

H*-Phosphonates: Versatile synthetic precursors to biologically active phosphorus compounds

Adam Kraszewski^{1,‡} and Jacek Stawinski^{1,2,‡}

¹*Institute of Bioorganic Chemistry, Polish Academy of Sciences, Noskowskiego 12/14, 61-704 Poznan, Poland;* ²*Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, S-10691 Stockholm, Sweden*

Abstract: In this review, a short account of *H*-phosphonate chemistry and its application to the synthesis of biologically important phosphates and their analogs is given.

Keywords: *H*-phosphonates; phosphate analogs; biological activity; nucleic acids; drugs.

INTRODUCTION

Located at the crossroad of various bioinformation exchange pathways, phosphorus-containing compounds play a key role in living organisms as carriers of genetic information and important signalling, regulatory, energy transfer, and structural compounds [1]. Due to this pivotal role, biologically important phosphorus compounds have become therapeutic targets in various modern medicinal techniques, such as antisense [2] and antigene [3] approaches to modulation gene expression, or a gene silencing technique using short interfering RNA (siRNA) [4].

To maximize the desired biological effect and to minimize cytotoxicity, a biologically active compound has to have very precisely adjusted chemical and pharmacokinetic properties. This can be achieved by, e.g., changing pK_a values of the ionizable functions, changing electronegativity of the substituents, their size, hydrophobicity, etc. These features can also influence transport of a drug across cell membranes, its preferential degradation in normal or activation in the neoplastic or virus-infected cells, and can contribute to the overall efficiency of the drug. A prominent example here are antiviral pronucleotides in which the phosphate moiety is masked with alkyl or aryl groups that are removed chemically and enzymatically in cells to produce an active antiviral nucleotide [5].

Studies on phosphate analogs bearing single or multiple modifications at the phosphorus center are at the cutting edge of the contemporary nucleic acid research due to their importance (i) for the development of nucleic acids-based drugs and clinical diagnostics, and (ii) designing new research tools for investigation at the molecular level of diverse chemical and biochemical phenomena occurring in biopolymers. The underlying principle for these is a potent biological activity of numerous phosphorus compounds that constitutes a strong rationale for their increasingly growing applications, inter alia, as agrochemicals and medicinal compounds [6]. In the latter group, the most important class of compounds are nucleosides derivatives with antiviral and antitumor properties [7].

H-Phosphonate chemistry, which has been explored and developed in our and other laboratories [8–11], offers a unique opportunity for introducing various modifications at the phosphorus center by changing the oxidation conditions of suitable precursors [9]. Some of these modifications turned out to

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‡Corresponding authors

produce the desired therapeutical effects, as it is apparent from recent studies on the inhibition of HIV virus by antisense oligonucleotides in patients suffering from AIDS. Exploration of *H*-phosphonate and *C*-phosphonate chemistry may result in development of new therapeutics with novel medical properties. In 1998, the first antisense drug, Vitravene[®] of Isis Pharmaceuticals, for the treatment of cytomegalovirus-infected retinitis in AIDS patients, appeared on the market. The emergence in recent years of another, highly promising siRNA technique [4] for medical intervention via gene silencing, put new challenges for the chemical synthesis of nucleotide analogs as tools for elucidation of biochemical basis of the RNAi phenomenon (RNA interference) and development of suitable therapeutic agents based on this principle.

In this review, we do not intend to give an exhaustive coverage of phosphorus compounds useful in biology or medicine, but to show some aspects of *H*-phosphonate chemistry, which, due to its “flexibility”, makes *H*-phosphonate derivatives versatile synthetic intermediates in the preparation of a diverse array of biologically important phosphonates and their analogs.

