hydroxy group-selectivities were simultaneously achieved, and the selectivity for the 5′-hydroxy groups was up to 97% regardless of the base moiety of the 2′-deoxyribonucleosides. The 3′-O-isomers and the 5′-O-isomers were easily separated by silica gel column chromatography or crystallization to give the pure 2′-deoxyribonucleoside 5′-phosphites in moderate to good yields.

1. Introduction

Nucleoside 5′-phosphates and their analogs are widely used as biologically active compounds,[1] model compounds for the molecular recognition of nucleotides,[2] precursors for the synthesis of α-P-modified nucleoside 5′-triphosphate analogs,[3] and synthetic intermediates for artificial nucleic acids conjugated with some functional molecules, such as reporter molecules.[4] Natural nucleoside 5′-phosphates (5′-nucleotides) can be easily obtained by the conventional Yoshikawa's method,[5] in which the 5′-hydroxy groups of nucleosides are phosphorylated by treatment with phosphorus oxychloride in trimethyl phosphate, and followed by alkaline hydrolysis. However, application of this method as well as analogous phosphorylation methods[6] is limited to the synthesis of natural 5′-nucleotides, their thiophosphate analogs,[3a] and methylphosphonate analogs.[6f] The harsh reaction conditions including the acidic reaction medium due to HCl generated from phosphorus oxychloride and the alkaline hydrolysis also make the method inapplicable to the synthesis of functionalized nucleoside 5′-phosphate analogs which are unstable to acids and/or bases. In addition, time-consuming purification procedures are required for the isolation of nucleoside 5′-phosphates from reaction mixtures.

In order to develop a versatile method applicable to the synthesis of a wide variety of functionalized nucleoside 5′-phosphate derivatives, we focused our attention on the chemo- and regioselective phosphitylation of base-unprotected nucleosides. The advantages of this method would be as follows: (1) O-Selective phosphitylation of N-unprotected nucleosides; (2) The resultant nucleoside 5′-phosphite triesters can be easily purified owing to the lipophilicity of phosphorus protecting groups; (3) The phosphite triesters as well as the corresponding nucleoside 5′-*H*-phosphonates, which are obtained by deprotection of the phosphite triesters,[7] can be converted into a wide variety of nucleoside 5′-phosphate and phosphonate analogs, such as nucleoside 5′-alkylphosphonates, boranophosphates, thiophosphates, etc.

Although there are several examples of the chemo- or regioselective phosphitylations of nucleosides,[8,9] the efficient chemo- and regioselective phosphitylation of nucleosides to afford nucleoside 5′-phosphites in one pot has not been reported. In addition, the phosphitylation of nucleosides with high regioselectivity still needs further innovation at present, although excellent chemoselective phosphitylations have been reported, especially for the synthesis of DNA analogs.[9] For example, the regioselective phosphitylations of a nucleoside or analogous carbohydrates with bis(2-cyanoethyl) or dibenzyl

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N,*N*-diisopropylphosphoramidite reported by Graham et al. result in modest to good regioselectivity. However, separation of the corresponding 3′-phosphates and 3′,5′-diphosphates from the desired 5′-phosphates by tedious column chromatography is necessary.[8]

Given this situation, we have sought a novel chemo- and regioselective phosphitylation applicable to the facile synthesis of nucleoside 5′-phosphates. In this letter, we wish to report our preliminary results of this study, in which the highly chemo- and regioselective 5′-phosphitylation of nucleosides was performed by the simple use of a phosphitylating reagent bearing bulky tertiary alkyl groups.

Di-*tert*-butyl *N*,*N*-diethylphosphoramidite (**2**), which is usually used for the synthesis of phosphopeptides, was chosen as a key compound of the present method.[10] We expected that the two bulky *tert*-butyl groups would offer a significant steric congestion behind the P–N bond of **2**, which would be allowed to take place the preferential nucleophilic attack of a less-hindered 5′-OH of nucleosides to **2** (Scheme 1).

