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Studies on the Reaction of Trityl Derivatives with *H*-Phosphonate Diesters: Their Relevance to the Synthesis of 4-Pyridylphosphonates

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ABSTRACT: *Transesterification of diphenyl H-phosphonate with tritanol in pyridine afforded equimolar amounts of phenyl H-phosphonate monoester and diphenyl 4-pyridylphosphonate as the only phosphorus-containing species. Using ^{31}P NMR spectroscopy a plausible reaction pathway for the observed transformation was proposed and some of the postulated intermediates were identified. These studies also enabled us to develop an efficient protocol for the formation of diphenyl and diethyl 4-pyridylphosphonates from the corresponding H-phosphonate diesters under mild reaction conditions.* © 1999 John Wiley & Sons, Inc. Heteroatom Chem 10: 492–499, 1999

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INTRODUCTION

A primary rationale of using C-phosphonates as analogs of natural phosphates is that because of the presence of the P–C bond, these compounds are usually resistant to enzymatic hydrolysis under conditions that cleave phosphate esters. Despite this favorable property, C-phosphonate derivatives of natural products are less frequently used than other phosphate analogs in biological studies, mainly because of difficulties in their preparation [1,2]. In contrast to many other phosphate analogs, which can be conveniently prepared via *H*-phosphonate [3] or phosphoramidite [4] intermediates, synthesis of C-phosphonate derivatives usually involves lengthy and less efficient routes [5]. Because most of these methods make use of phosphorus reagents that already possess the P–C bond [1,2], they usually suffer from the same disadvantages, for example, a low rate of coupling, low efficiency of phosphonate diesters formation, and lack of versatility in terms of possible analogs that can be synthesized from a common precursor. To make up for these shortcomings, we searched for an alternative approach where the phosphorus–carbon linkage would be formed in the later stages of the synthesis from readily accessible precursors, for example, from compounds containing the P–H bond.

As part of our studies in *H*-phosphonate chemistry, we recently reported on aryl *H*-phosphonates as new synthetic intermediates [3,6–12]. The most notable feature of aryl *H*-phosphonates is that the phosphorus atom in these compounds is usually the most electrophilic center of the molecule, and thus the issue of chemoselectivity in the reactions with nucleophiles (which can arise in the instance of mixed anhydrides) is alleviated. Also, since the underlying chemical principle for the conversion of aryl *H*-phosphonate diesters into various derivatives is different from that of coupling procedures based on condensing agents, this type of reactive intermediate significantly widens the scope of the *H*-phosphonate methodology [13] for the preparation of biologically important phosphorus compounds.

Another important characteristic of aryl *H*-phosphonates is that the P–H bond in these compounds is more acidic than that in dialkyl *H*-phosphonates, which makes them more susceptible to reactions with various electrophiles. Recently, we have exploited this feature for the efficient formation of the P–C bond under modified Michaelis-Becker conditions [14] by reacting aryl *H*-phosphonate diesters with various pseudohalide substrates in acetonitrile in the presence of 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU). During these studies, we have observed that certain types of alkyl halides and pseudohalides reacted smoothly in pyridine with diphenyl *H*-phosphonate, affording products different from those formed in the Michaelis–Becker reaction.

In this article, we describe the ^{31}P NMR spectroscopy studies on reactions of trityl and substituted trityl derivatives with diphenyl and diethyl *H*-phosphonates in pyridine under various experimental conditions. On this basis, we proposed a plausible mechanism for the observed transformations and suggested an efficient synthetic protocol for the preparation of 4-pyridylphosphonate esters under mild reaction conditions.

