A novel and convenient method for synthesizing unsymmetrical *N*-benzyloxycarbonyl-protected 1-amino-1-arylalkylphosphonate mixed diesters

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Unsymmetrical *N*-benzyloxycarbonyl-protected 1-amino-1-arylalkylphosphonate mixed diesters were synthesized using a one-pot reaction involving benzyl carbamate, aromatic aldehydes and alkoxydichlorophosphine, followed by treatment with alcohols in the presence of triethylamine. The reactions were followed by ^{31}P NMR and a mechanism is proposed.

Introduction

Phosphonate esters are recognized as an important class of enzyme inhibitors either as transition-state analogues[1] or as nonhydrolyzable phosphate surrogates.[2] They are also widely used in the design of transition-state analogues as haptens for the production of catalytic antibodies with esterase or amidase activity.[3] Thus, it is very important to develop a general and convenient synthetic method that allows the synthesis of phosphonates, especially unsymmetric phosphonate mixed diesters.

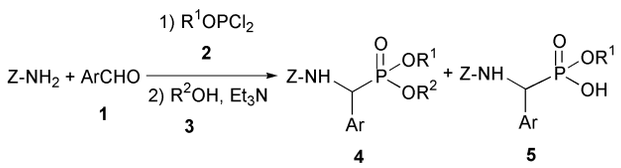
Symmetric 1-aminoalkylphosphonates have been synthesized using Mannich-type reactions of aldehydes, amines and dialkyl or trialkyl phosphites,[4,5] phosphite addition to imines,[6] Arbuzov–Michaelis reactions followed by reductive amination,[7] conversion of the hydroxy group in 1-hydroxyalkylphosphonates to an amino group to synthesize 1-aminoalkylphosphonates,[8] and our recent method through reaction of carbamate, aldehydes and dialkoxychlorophosphines.[9] Unsymmetrical phosphonate mixed diesters have been prepared from the reactions of alcohols with phosphonochloridates.[10,11] These phosphonochloridates can be prepared by treating phosphonate diesters with $POCl_3$,[12] PCl_5[11] or by chlorinating phosphonate monoacids with thionyl chloride[10] or oxalyl chloride.[13] Phosphonic acid monoesters are readily synthesized by saponification of dialkyl alkylphosphonates[10] or by direct synthesis *via* Mannich-type reactions of carbamates, aldehydes and alkoxydichlorophosphine, followed by hydrolysis.[14] An interesting modification of these procedures involves the *in situ* formation of phosphonochloridates from the corresponding phosphonates in an oxidative Atherton–Todd process.[15] An alternative synthesis of unsymmetrical 1-aminoalkylphosphonate mixed diesters involves the condensation of phosphonate monoacids with alcohols as in Karenewsky's coupling method.[16] The condensation has been improved by the use of coupling reagents such as DCC,[17] trichloroacetonitrile,[18] BOP [(benzotriazol-1-yloxy)-tris(dimethylamino)phosphonium hexafluorophosphate] or PyBOP,[19] or Campbell's extended and modified Mitsunobu condensation method.[20] The third method involves phosphonic dichlorides, which are prepared from phosphonic acids and PCl_5[21] followed by successive treatment with different alcohols.[22] In all of the above methods, it is necessary to first synthesize phosphonic acid, phosphonate monoacid, or symmetric phosphonate diester.[23] A shorter synthesis of this important class of molecules would be beneficial.

Table 1 Synthesis of unsymmetrical N-protected 1-aminoalkylphosphonate mixed diesters **4** and monoacids **5**

Entry	Ar	R^1	R^2	Yield of **4** (%)	Yield of **5** (%)
a	Ph	Me	Et	47	39
b	*o*-MeOPh	Me	Et	31	32
c	*p*-ClPh	Me	Et	35	45
d	*p*-NO_2Ph	Me	Et	45	29
e	*p*-NO_2Ph	Me	Pr^i	41	27
f	*p*-NO_2Ph	Me	Bu	24	31
g	*p*-NO_2Ph	Me	Ph	11	37
h	*p*-NO_2Ph	Ph	Et	38	24

Results and discussion

We report a novel, facile method to synthesize unsymmetrical N-protected 1-aminoalkylphosphonate diesters using a four component one-pot reaction. Benzyl carbamate and an aldehyde are first treated with an alkoxydichlorophosphine, followed by the addition of an alcohol and triethylamine in anhydrous benzene. It is not necessary to synthesize phosphonic acids, their monoacids or their symmetric diesters. This reaction yielded unsymmetrical phosphonate mixed diesters **4** in satisfactory yields under simple and mild conditions and gave the corresponding monoacids **5** simultaneously as the main byproducts (Scheme 1, Table 1).