At first, thymidine (**1a**) was employed in order to examine the regioselectivity of the phosphitylation reaction with **2**. Compound **1a** was allowed to react with **2** in the presence of an acidic activator, pyridine hydrochloride (2 equiv to **1a**), in pyridine. This acid activator has been used for the chemoselective phosphitylation of nucleosides in the presence of imidazole. Nevertheless, perfect O-selectivity was not realized with the conventional phosphoramidites even though the reactivity of the active intermediate was lowered by the exchange of the leaving group from chlorine to imidazole.[9a] When the mixture of pyridine hydrochloride and imidazole, 4,5-dicyanoimidazole, or tetrazole was employed as an activator of this reaction the regioselectivity was not improved at all.

The ^{31}P NMR analysis of the crude mixture clearly demonstrated the preferential generation of the desired thymidine 5′-phosphite **3a**.[11] Considering the fact that the purity of **2** was about 86%, the yield could be maximized when a small excess amount of **2** was used (Table 1).

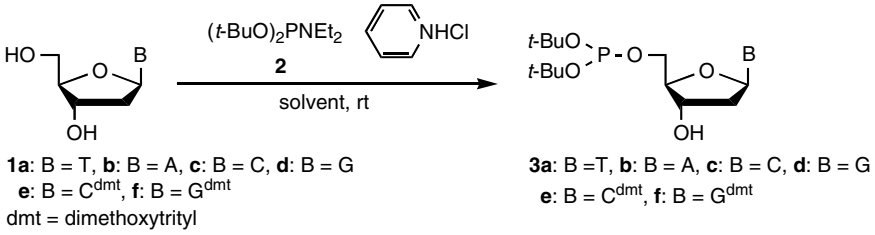
In the next stage, we investigated the highly chemo- and regioselective phosphitylation reactions of 2′-deoxyadenosine (**1b**), 2′-deoxycytidine (**1c**), and 2′-deoxyguanosine (**1d**) (Table 2). The regioselectivity of the phosphitylation of **1b** under the conditions optimized for **1a** was as excellent as that of **1a** (entry 2). On the other hand, in the cases of **1c** and **1d**, the formation of a large amount of the corresponding 3′,5′-diphosphite was observed by ^{31}P NMR (entries 3 and 4). Especially, in the case of **1d**, the 3′,5′-diphosphite was formed as the sole phosphitylated nucleoside species. These results would be attributed to the low solubility of **1c** and **1d** in pyridine. Under these conditions, a large excess amount of **2** to **1c** or **1d** exists in the solution-phase to result in the preferential generation of the 3′,5′-diphosphites. Noteworthy, no phosphitylation of the exocyclic amino groups around 123–127 ppm was observed by ^{31}P NMR in all the cases.[9b] This is rather surprising because the O-selectivity of the phosphitylation of nucleosides bearing free amino groups with conventional phosphoramidites activated by pyridine hydrochloride was reported to be incomplete.[9a] The perfect chemoselectivity of the phosphitylation with **2** would be attributed to the synergetic effect of the inherent O-selectivity of an active P(III) species generated from **2** and pyridine hydrochloride owing to secondary HOMO–LUMO orbital interactions that can be observed only for the combination of alcohols and the P(III) species,[9d,12,13] and owing to the steric congestion of **2**, which retard a nucleophilic substitution reaction.[14]

Table 1. The selective phosphitylation of thymidine **1a** with **2**

Entry	Equiv of **2**[a]	Ratio of phosphates (%)			Conversion[b] (%)
		5′-	3′-	5′,3′-	
1	0.5 (0.39)	94	5	1	39
2	0.8 (0.67)	93	5	2	66
3	1.0 (0.82)	92	5	3	80
4	1.5 (1.12)	86	2	12	100

[a] In the parenthesis, the effective equivalent of the phosphitylating reagent is given.
[b] The percentage of the consumed **1a** determined by ^{31}P NMR.