RESULTS AND DISCUSSION

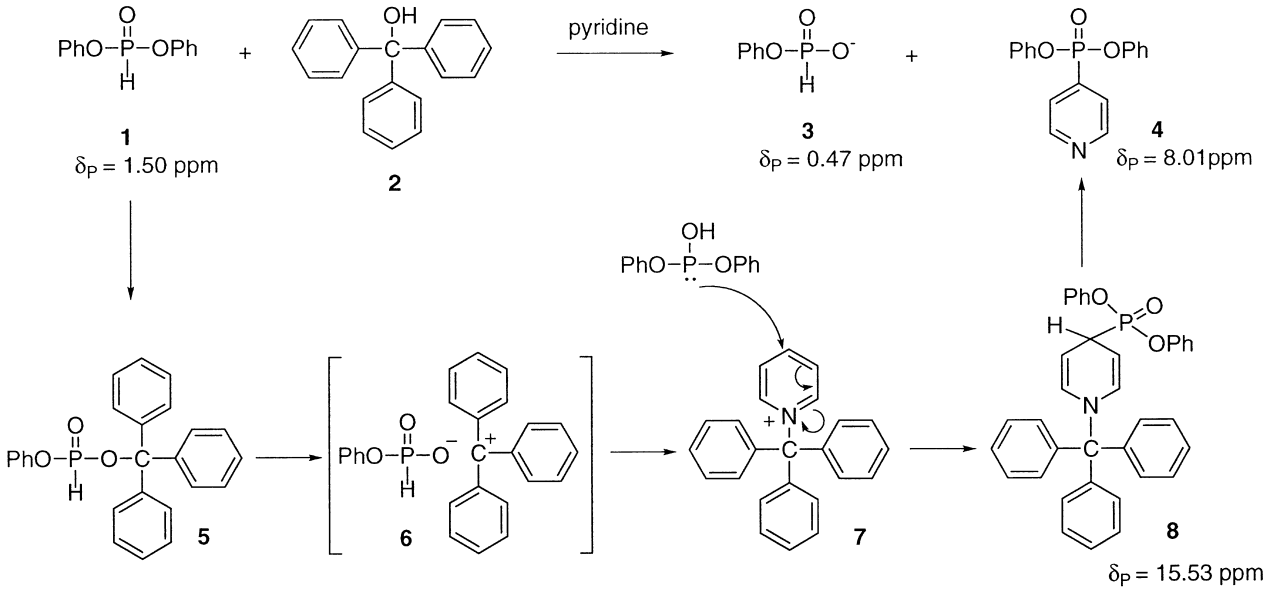
Reaction of Tritanol with Diphenyl H-Phosphonate in Pyridine

During our studies on transesterification of diphenyl *H*-phosphonate (**1**, DPP) with various alcohols [9], we observed that even the sterically hindered *tert*-butanol efficiently replaced a phenoxy group in **1** to produce *tert*-butyl phenyl *H*-phosphonate. This, upon hydrolysis, afforded *tert*-butyl *H*-phosphonate monoester in 91% overall yield.

We tried to employ this reaction for the preparation of trityl *H*-phosphonate monoester as a potential reagent for the introduction of the *H*-phosphonate moiety into organic molecules. We found that, similarly to other alcohols, the transesterification of **1** with tritanol **2** in acetonitrile in the presence of triethylamine or DBU was rather inefficient due to competing disproportionation of diphenyl *H*-phosphonate [15]. However, when diphenyl *H*-phosphonate **1** was treated with **2** (2 equiv.) in pyridine for 1 hour followed by concentration of the reaction mixture, the ^{31}P NMR spectra revealed the presence of two products resonating at δ_P = 0.47 and 8.0 ppm (ratio ~1:1) (Scheme 1). The compound resonating at higher field contained the P–H bond and was identified on the basis of its chemical shift, $^1J_{PH}$ coupling constants, and by comparison with an original sample, as phenyl *H*-phosphonate **3**. The second compound, resonating at δ_P = 8.0 ppm, lacked the P–H bond and thus could not be phenyl trityl *H*-phosphonate **5** nor the expected product of its hydrolysis, trityl *H*-phosphonate. This compound was stable under the reaction conditions and did not undergo any detectable changes upon addition of water or alcohols. Because it resonated in the range of chemical shifts characteristic for compounds having the phosphorus bound directly to an aromatic ring, we assumed that the compound might be an arylphosphonate. In the resolution-enhanced proton-coupled ^{31}P NMR spectrum, the signal at δ_P = 8.0 ppm appeared as a multiplet consisting of seven resonances (pseudoheptet). Spin simulation showed that this pattern can be due to coupling of the phosphorus to two pairs of nonequivalent protons. The magnitude of these coupling constants, 13.80 and 6.12 Hz, indicated coupling through three and four bonds, respectively, which was consistent with the presence of an arylphosphonate moiety in this compound.

