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Convenient Method for the Preparation of Heterodialkyl-*H*-phosphonates from Diphenyl-*H*-phosphonate

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Abstract: A procedure for the introduction of two different alkyl chains (myristyl, oleyl and phytanyl) leading to heterodialkyl-*H*-phosphonates is reported, based on two successive transesterification reactions of commercially available diphenyl-*H*-phosphonate with the corresponding alcohols.

Keywords: Alkyl chain, H-phosphonate, phosphite, phosphono lipids

INTRODUCTION

As *H*-phosphonate derivatives exist in solution as an equilibrium mixture of two tautomeric forms (i.e., a tetracoordinate phosphonate form and a tricoordinated phosphite form), these compounds behave similarly to phosphates and at the same time preserve characteristic features and reactivity of phosphites.[1] Consequently, *H*-phosphonate chemistry constitute an alternative to well-established methods based on phosphate [P(V)] and phosphite [P(III)] derivatives for the preparation of phosphorus-containing compounds, such as nucleotides or carbohydrates. Although several synthetic methods for the preparation of *H*-phosphonate derivatives bearing two identical alkyl chains ("homodialkyl-*H*-phosphonates") have been developed, such as direct

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esterification of phosphorus trichloride by the corresponding alcohol in the absence of solvent,[2] or by transesterification of commercial diphenyl-*H*-phosphonate (often miscalled diphenyl-phosphite) with an excess of the corresponding alcohol[3] (Scheme 1), there remains a need for a straightforward and general methodology toward the unsymmetrical introduction of two different alkyl chains under mild conditions, leading to "heterodialkyl-*H*-phosphonates."

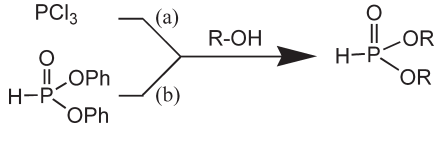
Indeed, in the past decade, a number of phosphonate-derived amphiphiles resembling the natural phosphonolipids of cell membranes that displayed some interesting features as nonviral vectors for gene delivery[4] were described. However, although phosphonolipids bearing two identical alkyl chains of various natures have been investigated as gene delivery vectors,[3,5–7] no attention has been paid to phosphonolipids possessing two different alkyl chains. In this work, we report a convenient procedure for the preparation of heterodialkyl-*H*-phosphonates that could serve as precursors for the preparation of such heterophosphonolipids. The method is based on two successive transesterification reactions of commercially available diphenyl-*H*-phosphonate (Scheme 2). As lipid chains, C_{14}-saturated (myristyl), C_{18}-unsaturated (oleyl), and phytanyl moities were chosen.

RESULTS AND DISCUSSION

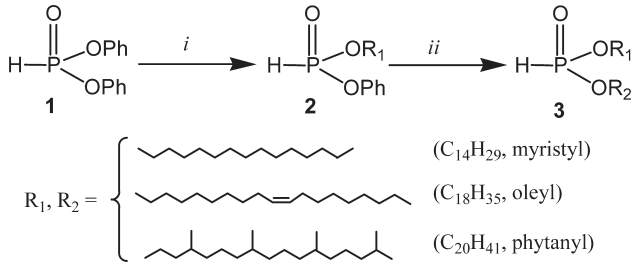
As expected, simultaneous or successive addition of the two alcohol chains to a solution of diphenyl-*H*-phosphonate in the presence of pyridine resulted in a mixture of both homodimeric and heterodimeric *H*-phosphonates, as revealed by ^{31}P NMR, which were not separable by distillation or common chromatographic methods. Therefore, we developed a simple procedure for the unsymmetrical introduction of two different alkyl chains leading to heterodialkylphosphites, based on two successive transesterification reactions of commercially available diphenylphosphite.

Synthesis of Phenylalkyl-*H*-phosphonates (2) from Diphenyl-*H*-phosphonate (Scheme 2, Table 1)

By examining a variety of reaction conditions, we found that the process was most efficient at room temperature in the absence of solvent, with 1 equivalent



Scheme 1. Preparation of homodialkyl-*H*-phosphonates from (a) phosphorus trichloride[2] and (b) diphenylphosphite[3] in the presence of the corresponding alcohol (R-OH).



Scheme 2. Synthesis of heterodialkyl-*H*-phosphonates. Reagents and conditions: *i*, pyridine (0.8 eq.), R_1OH (0.8 eq.), 2 h; *ii*, pyridine (0.8 eq.), R_2OH (0.8 eq.), 3 h.

of diphenylphosphite, 0.8 equivalent of pyridine, and 0.8 equivalent of the corresponding alcohol (tetradecanol and phytanol, R_1OH, 0.8 equivalent). The reactions could be followed by ^{31}P NMR spectroscopy, observing the conversion of diphenylphosphite to the mono-alkylated *H*-phosphonate compound. The reactions were completed in 2 h, and no further significant changes in the NMR spectra could be observed. In these experimental conditions, the expected monoalkylated-*H*-phosphonates **2a** and **2b** were obtained with good yields (90 and 82%, respectively) and could be easily isolated by simple removal of the formed phenol and the excess of diphenyl-*H*-phosphonate by distillation.

