Aryl H-phosphonates. Part 11. Synthetic and ^{31}P NMR studies on the formation of aryl nucleoside H-phosphonates †

Jacek Cieslak,[a] Marzena Szymczak,[a] Malgorzata Wenska,[a] Jacek Stawinski and Adam Kraszewski *[a]

[a] *Institute of Bioorganic Chemistry, Polish Academy of Sciences, Noskowskiego 12/14, 61-704 Poznan, Poland*
[b] *Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, S-106 91 Stockholm, Sweden*

Received (in Lund, Sweden) 1st September 1999, Accepted and transferred from Acta Chem. Scand. 28th September 1999

The formation of aryl H-phosphonate diesters from the corresponding nucleoside 3′-H-phosphonates and various phenols was investigated in detail using ^{31}P NMR spectroscopy. The major reaction pathways of aryl nucleoside H-phosphonates under different experimental conditions have been identified and a general method for a clean and efficient generation of these valuable synthetic intermediates was developed.

The H-phosphonate methodology, due to its efficiency, reliability and experimental simplicity, has emerged in the last decade as a versatile and powerful approach to the synthesis of biologically active phosphates and their analogues.[1,2]

As part of our studies in this field, we have recently reported on aryl H-phosphonates as a new type of active H-phosphonate derivatives,[3–8] particularly useful in the synthesis of nucleoside phosphoramidates,[7] for the aminoalkyl functionalization of support-bound oligonucleotides,[8] or in the preparation of dinucleoside H-phosphonates *via* the transesterification approach.[5] We also found that inexpensive, commercially available diphenyl H-phosphonate can be the reagent of choice for simple and efficient preparation of nucleoside H-phosphonate monoesters[4] or various synthetically useful alkyl H-phosphonates.

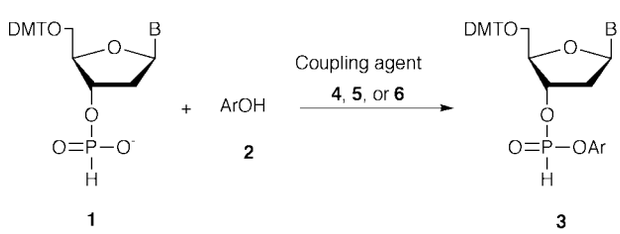
The main advantages of aryl H-phosphonates as synthetic intermediates stem from the fact that these compounds, in principle, possess only one electrophilic centre located on the phosphorus atom and, in contradistinction to other reactive H-phosphonate species, *e.g.* mixed H-phosphono-acyl anhydrides, their reactivity can be modulated by changing electronic and/or steric properties of substituents on the aromatic ring of an aryl moiety. These features significantly widen the synthetic applications of H-phosphonate methodology by enabling the syntheses of compounds otherwise difficult to prepare, *e.g.* nucleoside H-phosphoramidates.[7]

In contradistinction to various dialkyl H-phosphonates, *e.g.* dinucleoside H-phosphonate,[9,10] glycero alkyl H-phosphonates,[11] that can be prepared efficiently using the standard H-phosphonate approach, there are a few inherent problems associated with the synthesis of some aryl H-phosphonate diesters. These can be traced back to the highly electrophilic character of the phosphorus centre in reactive aryl H-phosphonates which leads to some additional reaction pathways, not available for dialkyl H-phosphonates. Indeed, our previous studies have shown, for example, that diphenyl H-phosphonate undergoes under anhydrous basic conditions a rearrangement[12] to triphenyl phosphite and phenyl H-phosphonates (a reaction not observed for dialkyl H-phosphonates), in addition, the activation pattern of these compounds can differ from that of simple alkyl H-phosphonate derivatives.[13]