To obtain some insight into a possible origin of the products observed, we followed progress of the transesterification of **1** with tritanol **2** by ^{31}P NMR spectroscopy. The reaction was found to be fast. The first ^{31}P NMR spectrum recorded (within 30 minutes) showed a complete disappearance of the starting material **1** and the presence of three resonances: at δ_P = 0.47 ppm (ca. 50%, due to phenyl *H*-phosphonate **3**), δ_P = 8.0 ppm (ca. 10%, tentatively assigned as above) and a new singlet at δ_P = 15.5 ppm. The intensity of the latter signal gradually decreased, and after ca. 5 days only signals due to **3** and an arylphosphonate (at 8.0 ppm) (ratio ~1:1) were present. The observed changes indicated a possible intermediacy of the compound resonating at δ_P = 15.5 ppm in the formation of the product at δ_P = 8.0 ppm.

In the proton-coupled ^{31}P NMR spectrum, the intermediate at δ_P = 15.5 ppm appeared as a doublet (J_{PH} = 19.5 Hz) with several additional small couplings constants that were not resolved even in the



SCHEME 1

resolution-enhanced spectrum. The observed splitting pattern together with the value of the chemical shift suggested that the intermediate most likely contained the phosphorus atom directly bound to an aliphatic carbon [spin system P(=O)–CH]. The spectral characteristics of the intermediate at δ_P = 15.5 ppm and of the product at δ_P = 8.0 ppm were consistent with the intermediacy of a semibenzene type of derivative (δ_P = 15.5 ppm) on the way to an arylphosphonate structure (signal at 8.0 ppm). Because the phosphorus chemical shift is primarily determined by the nature of atoms directly attached to the phosphorus center, we considered the two following types of compounds as compatible with the observed ^{31}P NMR data.

It is possible that the trityl cation formed under the conditions reacted (because of known ambident reactivity of the triphenylmethyl system [16,17]) with the DPP anion at the less crowded *para* carbon atom, affording a semibenzene type of intermediate [18] that gave rise to a resonance at δ_P = 15.5 ppm. Consequently, the product resonating at δ_P = 8.0 ppm should contain a *p*-substituted trityl moiety. Alternatively, since the transesterification of diphenyl *H*-phosphonate **1** with **2** occurred only in the presence of pyridine (see previous section), it was possible that pyridine was an indispensable part of the reaction system. Thus, the intermediate in question could be a dihydropyridine derivative of type **8**, and the final product of the reaction, diphenyl 4-pyridylphosphonate **4** (δ_P = 8.0 ppm). To resolve this point, we carried out the transesterification of **1** with tritanol on a preparative scale and isolated the product resonating at δ_P = 8.0 ppm in ^{31}P NMR. The compound showed three groups of aromatic protons in the ^{1}H NMR spectrum [at δ_H = 7.14 (10H), 7.79 (2H), and 8.81 (2H) ppm], indicating the presence of two phenyl residues and the 4-substituted pyridine system, consistent with diphenyl 4-pyridylphosphonate structure **4**. These results were further corroborated by ^{13}C and ^{31}P NMR, and ^{1}H-^{13}C-correlated NMR analysis.

Since phenyl *H*-phosphonate **3** and 4-pyridylphosphonate **4** were always formed in ~1:1 ratio, it was likely that both were products of one reaction. This, together with the ^{31}P NMR data and the known reactivity of diphenyl *H*-phosphonate **1** in transesterification reactions, allowed us to propose a plausible reaction pathway for the observed transformation (Scheme 1). Most likely, the transformation commenced with fast transesterification of **1** with tritanol **2** to produce phenyl trityl *H*-phosphonate **5**, followed by its conversion to ion pair **6**. The latter may gain further stabilization by acquiring a pyridine molecule to form triphenylmethylpyridinium cation **7** [19] and phenyl *H*-phosphonate **3**. Because the positive charge in **7** is delocalized in the pyridine ring, it is this moiety that should be attacked by the diphenyl phosphonate anion. Because of steric factors, the preferred position for such an attack should be carbon-4 of the pyridine ring to produce 1,4-dihydropyridine intermediate **8**, resonating in ^{31}P NMR at δ_P = 15.5 ppm. The conversion of **8** to the 4-pyridylphosphonate **4** occurred slowly upon stand-

ing (completion within 5 days) and was accompanied by the formation of triphenylmethane (TLC analysis).

