Synthetic studies on the preparation of nucleoside 5′-H-phosphonate monoesters under the Mitsunobu reaction conditions

Gaston Lavén[a] and Jacek Stawinski[a,b]*

[a]*Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University,S-10691 Stockholm, Sweden;* [b]*Institute of Bioorganic Chemistry, Polish Academy of Sciences, Noskowskiego 12/14, 61-704 Poznan, Poland*
E-mail: js@organ.su.se

Dedicated to Professor Harry Lönnberg on the occasion of his 60th birthday

Abstract
A reaction of suitably protected nucleosides with phosphonic acid in the presence of diethyl azodicarboxylate and triphenylphosphine in pyridine provided in good yields the corresponding 5'-H-phosphonate monoesters.

Keywords: H-Phosphonate monoesters, phosphonic acid, the Mitsunobu reaction

Introduction

The Mitsunobu reaction is a versatile and widely used method in organic synthesis because of its scope, stereospecificity, and mild experimental conditions.[1,2] Typically, it involves the condensation of an acidic pronucleophile (HNu, e.g. carboxylic acids, phenols, imides, etc.) and an alcohol (ROH), promoted by triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD), to afford the product RNu, along with diethoxycarbonylhydrazine and triphenylphosphine oxide. This redox mediated condensation is frequently used for the formation of C-O, C-N, C-S, or C-C bonds in a stereospecific manner, in the presence of a wide range of functional groups.[1] Due to known separation problems, many recent efforts in the Mitsunobu reaction research have been directed toward modifying triphenylphosphine and azodicarboxylate reagents[3,4] to facilitate purification procedures, or to develop special, usually chromatography-free, separation strategies.[4,5]

As part of our program in developing synthetic methods for biologically important phosphates and their analogues based on H-phosphonate chemistry,[6,7] we became interested in the Mitsunobu reaction for two reasons. Firstly, it permits a condensation to be carried out under mild, virtually neutral conditions, and secondly, it involves activation of a hydroxyl function of an alcohol, rather than conversion of a pronucleophile into a reactive species. The latter aspect

 ©ARKAT USA, Inc.

seemed particularly appealing for a stereospecific synthesis of phosphate analogues using P-chiral phosphorus precursors,[7,8] as it would alleviate a potential problem of epimerization at the phosphorus center.

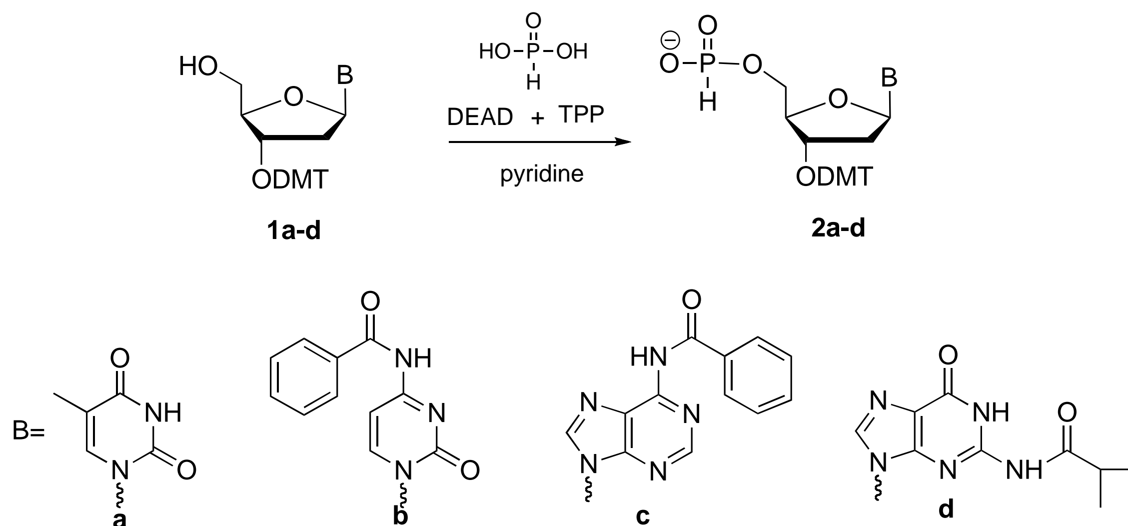
Owing to the importance and widespread use of the Mitsunobu reaction, its mechanism have been extensively investigated.[1,9,10] Although, inversion of configuration in the hydroxylic component is typically observed,[1] the mechanism turned out to be rather complex. The first step of the reaction is an irreversible addition of TPP to DEAD to form the Morrison-Brunn-Huisgen betaine,[11] which may cascade into a product (or by-products) in several ways, depending on reactivity of the alcohol and a pKa value of the acidic pronucleophile used.[12] Recent studies on lactonization of sterically hindered alcohols showed that the Mitsunobu reaction can occur with retention of configuration,[10] and the density functional investigations[13] supported the view that the Mitsunobu reaction is fundamentally capable to affording products either with inversion or retention of configuration. Thus, Mitsunobu type of reactions, particularly those involving new types of pronucleophiles, have to be carefully scrutinized for a mechanism operating.

