BODP – A Versatile Reagent for Phospholipid Synthesis

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Abstract: Benzyloxydichlorophosphine (BODP) has been found to be a convenient reagent for the synthesis of phospholipids. A series of artificial ether and ester phospholipids have been prepared in good to high yields.

Key words: ethers, esters, phospholipids, phosphorylation, protecting group

Despite over 80 years of synthetic efforts, the preparation of phospholipids remains a challenge.[1] We have recently initiated a program for the synthesis of artificial phospholipids and found it necessary to investigate new reactive intermediates for the introduction of a phosphate head group.[2] Here, we report on a convenient reagent, benzyloxydichlorophosphine (BODP, **1**), that was successfully used for the synthesis of various artificial choline phospholipids.

Typical ways to introduce a phosphocholine head group include both phosphorus(V) and phosphorus(III) reagents: for example, bromoethylphosphoric acid dichloride readily reacts with primary alcohols to give a stable intermediate that can be substituted to the choline using trimethylamine.[3] Dioxophospholanes can be opened to the corresponding choline.[4] Successful phosphorus(III) intermediates include H-phosphonates[5] and reagents such as methyl dichlorophosphite[6] and phosphoramidites,[7] which allow a stepwise addition of two different alcohols.

On attempting to phosphorylate a secondary alcohol, we found that phosphorus(V) reagents are generally too unreactive and phosphorus(III) reagents lead to oxidation after the addition of the first alcohol. This and the cost of phosphoramidite reagents led us to look for an alternative, a middle way using a reagent that at the same time was stable towards oxidation, but also reactive enough to allow the stepwise addition of two different alcohols in one pot. Benzyloxydichlorophosphine fulfills these criteria and, to our knowledge, was never before used for the synthesis of phospholipids. The reagent was initially synthesized under rudimentary conditions that lead to explosions during the distillation.[8] However, the reagent can be used without this purification step, is safe to handle,[9] and requires only moderately dry working conditions under nitrogen gas (BOPD is routinely used by undergraduate students in our laboratory). The starting materials (benzyl alcohol and PCl_3) are readily available, cheap, and can be used without purification or drying. Furthermore, the benzyl group can be easily removed under various mild conditions.

BODP has been used as a reactive intermediate for the synthesis of ribonucleotides,[9] phosphoramidates,[10] polyphosphates,[11] and in cyclization reactions.[12] When being reacted with phosphonates and amides BODP – like other phosphorus(III) reagents – presumably primarily formed the monochlorophosphine intermediate and not the doubly substituted phosphine,[9b,11b] making it less useful for symmetrical double substitution, but more interesting for stepwise addition of different nucleophiles. The reactivity is strongly dependent on the solvent used, with tetrahydrofuran being preferred over acetonitrile and dichloromethane.[13]

Here, BODP was successfully used in the synthesis of 3 phospholipids: miltefosine (**4**), Pet-PC-Pet (**7**), and Pes-PC-Pes (**10**). Others and we have recently suggested amendments to the existing IUPAC recommendation for phospholipid nomenclature.[2,14] The new classification focuses on the type of chemical linkage between the phospholipid tails and the lipid backbone. 'Pes' thus designates a C_{16} alkyl chain (P = palmitic) connected to the lipid backbone with an ester functionality. In 'Pet', the chemical linker is an ether. The order in which the substituents are attached to the glycerol backbone is represented by the order of the groups in the abbreviation: Pes-PC-Pes is a 1,3-substituted, and Pes-Pes-PC a natural, *sn*-1,2-substituted phospholipid.

Our nomenclature allows easy classification of artificial phospholipids based on their chemical linkage and is complementary to the impressive nomenclature of the International Lipid Classification and Nomenclature Committee.[15]

Benzyloxydichlorophosphine (**1**) was synthesized optimizing a reported procedure:[12b] benzyl alcohol was reacted with phosphorus trichloride in diethyl ether. Upon completion of the reaction, the excess of diethyl ether was evaporated leaving the BODP that was used without further purification.

Miltefosine (hexadecylphosphocholine, **4**) is an impressive example for an interdisciplinary collaboration between basic and clinical research. Miltefosine was initially identified for its antitumor potency and is now used clinically for the treatment of visceral and cutaneous leishmaniasis.[16] Miltefosine was synthesized by phosphorylation of hexadecan-1-ol with phosphorus oxychloride, ring closure with ethanolamine, and opening of the oxaza-