We presumed that the increase of the solubility of the nucleosides should improve the regioselectivity. One option would be the introduction of a lipophilic protecting group to these nucleosides. In fact, dC and dG protected with a dimethoxytrityl (DMTr) group at the exocyclic amino groups (dC^{dmt}, dG^{dmt}) completely dissolved in pyridine. In the case of **1f**, a side reaction at the O^6-position of the base moiety was observed by ^{31}P NMR (132.3 ppm).[15] This side reaction could be avoided by the use of an excess amount of **1f**. As a result, the phosphitylation reaction of **1e** and **1f** proceeded in a highly regioselective manner to give the desired 5′-phosphite



1a: B = T, **b**: B = A, **c**: B = C, **d**: B = G
e: B = C^{dmt}, **f**: B = G^{dmt}
dmt = dimethoxytrityl

3a: B =T, **b**: B = A, **c**: B = C, **d**: B = G
e: B = C^{dmt}, **f**: B = G^{dmt}

Scheme 1. Phosphitylation of 2′-deoxyribonucleosides.

Table 2. Chemo- and regioselective phosphitylation of 2′-deoxyribonucleosides

Entry	B	Solvent[a]	Equiv of **2**[b]	Ratio of products[c] (%)			Conversion[d] (%)	Yield[e] (%)
				5′-	3′-	5′,3′-		
1	T	A	1.1 (1.05)	89	4	7	98	82
2	A	A	1.2 (1.11)	95	1	4	100	74
3	C	A	1.2 (1.05)	68	1	31	80	—
4	G	A	1.2 (1.03)	0	0	100	51	—
5	C^{dmt}	A	1.0 (0.72)	89	7	4	83	45
6	G^{dmt}	A	0.6 (0.57)	97	2	1	56	55
7	C	B	1.2 (1.13)	84	3	13	86	49
8	G	C	1.2 (0.96)	92	1	7	91	52

[a] Solvent: A, pyridine; B, pyridine–NMP (1:2, v/v); C, pyridine–NMP (1:1, v/v).
[b] In the parenthesis, effective equivalent of the phosphitylating reagent is given.
[c] The ratio of the products was estimated after extraction of the reaction mixture.
[d] The percentage of the consumed nucleosides determined by ^{31}P NMR.
[e] The isolated yield of **3**.

in good yields (entries 5 and 6). However, this strategy requires extra protection–deprotection steps, which deteriorates the usefulness of this method.

Another option to realize high regioselectivity should be to use a solvent, which completely dissolves **1c** and **1d**. Upon extensive investigation on the solvent, we found that a mixture of pyridine and *N*-methylpyrrolidone (NMP) could dissolve **1c** and **1d** effectively, and that the phosphitylation of **1c** and **1d** in this mixed solvent was completed within 5 min with high regioselectivity (entries 7 and 8). It should be noted that the resultant **3a**, **3b**, and **3c** were easily isolated from the crude mixture containing the 3′-phosphite and the 3′,5′-diphosphite by crystallization after short column chromatography, respectively.[16]

In conclusion, we have developed a highly chemo- and regioselective phosphitylation of N-unprotected nucleosides using di-*tert*-butyl *N*,*N*-diethylphosphoramidite. Excellent selectivity was achieved by steric hindrance imposed by tertiary alkyl groups in the phosphitylating reagent. This is the first example of the excellent chemo- and regioselective phosphitylation of 2′-deoxyribonucleosides simultaneously to the best of our knowledge. The other advantages of the present phosphitylation over the conventional phosphorylation[5] are the fast reaction rate and the easy purification procedure of the products owing to their lipophilicity. We expect that this method would be applicable to the synthesis of a wide variety of nucleoside 5′-phosphate derivatives. Furthermore, the protected nucleoside 5′-phosphites obtained by this method would also be useful as new building blocks for the synthesis of oligonucleotides and their analogs.[7b]

2. Experimental

2.1. Assignment of the isomers

All three isomers (5′-phosphite, 3′-phosphite, and 5′,3′-diphosphite) were separated by silica gel column chromatography. ^{31}P NMR chemical shifts for thymidine derivatives were: 132.38 (br t, 5′-*P* of 5′,3′-diphosphite), 132.13 (d, $^{3}J_{PH} = 8.9$ Hz, 3′-*P* of 5′,3′-diphosphite), 132.90 (br t, 5′-*P* of 5′-phosphite), 132.38 (d, $^{3}J_{PH} = 7.8$ Hz, 3′-*P* of 3′-phosphite). All isomers were also assigned in a similar fashion in other cases.