Concerning preparation of phosphates or their analogues, Mitsunobu *et al.*[14,15] used TPP and DEAD as an activating system for phosphorylation of nucleosides with dibenzyl phosphate. The reaction gave acceptable yields of pyrimidine nucleoside phosphates (40-70%), but completely failed for adenosine and guanosine. More recently, the Mitsunobu reaction conditions were investigated for the purpose of C-phosphonate synthesis using methyl- and benzylphosphonate monoesters.[16] Although a variety of acidic pronucleophiles have been investigated,[1] there has been no report, to our knowledge, on the formation of H-phosphonate mono- and H-phosphonate diesters *via* the Mitsunobu coupling reaction.

In this paper we present our preliminary synthetic investigation on the preparation of nucleoside 5'-H-phosphonates under the Mitsunobu reaction conditions, and some ^{31}P NMR studies on the formation of H-phosphonate diesters in the presence of DEAD and TPP.

Results and Discussion

To check a possibility of formation of H-phosphonate monoesters under the Mitsunobu reaction conditions, we reacted 3′-*O*-protected thymidine derivative **1a** as a model 1° alcohol with phosphonic acid in the presence of DEAD and TPP under various experimental conditions. The reaction was very sensitive, in terms of the reaction time and purity of the product formed (^{31}P NMR spectroscopy analysis), to the ratio of the reactants, solvents, and the bases present. The best results were obtained when phosphonylation of nucleoside **1a** was carried out in pyridine in the presence of 2 equiv. each of DEAD and TPP, and by using 2 equiv. of phosphonic acid (Scheme 1). These conditions secured a quantitative formation of the desired nucleoside 5′-H-phosphonate **2a** within ca 20 min (^{31}P NMR analysis), and on a preparative run, compound **2a** was isolated in 85% as a triethylammonium salt.



DMT = 4,4'-Dimethoxytrityl; DEAD = diethyl azodicaroxylate; TPP = triphenylphosphine

Scheme 1

The above protocol was successfully applied to the other common nucleosides, namely to cytidine (**1b**), adenosine (**1c**) and guanosine (**1d**), derivatives, to produce the corresponding 5'-H-phosphonate monoesters **2b-d** in good isolated yields (74-84%).

One should emphasise here a relatively high yield of phosphonylation of adenosine derivative 1c (74%) under the developed reaction conditions. Purine nucleosides, and adenosine in particular, are known to be highly susceptible to intramolecular cyclization forming, *via* a nucleophilic attack of nitrogen N-3 of the purine base on the 5′-carbon atom, N^3,5′-cyclonucleosides, when the 5′-OH function is converted into a good living group.[15,17] For this reason, usually only pyrimidine nucleosides can be phosphorylated (or acylated) under the Mitsunobu reaction conditions, while purine nucleosides either cannot be used as substrates[14,15] or give mediocre yields.[16]