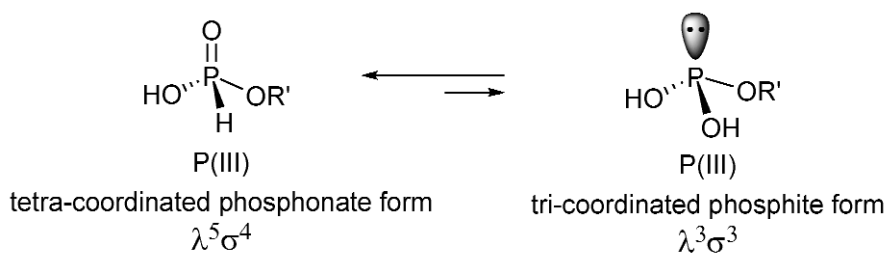
CHARACTERISTIC FEATURES OF *H*-PHOSPHONATES

Properties that are most important from the point of view of synthetic applications of *H*-phosphonate derivatives are: (i) tautomeric equilibria between their phosphite and phosphonate forms, (ii) high electrophilicity of the phosphorus center in *H*-phosphonate diesters and the activated *H*-phosphonate monoesters, (iii) configurational stability of the phosphorus center in *H*-phosphonates, and (iv) a facile oxidation to the phosphorus(V) compounds. These features are shortly discussed below.

Tautomeric equilibria

The most important feature of mono- and diesters of phosphonic acids (referred to as *H*-phosphonates) is that in solution these compounds exist as an equilibrium mixture of two tautomeric forms: a tetra-coordinate phosphonate form (λ^5, σ^4) and a trivalent phosphite (λ^3, σ^3) form (Scheme 1). Although both of them bear phosphorus atom in the +3 oxidation state, they differ fundamentally in chemical reactivity. Due to the presence of a lone electron pair located on the phosphorus atom, trivalent phosphorus(III) derivatives react readily with various electrophiles. For the tetraordinated phosphonate form, the lack of a lone electron pair on the phosphorus center makes these compounds less susceptible to electrophiles, and ultimately more stable and resistant to spontaneous oxidation. The phosphorus atom in this tautomeric form is a hard, electrophilic center, subject to reactions with hard nucleophiles, and its chemistry is dominated by the presence of the phosphoryl group (P=O), the formation of which is often a driving force for the reaction.

The tautomeric equilibria of mono- or diesters of phosphonic acid are practically completely shifted toward the *H*-phosphonate forms, and this permits synthesis of phosphorus compounds without recourse to phosphate protecting groups [9]. On the other hand, since these equilibria can also be shifted to the right, one gains access to two types of phosphorus chemistry that can be used for synthetic pur-



Scheme 1 Indices λ and σ stand for the valency and the coordination number of the phosphorus atom, respectively.

poses: chemistry of trivalent phosphorus(III) derivatives (phosphite chemistry) and chemistry of tetra-coordinated phosphorus(V) derivatives (*H*-phosphonate chemistry).

High electrophilicity at the phosphorus center

On the reactivity part, a characteristic feature of *H*-phosphonate diesters is their high susceptibility to hydrolysis under basic conditions. This exceeds by a factor of 10^5 hydrolysis rates of electrically neutral and base labile phosphate triesters [12]. Also, activated *H*-phosphonate monoesters are extremely reactive, as it is apparent from their high rates of condensation with alcohols [9–11].

Considering the structural features of *H*-phosphonate derivatives, the presence of the P–H bonds in these compounds is usually invoked as explanation for their unusually high reactivity. Since it is rather unlikely that low steric hindrance (due to the presence of the P–H bond) can produce in acyclic compounds such a high rate acceleration, an electronic effect of the P–H bond and ability to form trivalent species by these compounds (Scheme 1) remain viable options. Concerning the latter possibility, experiments showed that tetracoordinated *H*-phosphonic-carboxylic mixed anhydrides (Fig. 1) are more reactive than trivalent bisacyl phosphites, and thus high reactivity of *H*-phosphonates has to be due to electronic effects exerted by the P–H bond [13,14].