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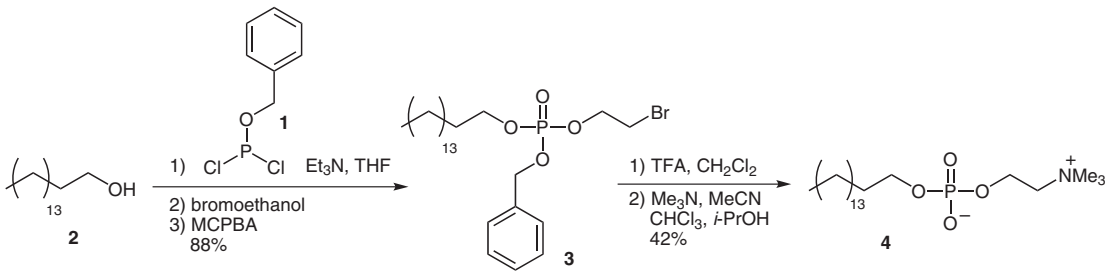


Scheme 1 Synthesis of miltefosine (hexadecylphosphocholine, **4**)

phospholane ring under acidic conditions. The alkylphosphoethanolamine was reacted to form the choline with dimethyl sulfate.[17]

Here, BODP (**1**) was reacted stepwise with hexadecan-1-ol (**2**), followed by bromoethanol, and oxidation to the protected phosphate triester **3**. Deprotection with trifluoroacetic acid and substitution with trimethylamine[3] lead to the choline derivative **4** in two steps and an overall yield of 37% (Scheme 1).

Surprisingly, changing from a natural 1,2-diacyl phospholipid to a symmetrical 1,3-diacyl phospholipid does not significantly alter the physical properties of the molecule in a membrane.[18] Similarly, changing between diacyl- and dialkylphosphocholines also does not introduce big alterations in the physical characteristics of the molecules.[19] These facts should allow new possibilities to produce membrane probes at more reasonable prices and an efficient synthesis is certainly appreciated.

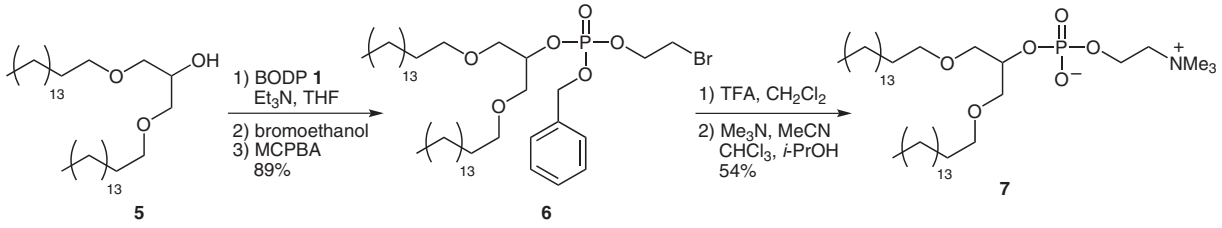
Pet-PC-Pet (**7**) had previously been accessed using bromoethyl dichlorophosphate that was substituted with trimethylamine.[19] Here, we started from the corresponding 1,3-dialkylpropan-2-ol **5** that was obtained from the reaction of hexadecan-1-ol with epichlorohydrin.[20] The intermediate was reacted with BODP (**1**) and bromoethanol to give the protected phosphate triester **6**. Again, substitution with trimethylamine led to the product **7** (Scheme 2) in 48% overall yield.

1,3-Diacyl phosphocholines were introduced in order to study the differences between natural 1,2- and artificial 1,3-diacyl phospholipids.[18,19]

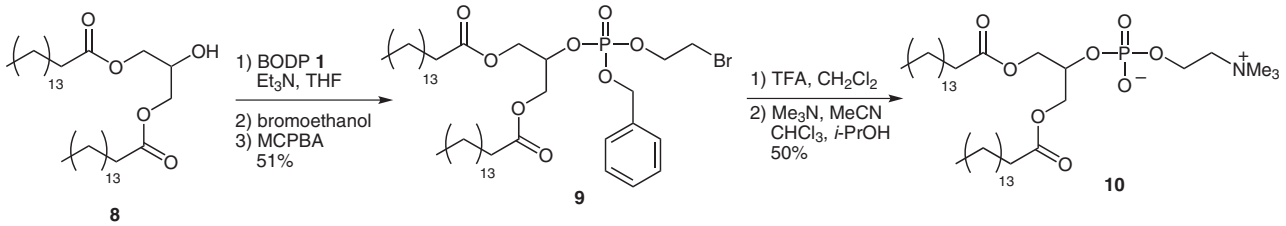
The starting alcohol **8** was available from a reaction of palmitoyl chloride with glycerol.[21] Reaction with BODP led to the reactive intermediate **9** that was deprotected and further substituted to Pes-PC-Pes (**10**) (Scheme 3). The compound was obtained in 26% yield which is comparable to earlier syntheses of Les-PC-Les (L = lauric).[22]

In conclusion, we have presented a rapid and high-yielding approach leading to alkylphosphocholines, 1,3-dialkyl-, and 1,3-diacylphosphocholines. The synthesis is based on benzyloxydichlorophosphine, a reagent rarely used for phosphorylations, but with many advantages over phosphoramidite reagents such as cost, stability and ease of handling. The presented approach for phospholipid synthesis is flexible, allowing the introduction of various head groups. Synthetic efforts in this direction are currently ongoing in our group.