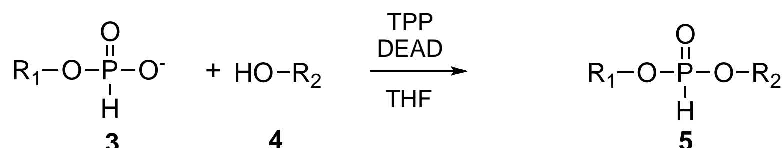
Although the Mitsunobu reaction of alcohols with carboxylic acids is assumed to proceed with the intermediacy of the corresponding alkoxyphosphonium salts, it is well documented that also carboxylic acid anhydrides can be formed under the reaction conditions.[18] Since H-pyrophosphonate in pyridine is known to act as a phosphonylating agent for nucleosides,[19] we could not exclude a possibility that this can be a reactive species involved in the reaction investigated. To verify this assumption, H-pyrophosphonate (generated *in situ* from phosphonic acid and pivaloyl chloride in pyridine)[19] was allowed to react with nucleoside 1a in pyridine. Unfortunately, the phosphonylation of **1a** was significantly slower (50% conversion after 4 h) than that under the Mitsunobu conditions, and thus it is unlikely that phosphonylation of nucleosides with phosphonic acid in the presence of DEAD and TPP involved as a kinetically significant intermediate, H-pyrophosphonate.

When the phosphonylation of nucleoside **1a** under the Mitsunobu conditions (Scheme 1) was carried out in the presence of triethylamine, the reaction became significantly slower (few hours for the completion), and for very strong bases, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), no product formation was observed even after prolonged reaction time (overnight). These experiments are consistent with the observed dependency of the Mitsunobu reaction on a pKa value of the acidic pronucleophiles,[12] (in our case, acidities of the conjugated acids) and may point to the importance of protonation of the Morrison-Brunn-Huisgen betaine.[11]

^{31}P NMR experiments on the formation of H-phosphonate diesters

We carried out also some preliminary ^{31}P NMR experiments on the formation of H-phosphonate diesters under the Mitsunobu coupling conditions (Scheme 2).

To this end we reacted H-phosphonate monoesters **3a,b** (triethylammonium salt, 0.1 mmol) with nucleoside **4b** (0.15 mmol) in the presence of DEAD (0.15 mmol) and TPP (0.15 mmol) in tetrahydrofuran (2 mL). The reactions were clean, went to completion within 2 h, and the produced H-phosphonate diesters **5b** and **5d**, respectively, were identical (^{31}P NMR data) to those prepared form H-phosphonates **3** and alcohols **4** using pivaloyl chloride as a condensing agent.[20] For the analogous reactions with ethanol, larger excess of DEAD, TPP and the alcohol (3 equiv. each) had to be used, apparently due to competing side reactions of the activated ethanol. In contrast to phosphonylation of nucleosides **1** with phosphonic acid (Scheme 1), the condensations of H-phosphonate monoesters **3** depicted in Scheme 2 did not work well in pyridine. For reasons to be identified yet, all the reactions in Scheme 2 proceeded only to 50% completion in pyridine, even after prolonged reaction time (overnight).



3a, R_1 = ethyl
3b, R_1 = 5'-*O*-dimethoxytritylthymidin-3'-yl
4a, R_2 = ethyl
4b, R_2 = 3'-*O*-dimethoxytritylthymidin-5'-yl
5a, R_1 = R_2 = ethyl
5b, R_1 = ethyl, R_2 = 3'-*O*-dimethoxytritylthymidin-5'-yl
5c, R_1 = 5'-*O*-dimethoxytritylthymidin-3'-yl, R_2 = ethyl
5d, R_1 = 5'-*O*-dimethoxytritylthymidin-3'-yl, R_2 = 3'-*O*-dimethoxytritylthymidin-5'-yl

Scheme 2

In conclusion, we developed an efficient protocol for the synthesis of nucleoside 5'-H-phosphonate monoesters by reacting suitably protected nucleosides with triethylammonium salt of H-phosphonic acid in pyridine under the Mitsunobu reaction conditions. The method works

well both for pyrimidine and purine nucleosides and can be considered and as an alternative procedure[19-21] for the preparation of H-phosphonate monoesters. ^{31}P NMR studies shown that also H-phosphonate diesters can be efficiently formed under the Mitsunobu coupling conditions.