Scheme 1

Attempts to improve the yields of the desired products **4** by avoiding the formation of **5** were unsuccessful. Varying the reaction solvents (*e.g.* ether, THF, CH_2Cl_2, alcohol-free $CHCl_3$, DMSO, toluene), extending the reaction time, or raising the reaction temperature only succeeded in reducing the formation of **5**, not eliminating it.

From the reaction, we know that the two alkyl groups of the unsymmetrical phosphonate mixed diesters may be introduced from different starting materials, either the alkoxydichlorophosphine or alcohols in the alcoholysis step. Phenol was intro-

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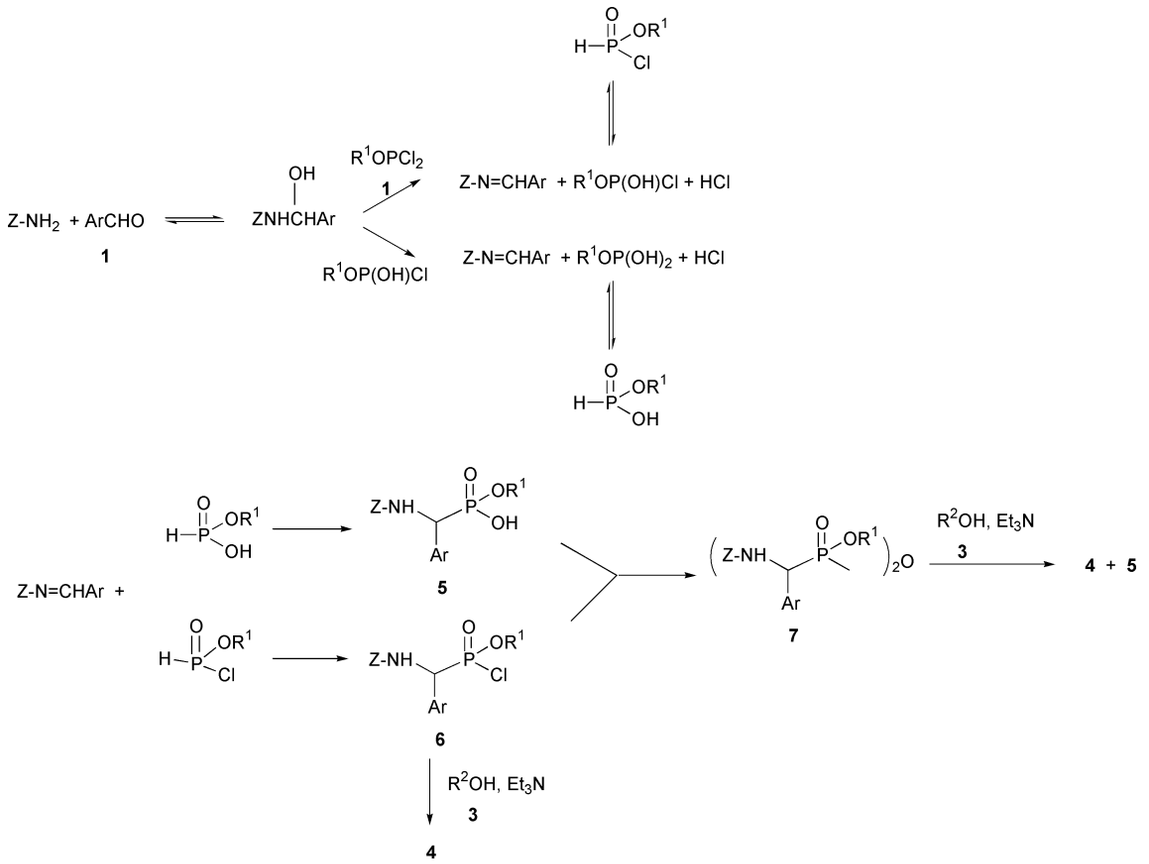


Scheme 2

duced more easily from phenoxydichlorophosphine than it was in the phenolysis step due to its weak nucleophilicity (entries **g** and **h**). Alcoholysis with *tert*-butyl alcohol was unsuccessful due to steric encumbrance.