To secure efficiency and reproducibility of synthetic methods making use of aryl H-phosphonates as intermediates, the chemistry of this class of compounds needs to be better understood. In this paper we address the most important factors, particularly those related to the reactivity of the P–H bond in these compounds, which may affect the formation and stability of nucleoside aryl H-phosphonates under various experimental conditions. Since reactivity of aryl H-phosphonate diesters, especially those of a synthetic value, may exceed that of H-phosphonic acyl mixed anhydrides, these compounds have to be viewed in a majority of cases as *sensu stricto* reactive intermediates. In this context, their clean and efficient *in situ* generation rather than the isolation were the major objectives of our work.[14]

Results and discussion

The synthesis of a nucleoside aryl H-phosphonate can be carried out either by phosphonylation of a suitable protected nucleoside with an appropriate phosphonylating reagent bearing an aryl moiety[15] or by reacting a nucleoside H-phosphonate with an appropriate phenol in the presence of a condensing agent.[7] We have pursued the latter approach (Scheme 1)



B = thymin-1-yl
DMT = 4,4-dimethoxytrityl

2a, **3a**, Ar = 2,4,6-trimethylphenyl
2b, **3b**, Ar = 4-methylphenyl
2c, **3c**, Ar = phenyl
2d, **3d**, Ar = 4-chlorophenyl
2e, **3e**, Ar = 2,4-dichlorophenyl
2f, **3f**, Ar = 4-nitrophenyl
2g, **3g**, Ar = 2,4,6-trichlorophenyl

Scheme 1

since it alleviates problems of preparing separate phosphonylating reagents for each kind of aryl H-phosphonate derivative and thus, in light of easily accessible H-phosphonate monoesters, seems to be more convenient and versatile.

† Part 10. I. Kers, J. Stawinski and A. Kraszewski, *Tetrahedron*, 1999, **55**, 11579.

Table 1 ^{31}P NMR data[a] of aryl nucleoside H-phosphonates of type **3** and other reaction products

Compound	δ/ppm	$^1J_{HP}$/Hz	$^3J_{HP}$/Hz	Compound	δ/ppm	$^1J_{HP}$/Hz	$^3J_{HP}$/Hz
3a	3.34, 3.50[b]	719.3, 721.1	7.4[c]	**8c**	125.97, 125.48[b]	—	8.3[g]
3b	4.63	725.8	7.4[d]	**8d**	125.69, 126.46[b]	—	9.3[g]
3c	4.44, 4.47[b]	712.6, 732.6	8.3[c]	**8e**	126.23[e]	—	9.3[g]
3d	4.63	737.9	8.3[d]	**8f**	124.8, 125.96[b]	—	9.3[g]
3e	4.04	737.1	—[e]	**8g**	127.19, 127.42[b]	—	9.3[g]
3f	4.07	750.8	—[e]	**11a**	−6.44, −5.56[b]	—	6.4[g]
3g	2.44, 2.87[b]	769.3, 760.6	8.3[d]	**11b**	−6.42, −6.54[b]	—	6.5[g]
7a	128.03	—	9.3[g]	**11c**	−6.55, −6.67[b]	—	6.5[g]
7b	128.10	—	9.3[f]	**11d**	−6.45, −6.63[b]	—	6.5[g]
7c	127.63	—	9.3[f]	**11e**	−6.66, −6.88[b]	—	6.5[g]
7d	127.91	—	9.3[f]	**11f**	−6.73, −6.85[b]	—	6.7[g]
7e	128.13	—	9.3[f]	**11g**	−8.02, −8.29[b]	—	6.9[g]
7f	126.45	—	8.3[f]				
7g	130.57	—	10.2[f]				

[a] In pyridine. [b] Two diastereoisomers. [c] Two doublets of doublets. [d] Doublet of doublets. [e] Broad singlet. [f] Doublet. [g] Two doublets.