For **3** and **4** to be formed in equimolar amounts, the rate determining step must be formation of phenyl trityl *H*-phosphonate **5**, which rapidly undergoes the subsequent reactions to dihydropyridine intermediate **8** with the intermediacy of triphenylmethylpyridinium cation **7.** The latter can either be formed directly from under the reaction conditions unstable trityl *H*-phosphonate **5** (via nucleophilic attack of pyridine on the carbinol carbon), or via ion pair **6**. The relative contribution of these two routes may probably vary with reaction conditions used and the stability of a trityl cation (see subsequent sections). One should note that the second part of this transformation is mechanistically related to the reaction reported by Redmore [20], who observed the formation of dialkyl 4-pyridylphosphonates upon heating at reflux for 2 hours of triphenylmethylpyridinium tetrafluoroborate with sodium salts of dialkyl phosphonates in the corresponding dialkyl *H*-phosphonates as solvents [21].

To substantiate the mechanism proposed in Scheme 1, we attempted to isolate the dihydropyridine intermediate **8**. Unfortunately, after work-up and by silica gel column chromatography, only 4-pyridylphosphonate **4** was obtained [22].

As to the importance of stability of the trityl cation in the above transformation, some further observations are pertinent. When we replaced carbinol **2** by 4,4′-dimethoxytritanol **9a** in the transesterification of **1** in pyridine, no pyridylphosphonate **4** was formed. Instead, the reaction furnished rapid formation of phenyl *H*-phosphonate **3** and dimethoxytritylphosphonate **10** (δ_P = 20.1 ppm) [23] in 1:1 ratio. These results were consistent with the mechanism proposed in Scheme 1 and can be explained in the following way. A less stable trityl cation apparently forms stronger complexes with pyridine (which provides an additional stabilization to the carbocation), and thus nucleophilic attack of the DPP anion occurs on carbon-4 of the pyridine ring. The dimethoxytrityl cation, generated from the initial product of the transesterification, is much more stable because of the presence of two electron-donating methoxy groups and thus probably forms rather weak complexes with pyridine [24]. In consequence, the DPP anion reacted in this instance with the dimethoxytrityl cation at its carbinol center [25].

Mild reaction conditions and the pivotal role played by trityl cations in the above transformations prompted us to investigate in more detail the reaction of *H*-phosphonate diesters with trityl halides with the aim of developing a general protocol for the synthesis of 4-pyridylphosphonates.

Reaction of Trityl Halides with Diphenyl H-Phosphonate in Pyridine

Assuming the mechanism in Scheme 1 and taking into account the observed kinetics of this transformation, it was expected that diphenyl *H*-phosphonate **1** would react with trityl halides in pyridine producing, with the intermediacy of dihydropyridine **8**, pyridylphosphonate **4**. To this end, **1** in pyridine was treated with trityl chloride (Tr-Cl, 2 equiv.) and the reaction was followed by ^{31}P NMR spectroscopy. The reaction was slow (completed overnight) but produced the anticipated dihydropyridine intermediate **8** (~60%) and the pyridylphosphonate **4** (~20%). Due to the extended reaction time, partial hydrolysis (due to adventitious water) and disproportionation of diphenyl *H*-phosphonate occurred; this was apparent from the presence of signals due to triphenyl phosphite (δ_P = 128.1 ppm, ~5%) and phenyl *H*-phosphonate **3** (~15%). After work-up, compound **4** was isolated from the reaction mixture and was found to be identical to that obtained during transesterification of **1** with tritanol.