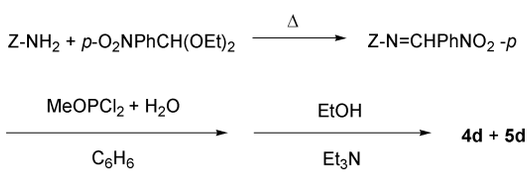
In order to expand this reaction, amides ($MeCONH_2$ and $PhCONH_2$) were also used instead benzyl carbamate, but this was unsuccessful. Aliphatic aldehydes (BuCHO and $PhCH_2$-CHO) were also unsuccessful.

In order to gain a better understanding of this reaction, ^{31}P NMR was used to follow the reaction. In entry **a**, both phosphonochloridate **6a** (38 ppm in ^{31}P NMR) and phosphonic anhydride **7a** (6 ppm in ^{31}P NMR) were observed as reaction intermediates by ^{31}P NMR. The signals were confirmed by comparison with the corresponding authentic samples, phosphonochloridate **6a** and phosphonic anhydride **7a**, which were synthesized from the corresponding monoacid **5a** using the standard thionyl chloride method.[10]

A possible mechanism is shown in Scheme 2, based on the identification by ^{31}P NMR of compounds **6a** and **7a**.

Although the yields of phosphonates **4** are modest, the method is quick and convenient for synthesizing unsymmetrical 1-aminoalkylphosphonate mixed diesters while at the same time synthesis of 1-aminoalkylphosphonate monoacids occurs in the second phase of the reaction. Furthermore, the byproducts, 1-aminoalkylphosphonate monoacids are also very useful as precursors for other phosphonic derivatives.

Further evidence for the proposed mechanism has been acquired from the reaction of methyl phosphonochloridate (MeO)HP(O)Cl, which was prepared by adding an equivalent amount of water to a solution of methoxydichlorophosphine $MeOPCl_2$ in anhydrous benzene prior to use, with the imine Z–N=CHPh–NO_2-*p*, which was prepared from benzyl carbamate and *p*-nitrobenzaldehyde diethyl acetal,[24] followed by ethanolysis in the presence of triethylamine. In the reaction an unsymmetrical diester **4d** was obtained in satisfactory yield and monoacid **5d** was also obtained simultaneously (Scheme 3).



Scheme 3

According to ^{31}P NMR tracing analysis, after an equivalent amount or less of water was added to a solution of methoxydichlorophosphine in anhydrous benzene, methyl phosphonochloridate (MeO)HP(O)Cl (−4.0 ppm in ^{31}P NMR) and also monomethyl phosphonate (MeO)HP(O)(OH) (8.7 ppm in ^{31}P NMR) were observed.[25] Only monomethyl phosphonate (MeO)HP(O)(OH) was observed after more than two equivalents of water were added to the solution.

All products were characterized by ^1H NMR, ^{31}P NMR and MS spectrometries and elemental analyses. The data of compounds **5** are in good agreement with the data in the literature.[14,26] In most cases the ^1H NMR spectra showed the CH_3 and CH_3CH_2 of the methoxy or ethoxy groups of compounds **4** are magnetically nonequivalent due to chiral carbon and/or phosphorus atoms in the molecules. The signals were split into doublets but with different chemical shifts.

In conclusion, a novel and facile method for the synthesis of unsymmetrical N-protected 1-aminoalkylphosphonate diesters has been developed using *in situ* one-pot reactions of commercially available benzyl carbamate, aldehydes and alkoxydichlorophosphine, followed by alcoholysis in the presence of triethylamine. The reaction procedure was traced by ^{31}P NMR analysis and a mechanism has been proposed.