Further synthetic and mechanistic studies on the Mitsunobu reaction involving H-phosphonates as acidic pronucleophiles are in progress in this Laboratory.

Experimental Section

General Procedures. Pyridine was distilled from CaH_2 and stored over molecular sieves 4Å. THF was distilled directly before the use from sodium/benzophenone. CH_2Cl_2 was distilled directly before the use from P_2O_5. Phosphonic acid and pivaloyl chlorides were commercial grades from Aldrich. A suitably protected nucleosides **1a-d** were prepared analogously to the published procedures.[22]

Progress of the reactions was monitored by thin layer chromatography (TLC) using silica gel-coated plates with a fluorescent indicator (Merck, Silica gel 60) and chloroform: methanol (9:1, v/v) as an eluent. Column chromatography was performed on silica gel (Grace Davison, Davsil, 0.035-0.070 mm). After chromatography, the fractions containing the desired products were pooled, evaporated, and dried under vacuum for 12 hours. ^{1}H-, ^{13}C-, and ^{31}P NMR spectra were recorded on Bruker Avance 400MHz instrument. Chemical shifts are reported in ppm, relative to TMS (^{1}H-, ^{13}C-NMR) and 85% aq. H_3PO_4 (^{31}P NMR). High resolution mass spectra (HRMS) were recorded on Bruker MicrOTOF ESI-TOF mass spectrometer.

A general procedure for the preparation of nucleoside 5′-H-phosphonates 2a-d

To a solution of a suitably protected nucleoside **1a-d** (0.5 mmol) in pyridine (2 mL) was added phosphonic acid (1 mmol). The reaction mixture was made anhydrous by repeated evaporation of the added pyridine (3 x 2 mL) and the residue was dissolved in the same solvent (10 mL). After addition of triphenylphosphine (1 mmol) and diethyl azodicarboxylate (1 mmol) the reaction mixture was stirred until complete disappearance of the starting material 1 (ca 20-30 min, TLC analysis). The solvent was removed under reduced pressure, the residue dissolved in dichloromethane, and purified by a silica gel column chromatography (a stepwise gradient of methanol and triethylamine in dichloromethane, 0-10% and 0.02-0.5%, respectively). Compounds **2a-d** (purity > 98%, ^{1}H NMR spectroscopy) were obtained as white, amorphous solids.

3'-*O*-(4,4-Dimethoxytrityl)thymidin-5'-yl H-phosphonate, triethylammonium salt (2a). Yield: 302 mg, 85%. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.71 (s, H6, 1H), 7.46-7.14 (m, Ar_{DMT}, 9H), 6.82 (m, $H3_{DMT}$, $H5_{DMT}$, $H3'_{DMT}$, $H5'_{DMT}$, 4H), 6.75 (d, $^{1}J_{P\text{-}H}$ = 614.9Hz, 1H), 6.48 (m, H1', 1H), 4.37 (m, H3', 1H), 3.89 (m, H4', 1H), 3.85-3.76 (m, 2×OCH_3, H5', 7H), 3.52 (m, H5", 1H), 2.96 (q, ^{3}J = 7.3 Hz, N(CH_2CH$_3$)$_3$, 6H), 1.91 (s, 5CH_3, 3H), 1.82 (m, H2', H2", 2H), 1.24 (t, ^{3}J = 7.3 Hz, N(CH$_2$CH_3)$_3$, 9H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 164.1(s), 158.8 (s), 150.8 (s), 145.3

(s), 136.7 (s), 136.5 (d), 130.4 (d), 128.5 (d), 128.2 (d), 127.2 (d), 113.52 (d), 113.50 (d), 111.3 (d), 87.4 (d), 85.5 (d, $^3J_{POCC}$ = 8.1 Hz, C4'), 85.0 (s), 75.5 (d), 63.8 (d, $^2J_{POC}$ = 4.4 Hz, C5'), 55.4 (q), 45.6 (t), 39.6 (t), 12.6 (q), 8.8 (q). ^{31}P NMR (162 MHz, $CDCl_3$): δ= 4.78 ppm ($^1J_{PH}$ = 615 Hz). HRMS: *m/z* 607.1821 ([M-TEAH]$^-$, $C_{31}H_{32}N_2O_9P^-$ calcd. 607.1851).