The low rate of the reaction **1** + Tr-Cl in pyridine indicated that under these reaction conditions the concentration of pyridinium cation **7** (generated from Tr-Cl and pyridine) was lower than that during the transesterification (generated from tritylphosphonate **5** and pyridine). Attempts to speed up this reaction were only partially successful. Trityl bromide should provide a higher concentration of the trityl cation in pyridine, but it was sparingly soluble in pyridine and the reaction, probably due to heterogeneity of the system, was slow (overnight). The reaction of diphenyl *H*-phosphonate **1** and trityl chloride (1 equiv.) in pyridine in the presence of DBU (2 equiv.) was, as anticipated, fast (less than 5 minutes) but not very clean. Although the dihydropyridine derivative **8** was the major product of the reaction (ca. 40%), the concomitant formation of tritylphosphonate **12** (ca. 20%) and the disproportionation products of **1** (ca. 20%) were observed.

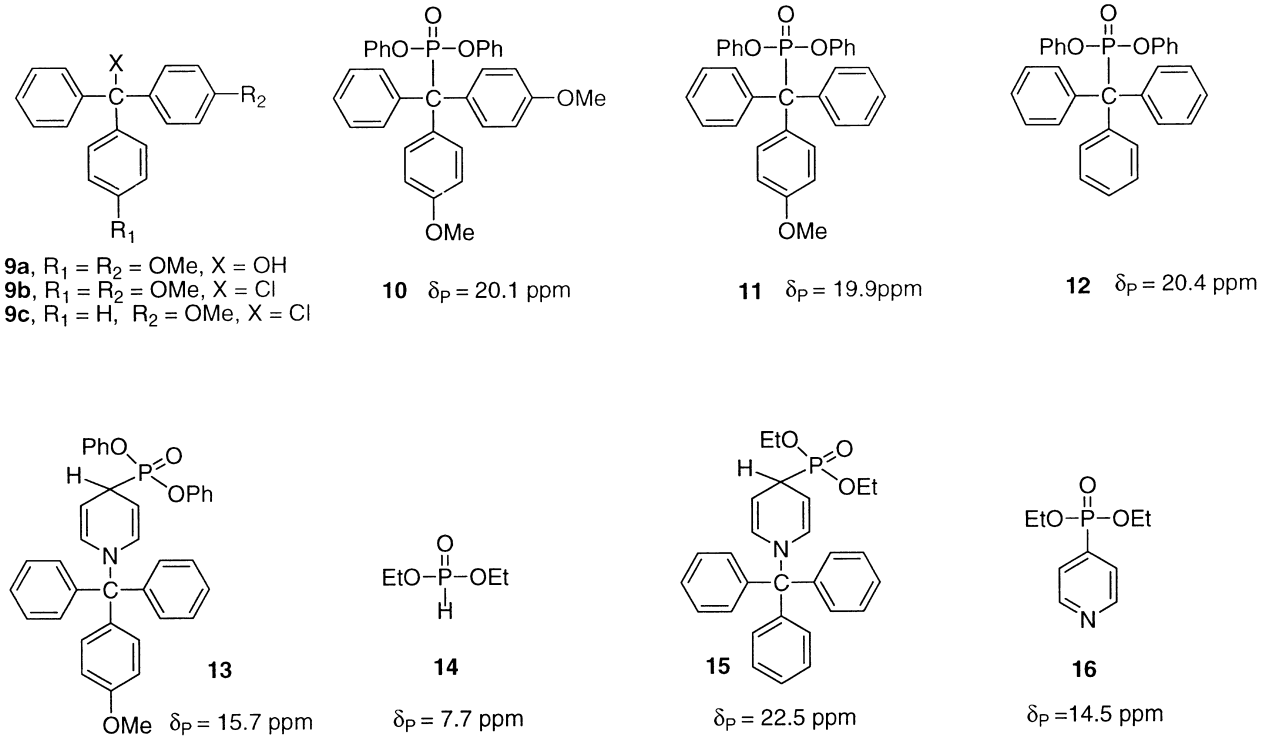
Dimethoxytrityl chloride **9b** (DMT-Cl, 1 equiv) reacted fast with **1** in neat pyridine (a few minutes) and, in agreement with the results from the transesterification of **1** with dimethoxytritanol **9a** (see previous section), it afforded almost exclusively dimethoxytritylphosphonate **10** (δ_P = 10.2 ppm; isolated from the reaction mixture in 83% yield). Monomethoxytrityl chloride **9c**, which in pyridine should