2.2. Thymidine 5′-di-*tert*-butyl phosphite (3a)

Pyridine hydrochloride (79.7 mg, 0.69 mmol) was dried by repeated coevaporation with dry pyridine and dissolved in pyridine (2.76 mL). Thymidine **1a** (72.5 mg, 0.3 mmol) was dried by repeated coevaporation with dry pyridine and finally dissolved in dry pyridine (0.24 mL) and the solution of pyridine hydrochloride (2.76 mL). To the solution was added di-*tert*-butyl *N*,*N*-diethylphosphoraimidite (82.3 mg, 0.33 mmol). After being stirred for 1 h, the mixture was diluted with $CHCl_3$ (10 mL), and the mixture was washed three times with satd $NaHCO_3$ aq (10 mL × 3), and the organic layer was backextracted with $CHCl_3$ (10 mL × 3). The organic layer was dried over Na_2SO_4, filtered, concentrated to dryness under reduced pressure, and coevaporated by dry toluene (5 mL × 5) and $CHCl_3$ (5 mL × 5). The residue was loaded onto a column of silica gel (10 g of silica gel). Chromatography was performed with a step gradient of hexane–ethyl acetate–triethylamine (80:18:2, v/v/v) to hexane–ethyl acetate–triethylamine (0:98:2, v/v/v), followed by ethyl acetate containing 2% triethylamine, applying a gradient of methanol (0–5%). The fractions containing **3a** were combined and concentrated to dryness under reduced pressure to give **3a** (102.8 mg, 0.25 mmol, 82%) as a colorless foam. Crystallization from ethyl acetate gave **3a** as a colorless crystal: mp 92–94 °C (dec); ^{31}P NMR ($CDCl_3$) δ 132.93; ^{1}H NMR ($CDCl_3$) δ 9.28 (s, 1H, 3-NH), 7.67 (d, 1H, $^{4}J_{HH} = 1.2$ Hz, 6-H), 6.39 (dd, 1H, $^{3}J_{HH} = 6.6$ Hz, 1′-H), 4.47–4.46 (m, 1H, 3′-H), 4.14–4.07 (m, 2H, 4′-H and 5′-H), 4.00–3.93 (m, 1H, 5″-H), 3.04 (s, 1H, 3′-OH), 2.42–2.34 (ddd, 1H, $^{2}J_{HHgem} = 13.4$ Hz, 2′-H), 2.22–2.13 (ddd, 1H, 2″-H), 1.92 (d, 3H, 5-CH_3, $^{4}J_{HH} = 0.9$ Hz), 1.40 (s, 18H, –CH_3 of *t*-Bu); ^{13}C NMR ($CDCl_3$) δ 163.35, 149.99, 135.67, 110.67, 85.61 ($^{3}J_{PC} = 4.3$ Hz), 84.46, 76.32, 71.92, 58.39, 40.48, 31.06 ($^{2}J_{PC} = 5.5$ Hz), 30.94 ($^{2}J_{PC} = 5.5$ Hz), 12.57; FAB^{+} *m*/*z* calcd for $C_{18}H_{32}N_2O_7P$ $[M+H]^{+}$ 419.1947, found 419.1952.