Experimental

Melting points were obtained on a Yanaco melting point apparatus and are uncorrected. ^1H NMR spectra were recorded

on a Varian Mercury 200 spectrometer in $CDCl_3$ with TMS as an internal standard. ^{31}P NMR spectra were recorded on the same spectrometer at 81 MHz, and the chemical shifts were referenced to 85% H_3PO_4 with negative shifts upfield. Mass spectra were obtained on a VG-ZAB-HS mass spectrometer. CHN analyses were recorded on a Vario EL analyzer. Methoxydichlorophosphine,[27] and phenoxydichlorophosphine[28] were synthesized following literature procedures. All remaining chemicals were purchased from Beijing Chemical Co. Benzene was refluxed over sodium and distilled prior to use. Triethylamine was also refluxed over sodium hydroxide and distilled prior to use.

General procedure

Alkoxydichlorophosphine **2** (3 mmol) was slowly added dropwise to a stirred mixture of benzyl carbamate (0.45 g, 3 mmol) and aldehyde **1** (3 mmol) in anhydrous benzene (15 mL) at room temperature. After stirring the reaction mixture for 6 h at RT, it was then refluxed for 1 h. After cooling, alcohol **3** (6 mmol) was added dropwise (ice–water bath). After about 10 min, triethylamine (0.67 g, 6.6 mmol) was added dropwise, and then the reaction mixture was allowed to stir overnight. After adding ethyl acetate and water to make the reaction solution clear, the organic phase was separated and washed with saturated aqueous NaCl solution 3 to 5 times, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was separated on a silica gel column with petroleum ether and ethyl acetate (1 : 1) as eluent to yield phosphonate mixed diester **4**. The aqueous phase was acidified with 10% HCl to precipitate the byproduct monoacid **5**.

Ethyl methyl (*N*-benzyloxycarbonylamino)(phenyl)methylphosphonate (4a). White solid; mp 95–97 °C (lit.,[29] 103–105 °C, no spectral data reported). ^{31}P NMR (81 MHz, $CDCl_3$) δ: 23.39; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.09 and 1.26 (t, J = 7 Hz, 3 H, CH_3), 3.48 and 3.72 (d, J_{PH} = 10.6 Hz, 3 H, POMe), 3.88–4.14 (m, 2 H, OCH_2), 5.02–5.25 (m, 3 H, Ph**C**$\mathbf{H_2}$O and CHP), 5.90 (br s, 1 H, CONH), 7.33–7.40 (m, 10 H, ArH); EI-MS *m*/*z*: 363 (M^+, 28%). Anal. calcd. for $C_{18}H_{22}NO_5P$: C, 59.50; H, 6.10; N, 3.85. Found: C, 59.89; H, 6.32; N, 3.64%.

Ethyl methyl (*N*-benzyloxycarbonylamino)(2-methoxyphenyl)methylphosphonate (4b). White solid; mp 109–111 °C. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 22.93; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.11 and 1.26 (t, J = 6.8 Hz, 3 H, CH_3), 3.49 and 3.72 (d, J_{PH} = 10.6 Hz, 3 H, POMe), 3.80 (s, 3 H, *o*-**Me**OPh), 3.92 and 4.08 (q, J = 6.8 Hz, 2 H, OCH_2), 5.00–5.18 (m, 3 H, Ph**C**$\mathbf{H_2}$O and CHP), 5.83 (br s, 1 H, CONH), 6.86–7.35 (m, 9 H, ArH); FAB-MS *m*/*z*: 394 (MH^+, 19%). Anal. calcd. for $C_{19}H_{24}NO_6P$: C, 58.01; H, 6.15; N, 3.56. Found: C, 58.29; H, 6.19; N, 3.20%.

Ethyl methyl (*N*-benzyloxycarbonylamino)(4-chlorophenyl)methylphosphonate (4c). White solid; mp 84-86 °C. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 22.03; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.13 and 1.26 (t, J = 7 Hz, 3 H, CH_3), 3.52 and 3.72 (d, J_{PH} = 11 Hz, 3 H, POMe), 3.91–4.16 (m, 2 H, OCH_2), 5.02–5.17 (m, 3 H, $PhCH_2O$, CHP), 5.97 (br s, 1 H, CONH), 7.17–7.44 (m, 9 H, ArH); EI-MS *m*/*z*: 397 (M^+, 31%). Anal. calcd. for $C_{18}H_{21}ClNO_5P$: C, 54.35; H, 5.32; N, 3.52. Found: C, 54.61; H, 5.43; N, 3.57%.