The presence of an electron-withdrawing aryloxy group at the phosphonate centre causes the P–H bond in aryl H-phosphonate diesters to be usually more acidic than that in dialkyl H-phosphonates and may facilitate conversion of the tetracoordinated phosphonates into tervalent phosphite forms. Although ^{31}P NMR spectra of these compounds show the presence of only the phosphonate form,[12,13] one cannot exclude the possibility that a significantly higher concentration exists below the detection level of ^{31}P NMR spectroscopy, of the phosphite form in aryl H-phosphonates. Since most of the synthetic applications of H-phosphonates take advantage of the high stability of the H-phosphonate function under the reaction conditions, changes in the phosphonate–phosphite equilibria may cause some synthetic complications. Indeed, a propensity of some aryl H-phosphonates to form tervalent derivatives of type **7**–**9** (Chart 1) is consistent with this assumption. To remedy this we tried to pin-point the most important factors affecting the stability of the phosphonate form of aryl H-phosphonate diesters. For this purpose the formation and stability of nucleoside aryl H-phosphonates **3** were investigated as a function of the aryl moiety, type of condensing agent used, and basicity of the reaction medium.

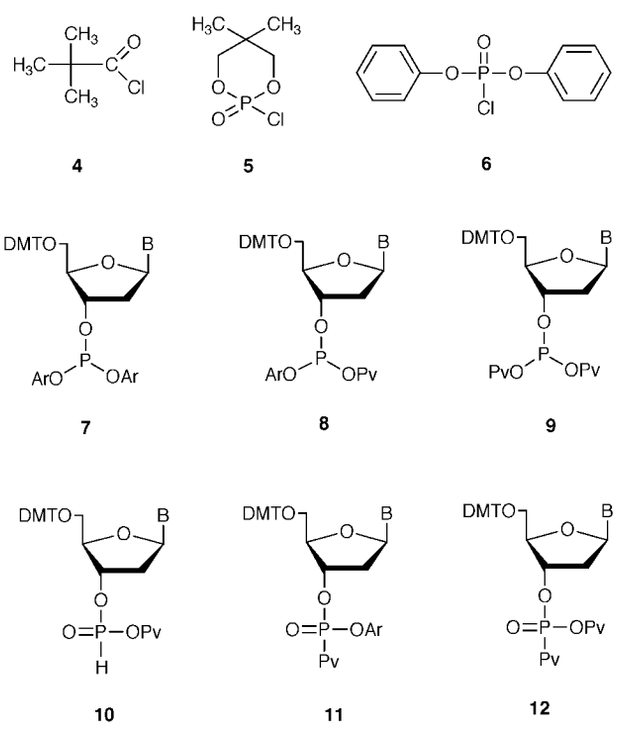


Chart 1

Condensations of H-phosphonate 1 with phenols 2 in pyridine in the presence of pivaloyl chloride

Initially, we attempted the synthesis of various nucleoside aryl H-phosphonates **3** under standard condensation conditions that have been shown to give clean and quantitative formation of dinucleoside H-phosphonate diesters.[16,17] To this end nucleoside H-phosphonate **1** (Scheme 1) was reacted with various phenols **2** (1.2 molar equiv.) in the presence of pivaloyl chloride (**4**, 3.0 molar equiv.) in neat pyridine. ^{31}P NMR spectra of the reaction mixtures revealed that the efficiency of the formation of the desired product **3** varied significantly, depending on the kind of phenol used. Aryl H-phosphonates **3** bearing electron-donating groups on the aromatic ring (2,4,6-trimethyl- and 4-methylphenyl derivatives **3a** and **3b**) were formed readily (*ca*. 3 min) and virtually quantitatively. In the reactions of unsubstituted phenol **2c** or 4-chlorophenol **2d** the formation of the corresponding aryl H-phosphonate **3c** or **3d** was less clean (*ca*. 92% and 85% of the desired product, respectively), and the reaction mixtures were contaminated by side products which resonated in the chemical shift range of tervalent phosphorus derivatives (species of type **7** and **8**, Chart 1 and also Table 1). This tendency was even more pronounced for more acidic phenols investigated (2,4-dichloro- **2e**, 4-nitro- **2f** and 2,4,6-trichloro- **2g** derivatives). In these instances, the corresponding aryl H-phosphonates **3** were the minor reaction products (**3e**, 47%; **3f**, 6%; **3g**, 12%), formed with various proportions of tervalent species **7**, **8** and **9**. Upon standing, compositions of these reaction mixtures underwent further changes, and additional side products, **11** and **12**, started to form (see below).