2.3. 2′-Deoxyadenosine 5′-di-*tert*-butyl phosphite (3b)

Mp 102–104 °C (dec); ^{31}P NMR ($CDCl_3$) δ 133.50; ^{1}H NMR ($CDCl_3$) δ 8.32 (s, 1H, 2-H), 8.15 (s, 1H, 8-H), 6.49 (dd, 1H, $^{3}J_{HH} = 6.5$ Hz, 1′-H), 5.63 (br s, 2H, 6-NH2), 4.72–4.67 (m, 1H, 3′-H), 4.18–4.06 (m, 1H, 5′-H and 4′-H), 4.02–3.95 (m, 1H, 5″-H), 2.80–2.71 (m, 1H, 2′-H), 2.58–2.50 (ddd, 1H, 2″, $^{2}J_{HHgem} = 13.5$ Hz), 1.39 (s, 18H, –CH_3 of *t*-Bu); ^{13}C NMR ($CDCl_3$) δ 155.24, 152.60, 149.18, 138.78, 119.51, 86.05 ($^{3}J_{PC} = 3.7$ Hz), 84.06, 76.41, 76.29 ($^{2}J_{PC} = 1.7$ Hz), 72.21, 58.96, 40.85, 31.04 ($^{2}J_{PC} = 1.8$ Hz), 30.93 ($^{2}J_{PC} = 1.8$ Hz); FAB$^+$ *m*/*z* calcd for $C_{18}H_{31}N_5O_5P$ $[M+H]^+$ 428.2063, found 428.2068.

2.4. 2′-Deoxycytidine 5′-di-*tert*-butyl phosphite (3c)

Mp 140–142 °C (dec); ^{31}P NMR ($CDCl_3$) δ 132.9; ^{1}H NMR ($CDCl_3$) δ 7.85 (d, 1H, $^{3}J_{HH} = 7.2$ Hz, 6-H), 6.47 (dd, 1H, $^{3}J_{HH} = 6.3$ Hz, 1′-H), 5.69 (d, 1H, $^{3}J_{HH} = 7.2$ Hz, 5-H), 4.37–4.35 (m, 1H, 3′-H), 4.16–4.13 (m, 1H, 4′-H), 4.07–3.93 (m, 2H, 5″-H and 5′-H), 2.65–2.58 (m, 1H, 2′-H), 2.08–1.99 (m, 1H, 2″-H), 1.40 (s, 18H, –CH_3 of *t*-Bu); ^{13}C NMR ($CDCl_3$) δ 165.46, 155.98, 140.90, 94.46, 86.20, 76.41, 76.29 ($^{2}J_{PC} = 9.2$ Hz), 76.17 ($^{2}J_{PC} = 9.2$ Hz), 72.12, 58.83, 41.46, 31.06 ($^{2}J_{PC} = 3.0$ Hz), 30.94 ($^{2}J_{PC} = 3.0$ Hz); FAB$^+$ *m*/*z* calcd for $C_{17}H_{31}N_3O_6P$ $[M+H]^+$ 404.1951, found 404.1948.

2.5. 2′-Deoxyguanosine 5′-di-*tert*-butyl phosphite (3d)

^{31}P NMR ($CDCl_3$) δ 131.3; ^{1}H NMR ($CDCl_3$) δ 7.96 (s, 1H, 8-H), 6.27 (dd, $^{3}J_{HH} = 6.6$ Hz, 1H, 1′-H), 4.56–4.52 (m, 1H, 3′-H), 4.08–4.04 (m, 1H, 4′-H), 4.02–3.92 (m, 2H, 5′-H), 2.71–2.62 (m, 1H, 2′-H), 2.43–2.35 (1H, ddd, 2″-H, $^{2}J_{HHgem} = 13.5$ Hz), 1.37, 1.36 (2s, 18H, –CH_3 of *t*-Bu); ^{13}C NMR ($CDCl_3$) δ 159.16, 155.10, 152.57, 137.48, 87.75 ($^{3}J_{PC} = 4.58$ Hz), 85.03, 77.35 ($^{2}J_{PC} = 7.4$ Hz), 76.34 ($^{2}J_{PC} = 1.6$ Hz), 76.22 ($^{2}J_{PC} = 1.6$ Hz), 72.88, 60.17, 41.28, 31.45 ($^{2}J_{PC} = 1.0$ Hz), 31.34 ($^{2}J_{PC} = 1.0$ Hz); FAB$^+$ *m*/*z* calcd for $C_{18}H_{31}N_5O_6P$ $[M+H]^+$ 444.2012, found 444.2011.