generate a trityl cation of an intermediate stability between that of unsubstituted trityl and the dimethoxytrityl cation, afforded in the reaction with **1** a mixture of 4-methoxytritylphosphonate **11** (δ_P = 19.6 ppm) and pyridylphosphonate **4** [26], in almost equal amounts. See Scheme 2 for structures of compounds **9–16**.

Reaction of Trityl Halides with Diethyl H-Phosphonate in Pyridine

To check the reactivity of dialkyl *H*-phosphonates toward tritylpyridinium cation **7**, we reacted diethyl *H*-phosphonate **14** with equimolar amounts of trityl chloride or trityl bromide. No reaction occurred within several hours, but the addition of DBU (2 equiv.) furnished fast and clean formation of two products, resonating at δ_P = 22.5 ppm (ca. 80%) and 24.0 ppm (ca. 20%). Spiking the reaction mixture with an authentic sample of diethyl tritylphosphonate (δ_P = 26.0 ppm) excluded this structure as a possible product and instead, indicated a dihydropyridine derivative of type **15**. When the reaction mixture was left standing overnight, the signal at 24.0 ppm disappeared and ^{31}P NMR spectroscopy revealed the presence of only two resonances at δ_P = 22.5 ppm (ca. 60%) and 14.5 ppm (ca. 40%). When the reaction mixture was concentrated and dissolved in pyridine, only the latter resonance was detected in the ^{31}P NMR spectrum. The product that resonated at δ_P = 14.5 ppm was isolated from the reaction mixture (75% yield), and its structure was determined as diethyl 4-pyridylphosphonate **16** (^{1}H, ^{13}C, ^{31}P NMR analysis and comparison with an authentic sample).

As to the identity of intermediates resonating at δ_P = 22.4 and 24.0 ppm, we assumed that these were, most likely, the expected 1,4-dihydropyridine **15** and its 1,2-isomer. Disappearance of the latter over time is explained by its isomerization under the reaction conditions to a more stable 4-substituted derivative **15**. This assignment was substantiated by detailed ^{31}P NMR analysis (iterative computer-assisted line fitting to extract J_{PH} coupling constants; see the Experimental section). In the resolution-enhanced proton-coupled ^{31}P NMR spectra, the signal at δ_P = 22.4 ppm appeared as a not completely resolved multiplet with a large coupling constant to one proton ($^2J_{PH}$ = 23.10 Hz), two smaller coupling constants to four protons ($^3J_{PH}$ = 7.44 Hz), and two protons ($^3J_{PH}$ = 3.54 Hz). This splitting was consistent with the spin system of the 1,4-dihydropyridine intermediate **15** that gave the multiplet an appearance of two partially overlapping pseudoquintets. A similar analysis



SCHEME 2

of the splitting pattern of the intermediate resonating at δ_P = 24.0 ppm showed that this signal could arise from the 1,2-dihydropyridine isomer of **15** [$^2J_{PH}$ = 21.02 Hz (1 H), $^3J_{PH}$ = 7.09 Hz (4 H), $^3J_{PH}$ = 2.00 Hz (1 H), and $^4J_{PH}$ = 1.00 Hz (1 H)].