3'-*O*-(4,4-Dimethoxytrityl)-*N*^{4}-benzoyldeoxycytidin-5'-yl H-phosphonate, triethyl-ammonium salt , triethylammonium salt(2b). Yield: 336 mg, 84%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (d, ^3J = 7.4 Hz, H3, 1H), 7.88 (m, $H2_{Bz}$, $H6_{Bz}$, 2H), 7.60-7.19 (m, DMT, Bz, H4, 15H), 6.83 (m, $H3_{DMT}$, $H5_{DMT}$, $H3'_{DMT}$, $H5'_{DMT,}$ 4H), 6.70 (d, $^1J_{P\text{-}H}$ = 615.6 Hz, 1H), 6.50 (m, H1', 1H), 4.37 (m, H3', 1H), 3.78 (m, 2×OC*H*$_3$, H5', 7H), 3.76 (m, H4', 1H), 3.36 (m, H5", 1H), 3.02 (q, ^3J = 7.3 Hz, N(C*H*$_2$CH$_3$)$_3$, 6H), 2.43 (m, H2", 1H), 1.87 (m, H2', 1H), 1.28 (t, ^3J = 7.3 Hz, N(CH$_2$C*H*$_3$)$_3$, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0 (s), 158.7 (s), 145.7(s), 145.2(s), 136.5 (s), 136.4 (s), 133.1 (d), 130.31 (d), 130.26 (d), 129.0 (d), 128.4 (d), 128.0 (d), 127.6 (d), 127.1 (d), 113.4 (d), 96.6, 87.7, 87.3 (s), 86.3 (d, $^3J_{POCC}$ = 8.0 Hz, C4') 75.3, 63.4 (d, $^3J_{POC}$ = 3.9 Hz, C5'), 55.3 (q), 45.5 (t), 41.4 (t), 8.6 (q). ^{31}P NMR (162 MHz, $CDCl_3$): δ= 4.57 ppm ($^1J_{PH}$ = 616 Hz). HRMS: *m/z* 696.2143 ([M-TEAH]$^-$, $C_{37}H_{35}N_3O_9P^-$ calcd. 696.2116).

3'-*O*-(4,4-Dimethoxytrityl))-*N*^{6}-benzoyldeoxyadenosin-5'-yl H-phosphonate, triethyl-ammonium salt (2c). Yield: 304 mg, 74%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.14 (bs, N6H, 1H), 8.80 and 8.70 (2×s, H2 and H8, 2H), 8.01 (m, $H2_{Bz}$, $H6_{Bz}$, 2H), 7.62-7.20 (m, DMT, Bz, 13H), 6.85 (m, $H3_{DMT}$, $H5_{DMT}$, $H3'_{DMT}$, $H5'_{DMT,}$ 4H), 6.74 (d, ^1J = 616.9 Hz, P-H, 1H), 6.70 (m, H1', 1H), 4.52 (m, H3', 1H), 3.94 (m, H4', 1H), 3.86-3.77 (m, H5', 2×OC*H*$_3$, 7H), 3.53 (m, H5", 1H), 2.99 (q, ^3J = 7.3 Hz, N(C*H*$_2$CH$_3$)$_3$, 6H), 2.44 (m, H2', 1H), 2.11 (m, H2", 1H), 1.23 (t, ^3J = 7.3 Hz, N(CH$_2$C*H*$_3$)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1 (s), 159.0 (s), 152.7 (s), 152.3 (s), 149.5 (s), 145.3(s), 142.6 (d), 136.5 (s), 134.1(s), 132.9 (d), 130.47 (d), 130.45 (d), 129.1 (d), 128.5 (d), 128.3 (d), 128.1 (d), 127.3 (d), 123.2 (d), 113.6 (d), 87.6 (s), 86.3 (d, $^3J_{POCC}$ =7.4 Hz, C4'), 84.5 (d), 75.8 (d), 63.9 (d, $^2J_{POC}$ = 4.3 Hz, C5'), 55.5 (q), 45.6 (t), 40.8 (t), 8.8 (q). ^{31}P NMR (162 MHz, $CDCl_3$): δ= 4.70 ppm ($^1J_{PH}$ = 618 Hz). HRMS: *m/z* 720.2264 ([M-TEAH]$^-$, $C_{38}H_{35}N_5O_8P^-$ calcd. 720.2229).