2.6. 4-*N*-Dimethoxytrityl 2′-deoxycytidine 5′-di-*tert*-butyl phosphite (3e)

^{31}P NMR ($CDCl_3$) δ 133.1; ^{1}H NMR ($CDCl_3$) δ 7.56 (d, 1H, 6-H, $^{3}J_{HH} = 7.65$ Hz), 7.27–7.22, 7.18–7.16 (m, 5H, 2″,3″,4″,5″,6″-H of DMTr), 7.11–7.08 (m, 4H, 2,2′,6,6″-H of DMTr), 6.81–6.78 (m, 4H, 3,3′,5,5′-H of DMTr), 6.43–6.39 (dd, $^{3}J_{HH} = 6.5$ Hz, 1H, 1′-H), 5.01 (d, 1H, 5-H, $^{3}J_{HH} = 7.7$ Hz), 4.33–4.37 (m, 1H, 3′-H), 4.12–4.15 (m, 1H, 4′-H), 3.93–3.90 (m, 2H, 5′-H), 3.78 (s, 6H, –OCH_3 of DMTr), 2.65–2.58 (ddd, 1H, 2′-H), 2.05–1.96 (m, 1H, 2′-H), 1.32, 1.27 (2s, 18H, –CH_3 of *t*-Bu); ^{13}C NMR ($CDCl_3$) δ 165.01, 158.30, 155.14 (s, C2), 144.31, 140.45, 136.08, 135.97, 129.62, 128.25, 128.04, 127.14, 113.30, 94.33, 86.02, 85.50, 76.20 ($^{2}J_{PC} = 9.8$ Hz), 71.84, 58.51, 55.12, 41.39, 30.98 ($^{2}J_{PC} = 4.0$ Hz), 30.87 ($^{2}J_{PC} = 4.0$ Hz); FAB$^+$ *m*/*z* calcd for $C_{38}H_{49}N_3O_8P$ $[M+H]^+$ 706.3257, found 706.3228.

2.7. 2-*N*-Dimethoxytrityl 2′-deoxyguanosine 5′-di-*tert*-butyl phosphite (3f)

^{31}P NMR ($CDCl_3$) δ 131.5; ^{1}H NMR ($CDCl_3$) δ 7.82 (s, 1H, 8-H), 7.57–7.28 (m, 5H, 2″,3″,4″,5″,6″-H of DMTr), 7.21–7.16 (m, 4H, 2,2′,6,6′-H of DMTr), 6.85–6.80 (m, 4H, 3,3′,5,5′-H of DMTr), 5.63 (dd, 1H, $^{3}J_{HH} = 6.5$ Hz, 1′-H), 4.21–4.16 (m, 1H, 3′-H), 3.93–3.89 (m, 1H, 4′-H), 3.87–3.83 (m, 2H, 5′-H), 3.76 (s, 6H, –OCH_3 of DMTr), 2.12–2.03 (m, 1H, 2′-H), 1.95–1.87 (ddd, 1H, $^{2}J_{HHgem} = 13.7$ Hz, 2″-H), 1.35 (s, 18H, –CH_3 of *t*-Bu); ^{13}C NMR ($CDCl_3$) δ 159.73, 159.04, 152.27, 150.93, 146.37, 138.35, 138.21, 137.63, 131.13, 131.10, 129.81, 128.67, 127.71, 113.96, 87.52, 87.47, 85.41, 78.27 ($^{2}J_{PC} = 3.6$ Hz), 78.15 ($^{2}J_{PC} = 3.6$ Hz), 72.44, 71.62, 60.23, 55.72, 41.51, 31.48, 31.37; FAB$^+$ *m*/*z* calcd for $C_{39}H_{49}N_5O_8P$ $[M+H]^+$ 746.3319, found 746.3344.