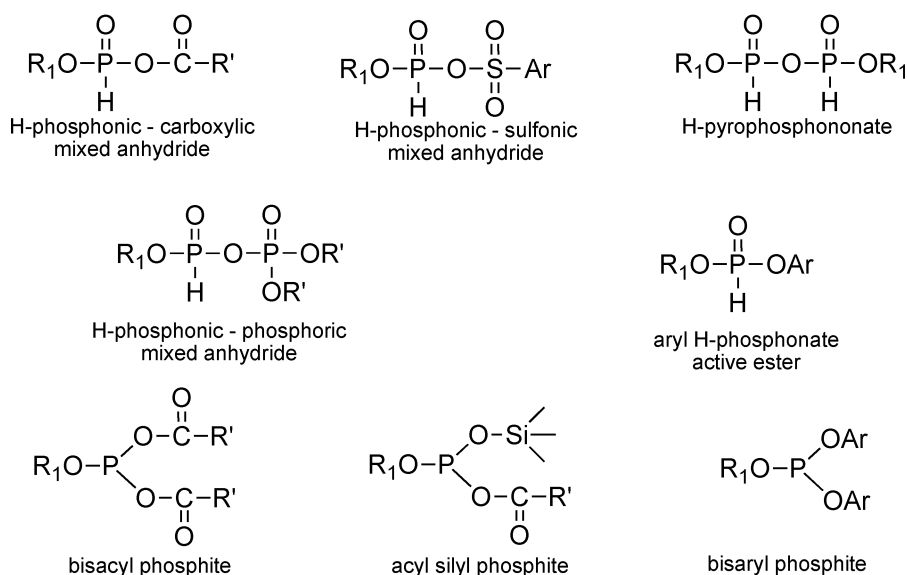


Fig. 1 R_1 = a nucleoside moiety or carbohydrate, lipid, alkyl, aryl, etc. R' = alkyl or aryl.

The origin of such an electronic effect is unknown, but probably it can be understood on the ground of chemical bonding at phosphorus that is dominated by back-donation from the substituents attached to the phosphorus [15]. For example, in phosphate triesters $[O=P(OR)_3]$, due to the difference in electronegativity of phosphorus (2.1) and oxygen (3.5), the P–O bonds are polarized toward oxygen ($P^{\delta+}-O^{\delta-}-R$). However, this activating effect is overshadowed by efficient back-donation of the lone electron pairs of the P–O–C bonds that lowers significantly electrophilicity of the phosphorus center in these compounds. In *C*-phosphonate diesters $[O=PR(OR)_2]$, the P–C bond, due to a smaller difference in electronegativity of phosphorus (2.1) and carbon (2.5), is less polarized but the phosphorus center in these compounds is more electrophilic than that in phosphate triesters since there are only two P–O–C groups that can back-donate electrons to the phosphorus. If this were the whole story, for *H*-phospho-

nate diesters [O=PH(OR)₂] one should expect lower reactivity than for *C*-phosphonates, as electronegativity of phosphorus and hydrogen are almost the same. Since the phosphorus center in *H*-phosphonate diesters is significantly more electrophilic than that in *C*-phosphonate diesters, there must be a mechanism that increases electron density at the phosphorus center in *C*-phosphonates. One can speculate that such a mechanism could invoke delocalization of the bonding σ -electrons of the adjacent PC–H or PC–C bonds on the phosphorus atom (analogously to back-donation or stabilization of α -carbanions by phosphorus) and should lower electrophilicity of the phosphorus center. Since in the instance of the P–H bond, there is apparently no appreciable transfer of electron density from this group to the phosphorus, *H*-phosphonate diesters and related compounds remain highly electrophilic species.

This explanation is consistent with the fact that phosphinate esters, which contain two P–H bonds, are even more susceptible to transesterification [16] than *H*-phosphonate derivatives.

Thanks to this inherently high electrophilicity of uncharged *H*-phosphonate derivatives, an array of coupling agents can be used to promote the condensation reactions [9,10,17–19]. The reactive species generated from *H*-phosphonate monoesters (Fig. 1) are diverse in structure and reactivity, and lend themselves to a powerful methodology for the preparation of biologically important phosphate esters and their analogs.

Configurational stability of the phosphorus center

Tetracoordinated phosphorus(III) derivatives (e.g., simple dioxaphosphanes [20], phosphinate derivatives [21], and dinucleoside *H*-phosphonates [22–26]) are configurationally stable at room temperature, and their conversion to trivalent species and vice versa (as, e.g., in Scheme 1) occurs without epimerization at the phosphorus center. This constitutes a basis for synthetic applications of these compounds as chiral precursors in various stereospecific transformations. Since some of these reactions are also frequently used in stereochemical correlation analysis to determine absolute configuration at the phosphorus center, any departure from the established stereochemical pattern requires meticulous scrutiny to pin-point a possible source of a stereochemical variation [27].