3'-*O*-(4,4-Dimethoxytrityl)-*N*^{2}-isobutyryldeoxyguanosin-5'-yl H-phosphonate, triethyl-ammonium salt (2d). Yield: 338 mg, 84%. ^{1}H NMR (400 MHz, $CDCl_3$): δ12.7 (s, N*H*, 1H), 12.3 (s, N*H*, 1H), 7.64 (s, H8, 1H), 7.45-7.17 (m, DMT, 9H), 6.80 (m, $H3_{DMT}$, $H5_{DMT}$, $H3'_{DMT}$, $H5'_{DMT,}$ 4H), 6.71 (d, $^1J_{P\text{-}H}$ = 620.0 Hz, 1H), 6.15 (m, H1', 1H), 4.34 (m, H3', 1H), 3.91 (m, H4', 1H), 3.85 (m, H5', 1H), 3.75 (s, 2×OC*H*$_3$, 6H), 3.67 (m, H5", 1H), 2.96-2.82 (m, (CH$_3$)$_2$C*H*ibu, N(C*H*$_2$CH$_3$)$_3$, H2", 8H), 1.64 (m, H2', 1H), 1.17-1.11 (m, (C*H*$_3$)$_2$CHibu, N(CH$_2$C*H*$_3$)$_3$, 15H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.0 (s), 158.7 (s), 155.9 (s), 148.5 (s), 148.1 (s), 145.0 (s), 139.1 (d), 136.1 (s), 130.1(d), 128.1 (d), 128.0 (d), 127.0 (d), 122.8 (d), 113.3 (d), 87.5 (s), 87.3 (d), 85.7 (d, $^3J_{POCC}$ = 8.4 Hz, C4'), 75.0 (d), 63.9 (d, $^2J_{POC}$ = 3.8 Hz, C5'), 55.2 (q), 45.4 (q), 37.7 (t), 35.2 (d), 19.3 (q), 18.9 (q), 8.5 (q). ^{31}P NMR (162 MHz, $CDCl_3$): δ= 4.93 ppm ($^1J_{PH}$ = 622 Hz). HRMS: *m/z* 702.2320 ([M-TEAH]$^-$, $C_{35}H_{37}N_5O_9P^-$ calcd. 702.2334).

Acknowledgements

Financial support from the Swedish Research Council is gratefully acknowledged.