The product distribution in the above reactions deserves some comment since it sheds light on general trends in the reactivity of aryl H-phosphonate diesters. It is likely that due to lower nucleophilicity the acidic phenols (*e.g.* **2d**–**g**) will couple slower than alkanols or less acidic phenols (*e.g.* **2a**–**c**) and thus the primary activation product of **1**, the mixed phosphonic carboxylic anhydride **10**,[18] may undergo further activation with pivaloyl chloride under the reaction conditions to produce bispivaloyl phosphite **9**.[18] This is an unfavourable situation since the latter species can react with the phenol present giving a mixture of side products, pivaloyl aryl **8** and bisaryl phosphite **7**. One should note that aryl pivaloyl phosphites **8** can also be

formed in a subsequent reaction of the produced aryl H-phosphonates **3** and pivaloyl chloride, and this is probably a low energy pathway for **3** with electron-withdrawing substituents on the phenyl ring, *e.g.* **3d**–**g**. For these reasons, the amounts of tervalent side products **7**, **8** and **9** and their relative ratio[19] correlated well with acidity of the phenol used for the condensation.

Although the formation of **3a** and **3b** was a clean reaction, these compounds were not completely stable under the reaction conditions and upon standing underwent a slow reaction with excess pivaloyl chloride to produce *P*-acylated products **11**. The formation of **11** most likely involves intermediacy of **8** (produced from **3**), but since **8a** and **8b** are probably formed slowly but undergo fast *P*-acylation, we did not observe these intermediates using ^{31}P NMR spectroscopy. However, for aryl H-phosphonates **3d**,**e**, the formation of the corresponding **8** was significantly faster, and since their *P*-acylation seemed to be rather slow (electronic effects), we observed in these instances the accumulation of **8d**,**e** and then their gradual transformation to **11d**,**e**. For the most acidic phenols investigated (*e.g.* 4-nitrophenol, 2,4,6-trichlorophenol), significant formation of pivaloyl phosphite **9** and its higher reactivity in the *P*-acylation than those of **8f** or **8g** led to the formation of the *P*-pivaloylated species **12**, rather than **11f** or **11g**.

Having established this general reactivity pattern of **3** in pyridine, we attempted to suppress the formation of side products **7**–**12** by optimizing the reaction conditions. By using less phenol **2** (1.1 molar equiv.) and reducing the amount of pivaloyl chloride to 1.1 equiv we were able to generate rapidly (less than 3 min) and cleanly aryl H-phosphonates **3a**–**d**. For the reaction of **1** with more acidic phenols (**2e**–**g**) we also observed an increase in the yield of the desired product (**3e**, 60%; **3f** 26%; **3g**, 22%), but these improvements were hardly satisfactory.[20]

Condensations of H-phosphonate 1 with phenols 2 in pyridine in the presence of chlorophosphates 5 and 6

To eliminate the formation of side products with the pivaloyl moiety (**8**–**12**), we attempted to use chlorophosphates as condensing agents, which are also known to efficiently promote the formation of H-phosphonate diesters.[21,22] Indeed, using diphenyl phosphorochloridate **6** (1.2 molar equiv.) or 2-chloro-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphinane **5** (2.5 molar equiv.) in pyridine, the formation of **3a**–**d** from **1** and the corresponding phenol **2** was practically quantitative and complete in less than 5 min. We observed, however, that in contradistinction to **3a** and **3b**, aryl H-phosphonate **3d** underwent a slow decomposition in pyridine yielding equimolar amounts of diaryl nucleoside phosphite **7d** and the starting material **1** (*ca*. 13% after 2 h). Compounds **7d** and **1** can be formed *via* disproportionation of **3d** under anhydrous basic conditions, a reaction previously observed for diphenyl H-phosphonate[12] and thus it seems that phosphite–phosphonate disproportionation can be a general reaction pathway accessible for reactive aryl H-phosphonate diesters. Since the rate of the disproportionation should grow with increasing electron-withdrawing character of an aryl moiety, it was anticipated that nucleoside aryl H-phosphonates **3f** and **3g** should undergo this reaction significantly faster than compounds **3a**–**d**.