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References and notes

1. Slotin, L. A. *Synthesis* **1977**, *11*, 737–752.
2. (a) Onoa, B.; Moreno, V. *Trans. Met. Chem.* **1998**, *23*, 485–490; (b) Groziak, M. P.; Thomas, D. W. *J. Org. Chem.* **2002**, *67*, 2152–2159.
3. (a) Burgess, K.; Cook, D. *Chem. Rev.* **2000**, *100*, 2047–2059, and references cited therein; (b) Tomasz, J.; Shaw, B. R.; Porter, K.; Spielvogel, B. F.; Sood, A. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1373–1375.
4. Kotera, M.; Dheu, M.-L.; Milet, A.; Lhomme, J.; Laayoun, A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 705–708.
5. Yoshikawa, M.; Kato, T.; Takenishi, T. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 3505–3508.
6. (a) Imai, K.; Fujii, S.; Takanohashi, K.; Furukawa, Y. *J. Org. Chem.* **1969**, *34*, 1547–1550; (b) Hes, J.; Martes, M. P. *J. Org. Chem.* **1974**, *39*, 3767–3769; (c) Uchiyama, M.; Aso, Y.; Noyori, R.; Hayakawa, Y. *J. Org. Chem.* **1993**, *58*, 373–379; (d) Goody, R. S.; Isakov, M. *Tetrahedron Lett.* **1986**, *27*, 3599–3602; (e) Eckstein, F. *Annu. Rev. Biochem.* **1985**, *54*, 367–402; (f) Battistini, C.; Franceschi, G.; Ungheri, D.; Verini, M. A.; Vioglio, S. PCT Int. Appl. WO 9104261, 1991.
7. (a) Wada, T.; Kato, Y.; Saigo, K. *Nucleic Acids Res. Suppl.* **2003**, *3*, 65–66; (b) Kato, Y.; Saigo, K.; Wada, T. *Nucleic Acids Res. Symp. Ser.* **2005**, *49*, 129–130.
8. Graham, S. M.; Pope, S. C. *Org. Lett.* **1999**, *1*, 733–737.
9. (a) Gryaznov, S. M.; Letsinger, R. L. *Nucleic Acids Res.* **1992**, *20*, 1879–1882; (b) Hayakawa, Y.; Kataoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 12395–12401; (c) Sekine, M.; Ohkubo, A.; Seio, K. *J. Org. Chem.* **2003**, *68*, 5478–5492; (d) Ohkubo, A.; Ezawa, Y.; Seio, K.; Sekine, M. *J. Am. Chem. Soc.* **2004**, *126*, 10884–10896; (e) Dabkowski, W.;

Ozarek, A.; Tworowska, I. *New J. Chem.* **2005**, *29*, 1396–1399.
10. Perich, J. W.; Johns, R. B. *Tetrahedron Lett.* **1988**, *29*, 2369–2372.
11. The isomers were characterized by ^{31}P NMR.
12. Wada, T.; Sato, Y.; Honda, F.; Kawahara, S.; Sekine, M. *J. Am. Chem. Soc.* **1997**, *119*, 12710–12721.
13. Sobkowski, M.; Stawinski, J.; Sobkowska, A.; Kraszewski, A. *J. Chem. Soc., Perkin Trans. 1* **1994**, *13*, 1803–1808.
14. Wada, T.; Moriguchi, T.; Sekine, M. *J. Am. Chem. Soc.* **1994**, *116*, 9901–9911.
15. Pon, R. T.; Damha, M. J.; Ogilvie, K. K. *Nucleic Acids Res.* **1985**, *13*, 6447–6465.
16. The moderate yields of these compounds would be attributed to the purification procedure, because the products are stable enough and the chemo- and regioselectivities of the reactions are sufficient. A part of the products were lost during the purification by crystallization or silica gel column chromatography.