A synthetic area where *H*-phosphonate intermediates proved to be most efficient is the preparation of P-chiral phosphorus compounds, e.g., nucleoside phosphorothioates [23,28–31], phosphoroselenoates [32,33], phosphoroselenothioates [33], phosphoramidates [34,35], etc.

Oxidation to the corresponding phosphorus(V) derivatives

H-Phosphonate derivatives, having a phosphorus atom in the +3 oxidation state, can be easily converted into various phosphorus(V) derivatives using different oxidizing reagents (e.g., iodine/water, elemental sulfur, selenium, etc.). However, since they lack an electron pair on the phosphorus center, *H*-phosphonates are at the same time significantly more resistant to spontaneous oxidation than trivalent phosphorus(III) derivatives. A synthetically important feature is that oxidation of P-chiral *H*-phosphonate derivatives is stereospecific and by changing oxidation conditions, various stereodefined bioorganic phosphate analogs can be prepared from the same precursor [8–11].

H-PHOSPHONATES AS SYNTHETIC PRECURSORS

Synthons based on *H*-phosphonate monoesters and their analogs

In the synthesis of phosphate esters and their analogs, four types of *H*-phosphonate monoester derivatives **1–4** (Fig. 1) are usually used. For those bearing nucleoside, carbohydrate, or lipid moieties, efficient synthetic methods are available [36]. Phosphonylation of suitable hydroxylic components with PCl₃/imidazole reagent system [37] or salicylchlorophosphite [38] to produce *H*-phosphonates **1** re-

quires that amino functions in the substrates are protected, while *H*-pyrophosphonate [39] and diphenyl *H*-phosphonate [40] can tolerate substrates with unprotected amino groups.

For synthons **2–4**, other synthetic methods were developed. *H*-Phosphonothioates **2** and *H*-phosphoselenoates **4** can be prepared in high yields and under mild conditions via sulfurization [41] or selenization [42] of the corresponding phosphinate intermediates, or by using dedicated thiophosphonylating [43–45] and selenophosphonylating reagents [46]. For *H*-phosphonodithioate **3**, a sulfohydrogenolysis of suitable phosphite intermediates [47–49] works best.

Also, methods based on non-oxidative thiation [50,51] of easily accessible *H*-phosphonate monoesters **1** can be used for the preparation of the thio analogs **2** or **3**.



Fig. 2 R_1 is a nucleoside moiety or carbohydrate, lipid, alkyl, aryl, etc.

Synthons based on *H*-phosphonate diesters and their analogs

H-Phosphonate diester derivatives of types **5–9** (Fig. 3) are the most important synthetic precursors from which a vast array of phosphate diesters and their analogs can be obtained [8–10]. These intermediates are usually obtained from the corresponding *H*-phosphonate monoesters **1–4** (Fig. 2) via condensation with suitable alcohols (synthons **5**, **6**, **9**) or amines (synthons **7** and **8**). Synthetic methods leading to these synthons are usually high-yielding, and since the coupling reactions involving *H*-phosphonate monoesters can be carried out under different experimental conditions and using different classes of condensing agents, compounds with diverse structural features can be obtained [8,52–57].