Synthesis of Dialkyl-*H*-phosphonates (3) from Phenylalkyl-*H*-phosphonate (Scheme 2, Table 1)

The introduction of the second alkyl chain was achieved by mixing the phenylalkyl-*H*-phosphonate intermediate (**2**) to 0.8 equivalent of the corresponding alcohol (R_2OH) and pyridine (0.8 equiv.) at room temperature. The reactions were followed by changes in the ^{31}P NMR spectra, which showed a shift toward to more positive values of the phosphonate peak, indicating the introduction of the second alkyl chain. After distillation under reduced pressure to remove phenol and pyridine, *H*-phosphonate

Table 1. Mono- (**2**) and di- (**3**) alkyl-*H*-phosphonates produced via Scheme 2

Compound	R_1	R_2	Yield (%)	^{31}P NMR δ (ppm)
2a	$C_{14}H_{29}$	—	90	4.8
2b	$C_{20}H_{41}$	—	82	4.7
3a	$C_{14}H_{29}$	$C_{18}H_{35}$	80	8
3b	$C_{20}H_{41}$	$C_{14}H_{29}$	72	7.9
3c	$C_{20}H_{41}$	$C_{18}H_{35}$	75	7.9

compounds **3** were obtained with yields in the 70–80% range. All compounds were then characterized by mass spectrometry and in solution by multinuclear NMR data.

In conclusion, a convenient and high-yielding route to heterodialkyl-*H*-phosphonates bearing two different alkyl chains has been developed using diphenyl-*H*-phosphonate as starting material. Compounds **3** were then successfully used as precursors for the synthesis of a series of pyridinium-based phosphonolipids that were evaluated as transfection agents.[8]

EXPERIMENTAL

All chemicals were obtained from Aldrich or Acros Organics and used without further purification. Nuclear magnetic resonance spectra were recorded on a Bruker AC 300 spectrometer (^{1}H and ^{13}C NMR) or on a Bruker AC 200 spectrometer (^{31}P NMR), and mass spectra were measured on a Nermag R10-10C mass spectrometer.

Phenyltetradecyl-*H*-phosphonate (2a)

Tetradecanol (0.9 g, 4.7 mmol) and anhydrous pyridine (0.37 g, 4.7 mmol) were added dropwise under argon to diphenylphosphite (1 mL, 5.3 mmol). After 2 h at room temperature under magnetic stirring, the excess of diphenylphosphite and phenol were removed by distillation (60 °C, 1 mm Hg) to obtain 1.3 g of **2a** as a white solid (yield: 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.87 (t, 3H, $^3J_{H\text{-}H} = 6.6$ Hz, *H*-14), 1.20–1.45 (m, 22H, *H*-3–*H*-13), 1.60–1.70 (m, 2H, *H*-2), 4.01 (q, 2H, $^3J_{H\text{-}H} = {}^3J_{H\text{-}P} = 6.8$ Hz, CH_2-O), 7.08 (d, 1H, $^1J_{H\text{-}P} = 716.4$ Hz, P-*H*), 7.10–7.20 (m, 3H, H_{arom}), 7.28–7.36 (m, 2H, H_{arom}). ^{31}P NMR (81 MHz, $CDCl_3$) δ (ppm): 4.8. MS (DCI/NH_3), m/z: 355 (MH^+).

Phenylphytanyl-*H*-phosphonate (2b)

This compound was obtained as a colorless oil from diphenylphosphite (5.3 mmol) and phytanol (4.2 mmol) by the same procedure used for the preparation of compound **2a**. Yield: 82% (1.5 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.81–0.89 (m, 12H, CH_3), 0.90 (d, 3H, $^3J_{H\text{-}H} = 6.1$ Hz, CH_3), 0.98–1.78 (m, 24H, *H*-2–*H*-15), 4.11 (q, 2H, $^3J_{H\text{-}H} = {}^3J_{H\text{-}P} = 6.8$ Hz, CH_2-O), 7.07 (d, 1H, $^1J_{H\text{-}P} = 716.5$ Hz, P-*H*), 7.10–7.20 (m, 3H, H_{arom}), 7.28–7.36 (m, 2H, H_{arom}). ^{31}P NMR (81 MHz, $CDCl_3$) δ (ppm): 4.7. MS (ES) m/z: 439 (MH^+).