The product distribution in the reaction of nucleoside H-phosphonate **1** with more acidic phenols (**2e**–**g**) in the presence of chlorophosphate **5** or **6** in pyridine seemed to support this assumption. The yields of the desired products **3** indeed decreased with the increasing acidity of the phenol used (after 5 min *ca*. 66% for **3e**, 42% for **3f** to 33% for **3g**), while the amount of the disproportionation products, **1** and **7**, increased along the series [ratio (**1** + **7**) : **3** *ca*. 1 : 2 for **3e**, 1.5 : 1 for **3f**, and 2 : 1 for **3g**; ^{31}P NMR spectroscopy].

Since disproportionation of aryl H-phosphonates **3** does not involve a condensing agent it probably also occurred to a similar extent in the pivaloyl chloride promoted condensations discussed above. However, due to different activation pathways of H-phosphonates by pivaloyl chloride[18] and those by chlorophosphates,[23–25] the disproportionation of aryl H-phosphonates **3** could be clearly detected only in the latter instances.

Condensations of H-phosphonate 1 with phenols 2 in methylene chloride

Although aryl nucleosides H-phosphonates **3a**–**d** could be produced rather cleanly in pyridine in the presence of chlorophosphates **5** or **6** as condensing agents, those bearing aryl moieties with strong electron-withdrawing substituents (**3e**–**g**) underwent a significant disproportionation under the reaction conditions.

To suppress this reaction pathway, we carried out the condensation of nucleoside H-phosphonate **1** with phenols **2** (1.1 molar equiv.) in methylene chloride using variable amounts of pyridine. Since 3 molar equiv. of pyridine relative to the condensing agent **4**, **5** or **6** secured stability of the 5′-*O*-dimethoxytrityl group, we used this amount of base in all experiments in methylene chloride.

Pivaloyl chloride **4** (1.1 molar equiv.) proved to be a useful condensing agent (coupling time *ca*. 5 min) under these conditions but only in the synthesis of aryl nucleoside phosphonates **3a**–**d**. For more acidic phenol derivatives **3e**–**g**, the synthesis was less efficient (**3e**, *ca*. 90%; **3f**, 76%; **3g** 72%) although the products did not undergo disproportionation. The observed low yields of the generation of **3** were due to the formation of phosphonic pivalic mixed anhydride **10** (*ca*. 10% in the instance of **3e**, 24% for **3f** and 28% for **3g**; ^{31}P NMR) probably occurring *via* an attack of the pivaloate anion on electrophilic phosphorus centres in **3e**–**g**. In agreement with these, the ratio **3e**–**g** : **10** varied with addition to the reaction mixtures of the appropriate phenol or pivalic acid, thus indicating the existence of a real equilibrium between these two species.

All problems experienced in the previous syntheses of aryl nucleoside H-phosphonates **3** have been alleviated by using diphenyl phosphorochloridate **6** (1.1 equiv.) in methylene chloride in the presence of pyridine (3 molar equiv.). The coupling of nucleoside H-phosphonate **1** with all investigated phenols **2a**–**g** was clean, relatively fast (*ca*. 20 min),[26] and the produced aryl H-phosphonates **3a**–**g** did not undergo any detectable changes within a few hours (^{31}P NMR spectroscopy). In light of these results, we considered this protocol as a general procedure for the *in situ* formation of aryl H-phosphonates **3a**–**g**. For less acidic phenol derivatives, however, other reaction conditions (*e.g.* condensation in pyridine) can also be used, if so desired.