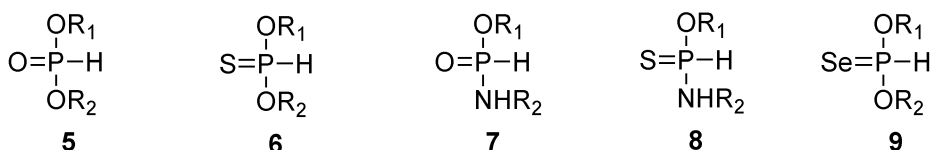


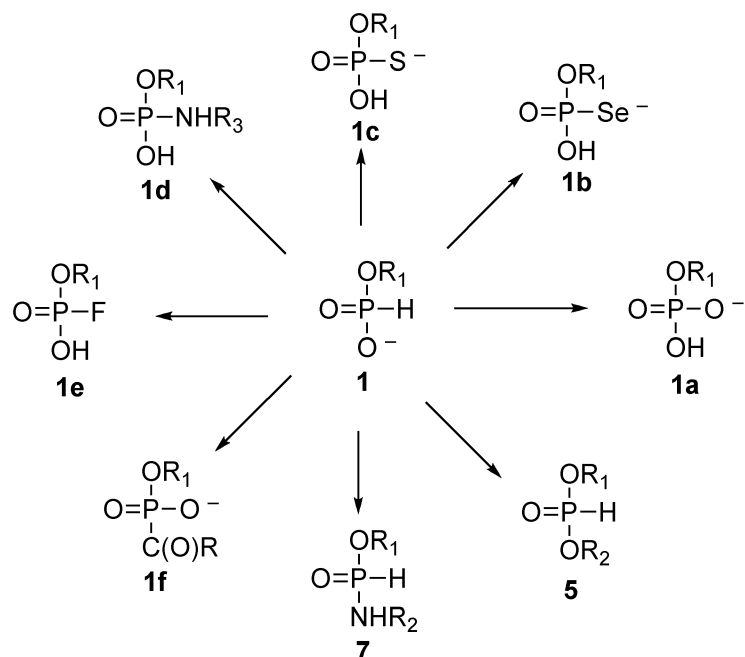
Fig. 3 R_1 and R_2 is a nucleoside moiety or carbohydrate, lipid, alkyl, aryl, etc.

EXAMPLES OF BIOLOGICALLY IMPORTANT PHOSPHATE ANALOGS

The most versatile approach for introducing modifications at the phosphorus center is oxidation of phosphorus(III) precursors, usually phosphite triesters [58] or *H*-phosphonate derivatives [10]. The latter ones often offer several advantages as due to the lack of a phosphate protecting group, the oxidation leads directly to the product, and potential problems with synchronization of various protecting groups are simplified or altogether alleviated. The modification usually involves the replacement of one of the non-bridging oxygens in the phosphodiester functions by heteroatoms, e.g., O, S, Se, N. This can be achieved by simply changing the oxidation conditions for suitable *H*-phosphonate precursors.

Phosphate monoesters and their analogs accessible from the *H*-phosphonate monoester synthons

Oxidative transformations of *H*-phosphonate monoester synthons **1–4** (Fig. 2) lead to a variety of phosphate monoesters analogs. *H*-Phosphonate monoesters **1**, which usually serve as starting materials in



Scheme 2 R_1 and R_2 = a nucleoside moiety or carbohydrate, lipid, alkyl, aryl, etc.

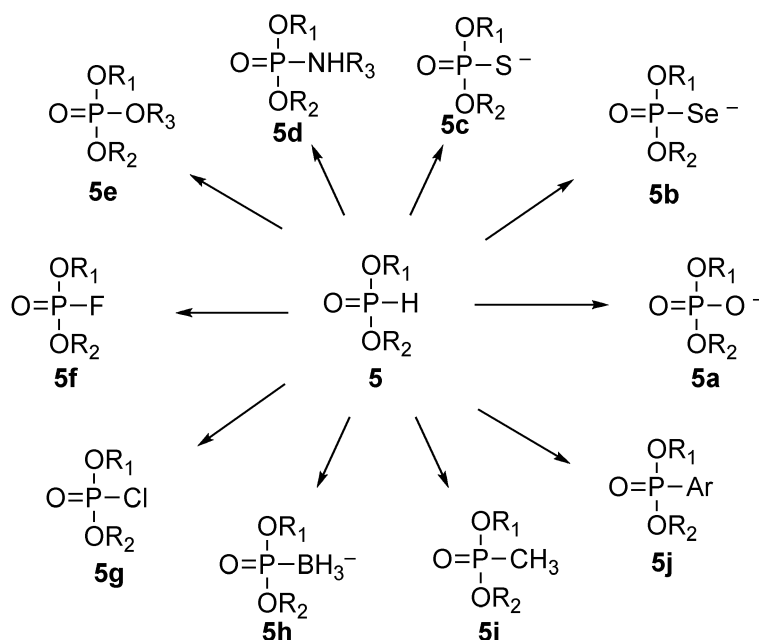
the synthesis of *H*-phosphonate diesters **5** [28,59–62], can also be used as substrates for oxidative transformations to provide variety of phosphate monoesters analogs (Scheme 2). The later ones are valuable tools in investigations of mechanism of enzymatic reactions or can be used as prodrugs of phosphate monoesters. A lot of different oxidation procedures and oxidizing reagents have been developed for *H*-phosphonate derivatives [9,11,30,34,62–70].