Ethyl methyl (*N*-benzyloxycarbonylamino)(4-nitrophenyl)methylphosphonate (4d). White solid; mp 143–146 °C. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 21.08; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.16 and 1.27 (t, J = 7.2 Hz, 3 H, CH_3), 3.58 and 3.77 (d, J_{PH} = 10.8 Hz, 3 H, POMe), 3.84–4.18 (m, 2 H, OCH_2), 5.03–5.11 (s, 2 H, Ph**C**$\mathbf{H_2}$O), 5.17–5.35 (m, 1 H, CHP), 6.14 (br s, 1 H, CONH), 7.33 (s, 5 H, Ph), 7.61 and 8.21 (d, J = 7.9 Hz, 4 H, $PhNO_2$); FAB-MS *m*/*z*: 409 (MH^+, 22%). Anal. calcd. for $C_{18}H_{21}N_2O_7P$: C, 52.94; H, 5.18; N, 6.86. Found: C, 52.93; H, 5.29; N, 6.45%.

Isopropyl methyl (*N*-benzyloxycarbonylamino)(4-nitrophenyl)methylphosphonate (4e). White solid; mp 141–143 °C. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 20.16; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.02–1.33 (m, 6 H, 2 CH_3), 3.55 and 3.78 (d, J_{PH} = 11 Hz, 3 H, POMe), 4.64–4.74 (m, 1 H, OCH), 5.03–5.31 (m, 3 H, Ph**C**$\mathbf{H_2}$O and CHP), 6.03 (br s, 1 H, CONH), 7.29–7.34 (m, 5 H, ArH), 7.60 and 8.21 (d, J = 8.0 Hz, 4 H, $PhNO_2$); FAB-MS *m*/*z*: 423 (MH^+, 17%). Anal. calcd. for $C_{19}H_{23}N_2O_7P$: C, 54.03; H, 5.49; N, 6.63. Found: C, 53.82; H, 5.50; N, 6.49%.

Butyl methyl (*N*-benzyloxycarbonylamino)(4-nitrophenyl)methylphosphonate (4f). White solid; mp 88–91 °C. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 21.34; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.81–0.99 (m, 3 H, CH_3), 1.16–1.76 (m, 4 H, CH_2CH_2), 3.57 and 3.74 (d, J_{PH} = 10.6 Hz, 3 H, POMe), 4.06 (dt, J_{PH} = 10.7, J = 6.9 Hz, 2 H, OCH_2), 5.03–5.38 (m, 3 H, Ph**C**$\mathbf{H_2}$O and CHP), 6.39 (br s, 1 H, CONH), 7.33 (s, 5 H, Ph), 7.62 and 8.20 (d, J = 7.7 Hz, 4 H, $PhNO_2$); FAB-MS *m*/*z*: 437 (MH^+, 42%). Anal. calcd. for $C_{20}H_{25}N_2O_7P$: C, 55.05; H, 5.77; N, 6.42. Found: C, 55.41; H, 5.59; N, 6.10%.

Methyl phenyl (*N*-benzyloxycarbonylamino)(4-nitrophenyl)methylphosphonate (4g). White solid; mp 138–143 °C. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 17.59; ^1H NMR (200 MHz, $CDCl_3$) δ: 3.63 and 3.80 (d, J_{PH} = 11 Hz, 3 H, POMe), 5.07–5.11 (m, 2 H, Ph**C**$\mathbf{H_2}$O), 5.38–5.58 (m, 1 H, CHP), 6.16 (br s, 1 H, CONH), 6.78–7.34 (m, 10 H, ArH), 7.62 and 8.19 (d, J = 7.5 Hz, 4 H, $PhNO_2$); FAB-MS *m*/*z*: 457 (MH^+, 27%). Anal. calcd. for $C_{22}H_{21}N_2O_7P$: C, 57.90; H, 4.64; N, 6.14. Found: C, 58.23; H, 4.63; N, 5.77%.

Ethyl phenyl (*N*-benzyloxycarbonylamino)(4-nitrophenyl)methylphosphonate (4h). White solid; mp 114–117 °C. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 16.52; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.11 and 1.23 (t, J = 7.2 Hz, 3 H, CH_3), 3.84–4.20 (m, 2 H, OCH_2), 5.01–5.15 (m, 2 H, Ph**C**$\mathbf{H_2}$O), 5.35–5.51 (m, 1 H, CHP), 6.07 (br s, 1 H, CONH), 6.91–7.33 (m, 10 H, ArH), 7.63 and 8.21 (d, J = 7.8 Hz, 4 H, $PhNO_2$); FAB-MS *m*/*z*: 471 (MH^+, 20%). Anal. calcd. for $C_{23}H_{23}N_2O_7P$: C, 58.72; H, 4.93; N, 5.95. Found: C, 59.04; H, 5.00; N, 5.61%.