In conclusion, we have found that the most important factors in the synthesis of nucleoside aryl H-phosphonates from nucleoside H-phosphonates **1** and the corresponding phenols **2** are (i) acidity (pK_a) of the phenols; (ii) the nature of the coupling agent used for the condensation, and (iii) basicity of the reaction medium. These factors affect the yields of the condensation to produce **3**, the extent of the subsequent reactions of the product **3** with the condensing agent and the rate of disproportionation of **3**, and thus ultimately determine the efficiency of generating aryl H-phosphonates as synthetic intermediates. Taking all these factors into account we have designed a synthetic protocol consisting of almost equimolar amounts of all reactants (nucleoside H-phosphonate monoester, the appropriate phenol and diphenyl phosphorochloridate) in methylene chloride containing a few molar equivalents of pyridine. These reaction conditions provided stability for the acid-sensitive protecting group (*e.g.* the dimethoxytrityl function) and secured a rapid and clean formation of nucleoside aryl H-phosphonates **3**, even those bearing aryl moieties with strongly electron-withdrawing substituents.

Experimental

^{1}H and ^{31}P NMR spectra were recorded on a 300 MHz spectrometer. The ^{31}P NMR experiments were carried out in 5 mm tubes using 0.1 mol L^{-1} concentration of phosphorus-containing compounds. For column chromatography, Kieselgel 60 Merck was used. The amount of water in solvents was measured with Karl Fisher coulometric titration. Methylene dichloride was dried over P_2O_5, distilled and kept over molecular sieves 4 Å until the amount of water was less than 10 ppm. Pyridine was stored over molecular sieves 4 Å until the amount of water was below 20 ppm. Triethylamine was distilled and stored over CaH_2. 5′-*O*-Dimethoxytritylthymidine 3′-H-phosphonate (triethylammonium salt) **1**[4] and 2-chloro-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphinane **5**[27] were prepared according to published procedures. Diphenyl phosphorochloridate and phenols **2a**–**d** were commercial grade from Aldrich. Pivaloyl chloride (Aldrich) was distilled and stored in a refrigerator.

The reference compounds used for the identification of some of the reaction products or intermediates were obtained as follows: diaryl nucleoside phosphites **7a**–**g**, by reaction of H-phosphonate **1** in pyridine with pivaloyl chloride (3 equiv.) followed by the addition of the appropriate phenol **2a**–**g** (4 equiv.); aryl pivaloyl nucleoside phosphites **8c**–**g**, by reaction of the appropriate aryl H-phosphonate **3c**–**g** with pivaloyl chloride (3 equiv.); bispivaloyl nucleoside phosphite **9**, by pivaloylation of H-phosphonate **1**;[18] aryl nucleoside pivaloylphosphonates **11**, by condensation of *P*-pivaloylated nucleoside phosphonates[28] with appropriate phenol and diphenyl chlorophosphate.

General procedure for the formation of aryl nucleoside phosphonates 3a–g

Nucleoside H-phosphonate **1** (1 molar equiv.) and appropriate phenol **2a**–**g** (1.1 molar equiv.) were rendered anhydrous by repeated evaporation of the added excess of pyridine. The residue was dissolved in methylene chloride (1 mL per 0.1 mmol of **1**) containing pyridine (3 molar equiv.) and treated with diphenyl chlorophosphate (1.1 molar equiv.). In all investigated instances the reaction was completed after *ca*. 20 min (^{31}P NMR) affording **3a**–**g** as the only nucleotidic material. Thus the aryl nucleoside H-phosphonates **3a**–**g** produced could be used for further reactions.

Synthesis and isolation of aryl nucleoside H-phosphonates 3a–c

The solution of aryl nucleoside H-phosphonates **3a**–**c** (produced as above, 0.1 mmol in 1 mL of CH_2Cl_2) was diluted with methylene dichloride (5 mL) and washed with saturated aqueous $NaHCO_3$ (3 × 5 mL). The organic phase was separated, dried (Na_2SO_4 anhydrous), and concentrated to an oil. The residue was purified by silica gel column chromatography using ethyl acetate as an eluent. Fractions containing pure products **3a**–**c** were collected, evaporated and freeze-dried from benzene to afford white amorphous powders.