For example, phosphate monoesters **1a** can be obtained via oxidation of the *H*-phosphonate synthon **1** with iodine/water, compounds **1d** and **1e**, using iodine/amine and iodine/fluoride, respectively, and compounds **1b** and **1c**, via selenization and sulfurization, respectively, of *H*-phosphonate monoesters **1**. Conversions of **1** into *H*-phosphonate **5** and *H*-phosphonamidate **7** are non-oxidative transformations and show how other synthetically useful intermediates can be obtained from *H*-phosphonate monoesters. Again here, single or multiple modifications at the phosphorus center can be introduced depending on the substrate used (e.g., by using instead of **1** other synthons **2–4**) and the choice of the reaction conditions.

Since *H*-phosphonate monoesters are more resistant to oxidation [9,63] than the corresponding *H*-phosphonate diesters, to facilitate the oxidative transformations, these compounds are usually converted into trivalent silyl phosphites prior to the reaction [63,70,71].

Phosphate diesters and their analogs accessible from the *H*-phosphonate diester synthons

In Scheme 3, various transformations that lead directly to phosphate diesters **5a** and their analogs with a single modification at the phosphorus center are shown. If instead of *H*-phosphonate diester **5**, other *H*-phosphonate diester synthons of types **6–9** (Fig. 3) are used, other families of phosphate analogs (not shown) with single, double, or triple modifications at the phosphorus center are obtained. Since the formation of *H*-phosphonate diester synthons **5–9** is usually quantitative, the oxidative transformations can



Scheme 3 R₁, R₂, R₃ = a nucleoside moiety or carbohydrate, lipid, alkyl, aryl, etc.

often be carried out on crude reaction mixtures or, if so desired, on isolated *H*-phosphonate intermediates.

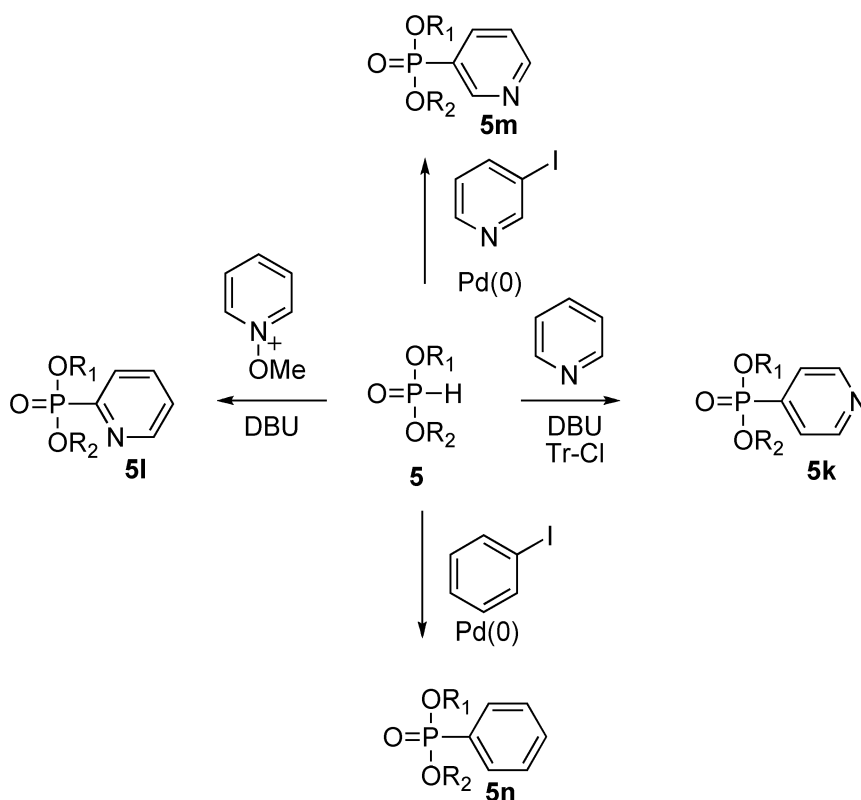
Most of the methods used for transformations of *H*-phosphonate monoester synthons into phosphorus(V) derivatives work excellently with the diester synthons **5–9** [9,11,30,63–69] providing the phosphate analogs **5a–5g** in high yields and under mild conditions. Boranophosphates **5h** can be obtained via silylation of synthon **5**, followed by the reaction with various borane complexes [72], and *C*-phosphonates of type **5i**, via the Arbuzov or the Michaelis–Becker reaction [25,73,74]. Synthetic aspects of arylphosphonates **5j** are shortly discussed below.