Identification of phosphonochloridate 6a and phosphonic anhydride 7a by ^{31}P NMR data[10]

To a stirred solution of 335 mg (1 mmol) of the phosphonate monoacid **5a** (21 ppm in ^{31}P NMR) in 2 mL of dry and ethanol-free chloroform was added 0.15 mL (2 mmol) of $SOCl_2$. After 4 h, the solvent and volatile materials were removed by a stream of dry nitrogen and then by drying under vacuum. The residue, phosphonochloridate **6a**, was identified by ^{31}P NMR (38 ppm in ^{31}P NMR).

The above residue was dissolved in 2 mL of dry and ethanol-free chloroform. The phosphonate monoacid **5a** (168 mg, 0.5 mmol) was added under stirring. After 1 h, the solvent was removed under vacuum. The residue was determined by ^{31}P NMR. Two peaks at 38 and 6 ppm were observed for phosphonochloridate **6a** and phosphonic anhydride **7a**, respectively. The residue was dissolved in dry and ethanol-free chloroform again. The monoacid **5a** (335 mg, 1 mmol) was then added under stirring. After 1 h, the solvent was removed again under vacuum. The residue was identified by ^{31}P NMR. Two peaks at 6 and 21 ppm were observed for anhydride **7a** and monoacid **5**, respectively.

Evidence for the proposed mechanism

In a 25 mL flask equipped with magnetic stirring bar and short-path distilling head were placed equivalent amounts of benzyl

carbamate (0.9 g, 6 mmol) and *p*-nitrobenzaldehyde diethyl acetal (1.35 g, 6 mmol), which was prepared from *p*-nitrobenzaldehyde and triethyl orthoformate in the presence of toluene-*p*-sulfonic acid.[30] The reaction mixture was heated at 150–180 °C in an oil bath until all the ethanol had ceased distilling over (about 0.5 h), at which time the solution was placed under high vacuum (about 0.1 mmHg) and allowed to cool to room temperature to give a solid residue, which showed an IR absorption at 1620 cm^{-1} (C=N). The residue was dissolved in 15 mL of anhydrous benzene. A mixture of methoxydichlorophosphine (0.80 g, 6 mmol) and water (0.10 g, 6 mmol) in anhydrous benzene (5 mL) was added dropwise to the resulting solution under stirring at room temperature. After stirring for 6 h at room temperature, it was refluxed for 1 h. After cooling to room temperature, anhydrous ethanol (0.55 g, 12 mmol) was added dropwise to the mixture in an ice–water bath. After about 10 min, triethylamine (1.34 g, 13.2 mmol) was added dropwise, and then the reaction mixture was allowed to stir overnight. After adding ethyl acetate and water to make the reaction solution clear, the organic phase was separated and washed with saturated aqueous NaCl solution 4 times, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified on a silica gel column with petroleum ether and ethyl acetate (1 : 1) as eluent to yield the unsymmetrical diester **4d** in 67% yield. The aqueous phase was acidified with 10% HCl to precipitate the monoacid **5d** in 24% yield.

Identification of methyl phosphonochloridate (MeO)HP(O)Cl by ^{31}P NMR

To a solution of methoxydichlorophosphine (133 mg, 1 mmol) in 0.5 mL of $CDCl_3$ was added 0.005 mL of water. After shaking for 5 min, ^{31}P NMR showed three peaks at 180.5, 8.7 and −4.0 ppm for $MeOPCl_2$, (MeO)HP(O)(OH) and (MeO)HP(O)Cl, respectively. Another 0.010 mL of water was added and the solution was shaken for 5 min. ^{31}P NMR showed the same peaks, but the intensity of the peak at 180.5 ppm was reduced. After adding another 0.022 mL of water and shaking for 5 min, the peaks at 180.5 and − 4.0 ppm disappeared. ^{31}P NMR showed no change after another 0.03 mL of water was added.

Acknowledgements

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