2,4,6-Trimethylphenyl 5′-*O*-dimethoxytritylthymidin-3′-yl phosphonate (3a). Yield 74%; ^{1}H NMR δ_H (in ppm, CD_2Cl_2) 1.41 and 1.43 (3H, 2s), 2.21, 2.47 (9H, 2s), 2.44, 2.60 (2H, 2m), 3.38 (2H, m), 3.77 (6H, s), 4.20 (1H, m), 5.32 (1H, m), 6.38, 6.41 (1H, 2m), 6.81, 6.84 (4H, 2d, J = 7.0 Hz), 7.13 and 7.17 (1H, 2d, $^1J_{HP}$ = 722.1, 720.2 Hz), 6.87–7.50 (11H, m), 8.78 (1H, br s, exch. D_2O) (multiplicity of some signals due to the presence of P diastereoisomers); for the ^{31}P NMR data, see Table 1. Anal. $C_{40}H_{43}N_2O_9P$: C, 66.11; H, 5.96; N, 3.85. Found: C, 66.16; H, 6.01; N, 3.83%.

4-Methylphenyl 5′-*O*-dimethoxytritylthymidin-3′-yl phosphonate (3b). Yield 71%; ^{1}H NMR δ_H (in ppm, CD_2Cl_2) 1.43 and 1.44 (3H, 2s), 2.30, 2.32 (3H, 2s), 2.43, 2.62 (2H, 2m), 3.38 (2H, m), 3.77 (6H, s), 6.40 (1H, m), 5.33 (1H, m), 6.40 (1H, m), 6.82, 6.85 (4H, 2d, J = 7.0 Hz), 6.96–7.41 (13H, m), 7.07 and 7.08 (1H, 2d, $^1J_{HP}$ = 725.6, 723.8 Hz), 7.48 (1H, m), 8.86 (1H, br m, exch. D_2O) (multiplicity of some signals due to the presence of P diastereoisomers); for the ^{31}P NMR data, see Table 1. Anal. $C_{38}H_{39}N_2O_9P$: C, 65.32; H, 5.63; N, 4.01. Found: C, 65.22; H, 5.67; N, 3.94%.

Phenyl 5′-*O*-dimethoxytritylthymidin-3′-yl phosphonate (3c). Yield 64%; ^{1}H NMR δ_H (in ppm, CD_2Cl_2) 1.43 and 1.44 (3H, 2s), 2.43, 2.62 (2H, 2m), 3.85 (2H, m), 3.77 (6H, s), 4.22 (1H, m), 5.33 (1H, m), 6.39, 6.42 (1H, m), 6.81, 6.84 (4H, 2d, J = 7.0 Hz), 7.09, 7.12 (1H, 2d, $^1J_{HP}$ = 727.67 and 725.58 Hz), 7.09–7.41 (14H, m), 7.47 (1H, m), 8.83 (1H, br s exch. D_2O); for the ^{31}P NMR data, see Table 1. Anal. $C_{37}H_{37}N_2O_9P$: C, 64.91; H, 5.45; N, 4.09. Found: C, 64.86; H, 5.48; N, 4.03%.

Acknowledgements

We are indebted to Professor Maciej Wiewiórowski and to Professor Per J. Garegg for their interest and helpful discussions. Financial support from the State Committee for Scientific Research, Republic of Poland [3 T09A 118 14], the Swedish Natural Science Research Council, and the Swedish Foundation for Strategic Research is gratefully acknowledged.