References and Notes

1. (a) Mitsunobu, O. *Synthesis* **1981**, *1*. (b) But, T. Y. S.; Toy, P. H. *Chem. Asian J.* **2007**, *2*, 1340.
2. But, T. Y. S.; Toy, P. H. *J. Am. Chem. Soc.* **2006**, *128*, 9636.
3. (a) Lipshutz, B. H.; Chung, D. W.; Rich, B.; Corral, R. *Org. Lett.* **2006**, *8*, 5069. (b) Veliz, E. A.; Beal, P. A. *Tetrahedron Lett.* **2006**, *47*, 3153. (c) Mahdavi, H.; Amani, J. *Tetrahedron Lett.* **2008**, *49*, 2204. (d) Dandapani, S.; Curran, D. P. *J. Org. Chem.* **2004**, *69*, 8751. (d) Elson, K. E.; Jenkins, I. D.; Loughlin, W. A. *Tetrahedron Letters* **2004**, *45*, 2491. (e) Fairfull-Smith, K. E.; Jenkins, I. D.; Loughlin, W. A. *Org. Biomol. Chem.* **2004**, *2*, 1979.
4. (a) Dandapani, S.; Curran, D. P. *Chem. Eur. J.* **2004**, 3130. (b) Dembinski, R. *Eur. J. Org. Chem.* **2004**, 2763.
5. Proctor, A. J.; Beautement, K.; Clough, J. M.; Knighta, D. W.; Li, Y. *Tetrahedron Lett.* **2006**, *47*, 5151.
6. Stawinski, J.; Kraszewski, A. *Acc. Chem. Res.* **2002**, *35*, 952.
7. Kraszewski, A.; Stawinski, J. *Pure & Appl. Chem.* **2007**, *79*, 2217.
8. (a) Hayakawa, Y.; Hirabayashi, Y.; Hyodo, M.; Yamashita, S.; Matsunami, T.; Cui, D. M.; Kawai, R.; Kodama, H. Eur. *J. Org. Chem.* **2006**, 3834. (b) Almer, H.; Szabo, T.; Stawinski, *J. Chem. Commun.* **2004**, 290.
9. (a) Grochowski, E.; Hilton, B. D.; Kupper, R. J.; Michejda, C. *J. Am. Chem. Soc.* **1982**, 104, 6876. (b) Varasi, M.; Walker, K. A. M.; Maddox, M. L. *J. Org. Chem.* **1987**, *52*, 4235. (c) Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, 110, 6487. (d) Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, *54*, 3045. (e) Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, *54*, 3049. (f) Crich, D.; Dyker, H.; Harris, R. J. *J. Org. Chem.* **1989**, *54*, 257. (f) Campbell, D. A. *J. Org. Chem.* **1992**, *57*, 6331. (g) McNulty, J.; Capretta, A.; Laritchev, V.; Dyck, J.; Robertson, A. *J. Ang. Chem. Int. Ed. Eng.* **2003**, *42*, 4051.
10. Ahn, C. J.; Correia, R.; DeShong, P. J. *Org. Chem.* **2002**, *67*, 1751.
11. (a) Morrison, D. *J. Org. Chem.* **1958**, *23*, 1072. (b) Brunn, E.; Huisgen, R. *Ang. Chem. Int. Ed.* **1969**, 8, 513.
12. Hughes, D. L.; Reamer, R. A. *J. Org. Chem.* **1996**, *61*, 2967.
13. Schenk, S.; Weston, J.; Anders, E. *J. Am. Chem. Soc.* **2005**, *127*, 12566.
14. (a) Mitsunobu, O.; Kato, K.; Kimura, J. *J. Am. Chem. Soc.* **1969**, *91*, 6510. (b) Mitsunobu, O.; Eguchi, M. *Bull. Chem. Soc. Jpn* **1971**, *44*, 3427.
15. Kimura, J.; Fujisawa, Y.; Yoshizawa, T.; Fukuda, K.; Mitsunobu, O. *Bull. Chem. Soc. Jpn* **1979**, *52*, 1191.

16. (a) Saady, M.; Lebeau, L.; Mioskowski, C. *Tetrahedron Lett.* **1995**, *36*, 2239. (b) Saady, M.; Lebeau, L.; Mioskowski, C. *Synlett* **1995**, 643.
17. Jahn, W. *Chem. Ber.* **1965**, *98*, 1705.
18. (a) Dodge, J. A.; Trujillo, J. I.; Presnell, M. J. *Org. Chem.* **1994**, *59*, 234. (b) Harvey, P. J.; von Itzstein, M.; Jenkins, I. D. *Tetrahedron* **1997**, *53*, 3933.
19. Stawinski, J.; Thelin, M. *Nucleosides Nucleotides* **1990**, *9*, 129.
20. Stawinski, J. Some Aspects of H-Phosphonate Chemistry. In *Handbook of Organophosphorus Chemistry*; R. Engel, Ed.; Marcel Dekker: New York, 1992; p. 377.
21. (a) Jankowska, J.; Sobkowski, M.; Stawinski, J.; Kraszewski, A. *Tetrahedron Lett.* **1994**, *35*, 3355. (b) Stawinski, J.; Strömberg, R. Di- and oligonucleotide Synthesis Using H-Phosphonate Chemistry. In *Oligonucleotide Synthesis: Methods and Applications*; P. Herdewijn, Ed.; Humana Press: Totowa, NJ, 2004; Vol. 288, p. 81.
22. Gait, M. J. Ed. Oligonucleotide synthesis. A practical approach; IRL Press: Oxford, 1984; p. 23.

 ©ARKAT USA, Inc.