C-Phosphonates and their analogs accessible from the *H*-phosphonate diester synthons

Phosphate analogs containing the P–C bond (*C*-phosphonates) are of particular biological interest since the presence of the P–C bond makes these compounds resistant to enzymatic hydrolysis [75] and introduces conformational preferences different from those in phosphates, which are important in interactions with other biomolecules [76].

The P–C bonds are usually formed via the Arbuzov or Michaelis–Becker reactions as mentioned above, but these methods are not applicable to the synthesis of arylphosphonates. Recently, we developed efficient synthesis of dinucleoside pyridylphosphonates **5k** and **5l** based on a DBU-catalyzed reaction of *H*-phosphonate diesters **5** with pyridine/trityl chloride reagent system (for 4-pyridylphosphonates **5k**) [77] or with *N*-methoxypyridinium salts (for 2-pyridylphosphonates **5l**) [78]. These methods were also used for the synthesis of dinucleoside pyridylphosphonothioates [79], starting from *H*-phosphonothioate synthon **6**.

For the synthesis of the third positional isomers of pyridylphosphonates, 3-pyridylphosphonates **5m**, we developed efficient cross-coupling reaction of dinucleoside *H*-phosphonate diesters **5** with 3-iodopyridine catalyzed by Pd(0) [80,81]. This method seems to be rather general, since all pyridylphosphonates **5k–5m** and also phenylphosphonates **5n** can be obtained in this way [81,82].



Scheme 4 R_1 and R_2 = a nucleoside moiety or carbohydrate, lipid, alkyl, aryl, etc. Tr-Cl = trityl chloride.

All the reactions in Scheme 4 are stereospecific and occur with retention of configuration at the phosphorus center. The produced pyridylphosphonates **5k–5m** with defined stereochemistry at the phosphorus center have been incorporated into oligonucleotides and physicochemical properties of such modified DNA fragments were investigated [83].

Other phosphate analogs accessible from the *H*-phosphonate synthons

There are also other types of phosphate analogs that are most conveniently accessed via *H*-phosphonate intermediates, but have not been mentioned in this review. These include α -aminoalkylphosphonates [84,85], α -hydroxyphosphonates [86–88], bisphosphonates [89,90], phosphate-phosphonate [88,91], and others [92–94].

CONCLUDING REMARKS

H-Phosphonate chemistry seems to combine advantages of the most important methodologies, namely, those based on tricoordinated phosphorus(III) and tetracoordinated phosphorus(V) compounds, and thus is the chemistry of choice for the preparation of phosphorus-containing natural products. *H*-Phosphonate derivatives preserve the most fundamental and synthetically useful properties of phosphorus(III) compounds, i.e., an ability to be oxidatively converted into phosphorus(V) derivatives, but are more stable and more easy to handle than tricoordinated phosphite derivatives. The major advantages of methods based on *H*-phosphonate intermediates are: (i) starting materials are stable, easy to handle, and resistant to air oxidation; (ii) high reactivity of various types of mixed anhydrides gener-

ated from these compounds during condensation; (iii) no need for protection of the phosphorus center, which facilitates synchronization of other protecting groups used in a synthesis; (iv) various phosphate analogs can be obtained from one precursor by changing oxidation conditions; and (v) the synthetic procedures are usually time- and cost-effective by comparison with other approaches.

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