During these studies, we also found that the transformation of 1,4-dihydropyridine intermediates **8** and **15** into the pyridylphosphonates **4** and **16**, respectively, which occurred cleanly upon concentration of the reaction mixtures, could also be effected by the addition of iodine. We used this data to corroborate our assignment of signals at δ_P = 22.4 and 24.0 ppm to different isomers of dihydropyridylphosphonates of type **15**. To accomplish this, we added iodine (2 equiv. dissolved in 2% aqueous pyridine) to the reaction mixture containing the intermediates resonating at δ_P = 22.4 and 24.0 ppm and found that besides the 4-pyridylphosphonate **16** (δ_P = 14.5 ppm), another compound was also formed (δ_P = 10.3 ppm, ca. 20%). Analysis of the resolution-enhanced ^{31}P NMR spectra showed that the splitting pattern of this signal [$^3J_{PH}$ = 8.0 Hz (4 H), $^3J_{PH}$ = 9.0 Hz (1 H), and $^4J_{PH}$ = 7.0 Hz (1 H)] was compatible with the structure of diethyl 2-pyridylphosphonate.

In conclusion, we found that the reactions of phosphite anions with trityl derivatives in pyridine may result in the formation of pyridylphosphonates or tritylphosphonates. The stability of the trityl cations formed seems to have a significant bearing for the course of these reactions. Since the formation of 4-pyridylphosphonates from dialkyl *H*-phosphonates occurs almost quantitatively and under exceedingly mild conditions, the presented protocol can probably be applicable also to the synthesis of the natural product analog bearing the 4-pyridylphosphonate moiety.

EXPERIMENTAL

Reactions were carried out in 10 mm NMR tubes and spectra were recorded on a Jeol GSX-270 FT or Varian 300 MHz spectrometer. For ^{31}P NMR experiments, 2% H_3PO_4 in D_2O was used as an external standard (coaxial inner tube). The values of the chemical shifts for the intermediates produced in situ in some experiments varied (±1 ppm) depending on the reaction conditions. A systematic trend of shifting ^{31}P NMR resonances to the lower field (~1.5–2 ppm) was observed upon changing the solvent from pyridine to acetonitrile.

Acetonitrile (Merck) and pyridine (Merck, distilled from CaH_2) were stored over molecular sieves (4 Å). Diethyl *H*-phosphonate, diphenyl *H*-phosphonate, trityl chloride, and trityl bromide (all from Aldrich), were commercial grade. 1,8-Diazabicyclo[5.4.0]undec-7-ene (Aldrich) was distilled before use.

The J_{PH} coupling constants for **4, 15**, and **16** were obtained from the iterative spin-spin simulation using a commercial package, gNMR ver. 3.6, IvorySoft. Approximate values for the position of resonances in multiplets (acquired from the resolution enhanced proton-phosphorus-coupled ^{31}P NMR spectra) were used as input data and the parameters (chemical shifts and coupling constants) were adjusted to achieve the best agreement between the experimental and the simulated spectrum.

The reference compounds **3, 4, 10, 11, 12**, and **16**, which have been used for the identification of some of the reaction products, were produced as follows. Phenyl *H*-phosphonate monoester (ammonium salt) was obtained via hydrolysis of **1** according to a published procedure [27]. Diphenyl and diethyl 4-pyridylphosphonates (**4** and **16**) were obtained by reacting equimolar amounts of sodium salts of diphenyl phosphite and diethyl phosphites, which were prepared in tetrahydrofuran (THF) from the corresponding *H*-phosphonate diesters **1** and **14**, respectively, using sodium hydride [14] with trityl chloride (1.0 equiv.) in pyridine. Diphenyl dimethoxytritylphosphonate **10**, diphenyl monomethoxytritylphosphonate **11**, and diphenyl tritylphosphonate **12** were obtained in the reaction of equimolar amounts of the sodium salt of **1** in THF with dimethoxytrityl chloride **9b**, monomethoxytrityl chloride **9c**, and trityl chloride, respectively [14].

Transesterification of Diphenyl H-Phosphonate **1** *with Tritanols*

To a solution of tritanol **2** (0.142 g, 0.5 mmole) or dimethoxytritanol **9a** (0.160 g, 0.5 mmole) in pyridine (2 mL) diphenyl *H*-phosphonate **1** (0.096 mL, 1 equiv.) was added. Progress of the reaction was checked using ^{31}P NMR spectroscopy. To identify products of the reactions, the reaction mixture was concentrated, dissolved in chloroform (10 mL) and washed with 5% aq. $NaHCO_3$ (2 × 10 mL). The organic layer was evaporated and chromatography was performed on the residue on a silica gel column. The isolated compounds **4** (from the reaction with tritanol **2**) and compound **10** (from the reaction with dimethoxytritanol **9a**) were identical with those obtained as described later.