Oleyltetradecyl-*H*-phosphonate (3a)

Pyridine (0.09 g, 1.12 mmol) and oleyl alcohol (*cis*-9-octadecen-1-ol, 0.30 g, 1.12 mmol) were added to **2a** (0.50 g, 1.41 mmol), and the solution was stirred for 3 h at room temperature. Pyridine (under reduced pressure) and phenol (distillated at 60 °C, 1 mm Hg) were then removed to afford 0.47 g (yield: 80%) of **3a** (white solid). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.87 (t, 6H, $^{3}J_{H\text{-}H} = 6.6$ Hz), 1.13–1.45 (m, 44H), 1.52–1.74 (m, 4H), 1.89–2.08 (m, 8H), 5.29–5.43 (m, 4H), 3.99–4.26 (m, 2H, CH_2-O), 6.81 (d, 1H, $^{1}J_{H\text{-}P} = 696.1$ Hz, P-*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm; oleyl chain, C-n; myristyl chain, C-n′): 14.1 (*C*-18, *C*-14′), 22.6 (*C*-17, *C*-13′), 25.5 (*C*-3, *C*-3′), 27.2 (*C*-8, *C*11), 29.1–29.6 (*C*-4–*C*-7, *C*-12–*C*-15, *C*-4′–*C*-11′), 30.6 (d, $^{3}J_{C\text{-}P} = 6.4$ Hz, *C*-2, *C*-2′), 31.8 (*C*-16, *C*-12′), 66.2 (d, $^{2}J_{C\text{-}P} = 6.8$ Hz, *C*-1, *C*-1′), 129.8 and 129.9 (*C*-9, *C*-10). ^{31}P NMR (81 MHz, $CDCl_3$) δ (ppm): 8.0. MS (ES) m/z: 529 (MH^+), 551 (MNa^+).

Phytanyltetradecyl-*H*-phosphonate (3b)

This compound was obtained as a colorless oil from **2b** (0.50 g) and 1-tetradecanol (0.19 g) by the same procedure used for the preparation of compound **3a**. Yield: 72% (0.36 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.80–0.87 (m, 24H), 0.90 (d, 3H, $^{3}J_{H\text{-}H} = 6.1$ Hz, CH_3), 0.98–1.78 (m, 48H), 4.11–4.32 (m, 4H, CH_2-O), 6.82 (d, $^{1}J_{H\text{-}P} = 695.2$ Hz, P-*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm; phytanyl chain, C-n; myristyl chain, C-n′): 14.0 (*C*-14′), 19.5 and 19.7 (3 × *C*H_3), 22.6 and 22.7 (2 × *C*H_3), 22.8 (*C*-13′), 24.4, 24.5, and 24.8 (*C*-5, *C*-9, *C*-13), 26.1 (*C*-3′), 28.0 (*C*-15), 29.1–29.6 (*C*-4′–*C*-11′, *C*-3), 30.6 (d, $^{3}J_{C\text{-}P} = 6.4$ Hz, *C*-2′), 31.8 (*C*-12′), 31.9 (*C*-16′), 32.8 (*C*-7, *C*-11), 37.0–37.8 (*C*-2, *C*-4, *C*-6, *C*-8, *C*-10, *C*-12), 39.4 (*C*-14), 65.4 (d, $^{2}J_{C\text{-}P} = 6.7$ Hz, *C*-1), 66.0 (d, $^{2}J_{C\text{-}P} = 6.0$ Hz, *C*-1′). ^{31}P NMR (81 MHz, $CDCl_3$ δ (ppm): 7.9. MS (ES) m/z: 559 (MH^+).

Oleylphytanyl-*H*-phosphonate (3c)

This compound was obtained as a colorless oil from **2b** (0.50 g) and oleyl alcohol (0.25 mL) by the same procedure used for the preparation of compound **3a**. Yield: 75% (0.51 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.80–0.87 (m, 15H), 0.90 (d, 3H, $^{3}J_{H\text{-}H} = 6.1$ Hz, CH_3), 1.00–1.77 (m, 48H), 1.89–2.08 (m, 4H), 4.11–4.32 (m, 4H, CH_2-O), 5.29–5.43 (m, 4H), 6.82 (d, $^{1}J_{H\text{-}P} = 696.2$ Hz, P-*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm; phytanyl chain, C-n; oleyl chain, C-n′): 14.0 (*C*-18′), 19.5 and 19.7 (*C*H_3), 22.6, 22.7, and 22.8 (2 × *C*H_3, C17′), 24.4, 24.5, and 24.8 (*C*-5, *C*-9, *C*-13), 25.6 (*C*-3′), 27.2 (*C*-8′, *C*-11′), 28.0 (*C*-15), 29.1–29.6 (*C*-4′–*C*-7′, *C*-12′–*C*-15′), 29.4 (*C*-3), 30.7 (d, $^{3}J_{C\text{-}P} = 5.9$ Hz, *C*-2′), 31.9 (*C*-16′),

32.8 (*C*-7, *C*-11), 37.0–37.8 (*C*-2, *C*-4, *C*-6, *C*-8, *C*-10, *C*-12), 39.5 (*C*-14), 65.4 (d, $^2J_{C\text{-}P} = 6.7$ Hz, *C*-1), 66.0 (d, $^2J_{C\text{-}P} = 6.0$ Hz, *C*-1′), 129.8 and 129.9 (*C*-9′, *C*-10′). ^{31}P NMR (81 MHz, $CDCl_3$) δ (ppm): 7.9. MS (ES) m/z: 613 (MH^+).

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