References

1 A. Kers, I. Kers, A. Kraszewski, M. Sobkowski, T. Szabó, M. Thelin, R. Zain and J. Stawinski, *Nucleosides Nucleotides*, 1996, **15**, 361.
2 J. Stawinski, in *Handbook of Organophosphorus Chemistry*, ed. R. Engel, Marcel Dekker, New York, 1992, pp. 377–434.
3 M. Sobkowski, J. Stawinski, A. Sobkowska and A. Kraszewski, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1803.
4 J. Jankowska, M. Sobkowski, J. Stawinski and A. Kraszewski, *Tetrahedron Lett.*, 1994, **35**, 3355.
5 J. Cieslak, M. Sobkowski, A. Kraszewski and J. Stawinski, *Tetrahedron Lett.*, 1996, **37**, 4561.
6 A. Kers, J. Stawinski, L. Dembkowski and A. Kraszewski, *Tetrahedron*, 1997, **53**, 12691.
7 A. Sobkowska, M. Sobkowski, J. Cieslak, A. Kraszewski, I. Kers and J. Stawinski, *J. Org. Chem.*, 1997, **62**, 4791.
8 M. Sobkowski, A. Kraszewski and J. Stawinski, *Nucleosides Nucleotides*, 1998, **17**, 253.
9 P. J. Garegg, I. Lindh, T. Regberg, J. Stawinski, R. Strömberg and C. Henrichson, *Tetrahedron Lett.*, 1986, **27**, 4051.
10 B. C. Froehler and M. D. Matteucci, *Tetrahedron Lett.*, 1986, **27**, 469.
11 I. Lindh and J. Stawinski, *J. Org. Chem.*, 1989, **54**, 1338.
12 A. Kers, I. Kers, J. Stawinski, M. Sobkowski and A. Kraszewski, *Tetrahedron*, 1996, **52**, 9931.
13 A. Kers, I. Kers, A. Kraszewski and J. Stawinski, *Collect. Czech. Chem. Commun.* (*Special Issue*), 1996, **61**, S246.
14 Some less reactive aryl nucleoside H-phosphonates were isolated and characterized. See the Experimental section.
15 V. Ozola, C. B. Reese and Q. L. Song, *Tetrahedron Lett.*, 1996, **37**, 8621.
16 J. Stawinski, R. Strömberg and R. Zain, *Tetrahedron Lett.*, 1992, **33**, 3185.
17 H. Almer, J. Stawinski, R. Strömberg and M. Thelin, *J. Org. Chem.*, 1992, **57**, 6163.
18 P. J. Garegg, T. Regberg, J. Stawinski and R. Strömberg, *Nucleosides Nucleotides*, 1987, **6**, 655.
19 In the reactions of **1** with **2c** and **2d**, no bispivaloyl phosphite **9** was present in the reaction mixtures and the major side products were those corresponding to diaryl phosphites **7** and aryl pivaloyl phosphites **8**. For more acidic phenols, **2e**–**g**, the amount of **9** increased along the series, and for a highly acidic pentachlorophenyl, it was the major reaction product (no formation of nucleoside pentachlorophenyl H-phosphonate was observed in this instance).
20 In these reactions, the unreacted starting material **1** and the side products **7** + **8** + **9** amounted to 19% and 21% (for **2e**), 40% and

34% (for **2f**), 41% and 38% (for **2g**), respectively (the composition of the reaction mixtures after *ca.* 5 min).
21 P. J. Garegg, T. Regberg, J. Stawinski and R. Strömberg, *Chem. Scr.*, 1985, **25**, 280.
22 R. Strömberg and J. Stawinski, *Nucleic Acids Symp. Ser.*, 1987, **18**, 185.
23 J. Stawinski, R. Strömberg, T. Szabó and E. Westman, *Nucleosides Nucleotides*, 1989, **8**, 1029.
24 J. Stawinski, R. Strömberg, M. Thelin and E. Westman, *Nucleosides Nucleotides*, 1988, **7**, 601.
25 P. J. Garegg, J. Stawinski and R. Strömberg, *J. Org. Chem.*, 1987, **52**, 284.
26 The coupling promoted by rather unreactive chlorophosphate **5** (2.5 molar equiv.) was significantly slower, and was complete after *ca.* 5 h.
27 R. L. McConnell and H. W. Coover, *J. Org. Chem.*, 1959, **24**, 630.
28 A. Kume, M. Fujii, M. Sekine and T. Hata, *J. Org. Chem.*, 1984, **49**, 2139.

Paper 9/07150D