Reaction of Diphenyl H-Phosphonate **1** *with Trityl Chloride in Pyridine*

Trityl chloride (0.558 g, 2 equiv.) was added to a solution of diphenyl *H*-phosphonate **1** (0.065 mL, 0.5

mmole) in pyridine (5 mL) and the reaction was left standing overnight. The reaction mixture was concentrated to dryness, coevaporated with added toluene to remove pyridine, and after dissolving in chloroform (20 mL), extracted with 5% aqueous $NaHCO_3$ (2 × 20 mL). The organic layer was concentrated and chromatography was performed on the residue on a silica gel column using as eluent toluene-ethyl acetate (4:1, v/v). Diphenyl 4-pyridyl phosphonate **4** was obtained as a yellow oil in variable yields (30–40%), due to instability of the product during chromatography.

Compound **4**: ^{1}H NMR (in ppm, $CDCl_3$), purity > 98%, 7.14–7.32 (m, 10 H, $(PhO-)_2$), 7.79 [m, 2H, C3-H & C5-H (Py)], 8.81 [m, 2H, C2-H & C6-H (Py)]; ^{13}C NMR (in ppm, $CDCl_3$) 150.27 [d, J_{PC} = 12.8 Hz, C2 & C6 (Py)], 149.91 [d,J_{PC} = 7.3 Hz, C1 (PhO−)], 135.80 [d, J_{PC} = 190.6 Hz, C4 (Py)], 129.92 [s, C3 and C5 (PhO−)], 125.60 [overlapping signals, C3 and C5 (Py) and C4 (PhO−)], 120.47 (d, J_{CP} = 3.6 Hz, C2 and C6 (PhO−); ^{31}P NMR (in ppm, pyridine) 8.08 (tt, $^3J_{PH}$ = 13.80 Hz, $^4J_{PH}$ = 6.12 Hz). HRMS $[M+H]^+$, found 312.0797. $C_{17}H_{15}O_3NP$ requires 311. 0789.

Reaction of Diethyl H-Phosphonate **14** *with Trityl Bromide in Pyridine*

To a solution of diethyl *H*-phosphonate **14** (0.129 mL, 1 mmole) in pyridine (10 mL), trityl bromide [28] (0.279 g, 1.2 equiv.) and DBU (0.358 mL, 2.4 mmole) were added. After incubating overnight, the reaction mixture was worked-up and purified as previously described for compound **4**, with exception that toluene-ethyl acetate (4:1, v/v) containing 5% methanol was used as eluent for the column chromatography. Diethyl 4-pyridylphosphonate **16** was obtained as a foam (0.162 g, 75% yield).

Compound **16**: ^{1}H NMR (in ppm, $CDCl_3$), purity > 98%, 1.35 (t, ^3J = 7.1 Hz, 6H, 2 × CH_3), 4.06–4.25 (m, 4H, $-CH_2$-O), 7.66 [m, 2H, C3-H & C5-H (Py)], 8.76 [m, 2H, C2-H and C6-H (Py)]; ^{13}C NMR (in ppm, $CDCl_3$) 150.08 [d, J_{PC} = 12.9 Hz, C2 and C6 (Py)], 137.45 [d, J_{PC} = 185.5 Hz, C4 (Py)], 125.60 [d, J_{CP} = 9.1 Hz) C3 and C5 (Py)], 62.72 (d, J_{CP} = 5.5 Hz, $-CH_2$-O), 16.31 (d, J_{CP} = 5.5 Hz, CH_3-); ^{31}P NMR (in ppm, pyridine) 14.42 (ttq, $^3J_{PH}$ = 13.44 Hz, $^3J_{PH}$ = 8.53 Hz, $^4J_{PH}$ = 4.92 Hz). HRMS $[M + H]^+$, found 216.0788. $C_9H_{15}O_3NP$ requires 216.0790.

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