Starting compounds and solvents were purchased from Sigma-Aldrich/Fluka or Acros and were used without further purification. Column chromatographic separations were carried out using 230–400 mesh silica gel. TLC plates were developed with $KMnO_4$. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded (as indicated) on either a Bruker 300 MHz, 400 MHz or 500 MHz spectrometer and are reported as chemical shifts (δ) in ppm relative to TMS (δ = 0). Spin multiplicities are reported as a singlet (s), doublet (d), or triplet (t)



Scheme 2 Synthesis of Pet-PC-Pet (**7**)



Scheme 3 Synthesis of Pes-PC-Pes (**10**)

with coupling constants (*J*) given in Hz, or multiplet (m). Broad peaks are marked as br. HRESI-MS were performed on QSTAR Pulsar (AB/MDS Sciex) spectrometer and are reported as mass-per-charge ratio *m/z*. IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer (ATR, Golden Gate). MCPBA provided by Sigma was 77% pure.

Benzyloxydichlorophosphine (BODP, 1)

The protocol was optimized from a literature procedure.[12b] Benzyl alcohol (6.00 mL, 58.0 mmol) was dissolved in anhyd Et_2O (120 mL) and added to PCl_3 (10.1 mL, 116 mmol) in anhyd Et_2O (90 mL) over 5 h. The first 20 min of the addition was performed at 0 °C, and then the ice bath was removed. After the addition, the stirring was continued for 2 h at 20 °C. The solvent was evaporated by distillation at 50 °C and the excess of PCl_3 was removed under reduced pressure. The product was used without further purification; colorless oil; yield: 11.4 g (94%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (s, 5 H), 5.32 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.8, 128.8, 128.5, 69.8.

^{31}P NMR (162 MHz, $CDCl_3$): δ = –177.37 (s).

Benzyl 2-Bromoethyl Hexadecyl Phosphate (3)

BODP (**1**; 1.00 mL, 6.10 mmol) and anhyd Et_3N (2.00 mL, 14.0 mmol) were dissolved in anhyd THF (20 mL) under N_2. Hexadecan-1-ol (400 mg, 1.65 mmol) in anhyd THF (20 mL) was added dropwise to the solution under stirring at 0 °C over 3 h [completion of the reaction was checked by TLC (MeOH–CH_2Cl_2, 2:98)]. Then, bromoethanol (910 μL, 12.8 mmol) was added at 0 °C and the mixture was stirred for 3 h (the reaction can be monitored by ^{31}P NMR spectroscopy, the signal should shift from 166 ppm to about 140 ppm). MCPBA (1.56 g, 9.60 mmol) was added to the reaction mixture at 0 °C and the mixture was stirred for 1 h (oxidation can be monitored by a signal shift from 140 ppm to about –5 ppm in ^{31}P NMR spectrum). The solution was treated with of aq 10% $Na_2S_2O_3$ (110 mL), sat. aq $NaHCO_3$ (30 mL), and extracted with CH_2Cl_2 (3 × 100 mL). The solvents from the combined organic phases were removed under reduced pressure. The crude product was purified on a silica gel column (eluent: pentane–EtOAc, 4:1) to give the pure product as a brownish oil; yield: 750 mg (88%); R_f = 0.23 (pentane–EtOAc, 4:1).

IR (ATR): 2923, 2853, 1457, 1379, 1270, 1215, 1000, 733, 696 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 7.2 Hz, 5 H), 5.10 (d, *J* = 8.5 Hz, 2 H), 4.25 (dd, *J* = 13.0, 6.5 Hz, 2 H), 4.04 (q, *J* = 6.8 Hz, 2 H), 3.47 (t, *J* = 6.3 Hz, 2 H), 1.63 (dd, *J* = 13.7, 6.7 Hz, 2 H), 1.25 (s, 25 H), 0.88 (t, *J* = 6.5 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 135.7, 128.7, 128.0, 69.5, 68.3, 66.5, 32.0, 30.2, 30.2, 29.7, 29.7, 29.7, 29.6, 29.6, 29.5, 29.5, 29.4, 29.2, 25.4, 22.7, 14.2.

^{31}P NMR (162 MHz, $CDCl_3$): δ = –0.63 (s).

HRMS (ESI+): *m/z* [M + H]$^+$ calcd for $C_{25}H_{45}BrO_4P$: 519.2236; found: 519.2233.

Hexadecylphosphocholine (4)

To a solution of **3** (292 mg, 0.562 mmol) in CH_2Cl_2 (2 mL) was added CF_3CO_2H (TFA, 98%, 3.00 mL, 40.3 mmol) and the mixture was stirred at r.t. for 20 h. Excess TFA was removed by bubbling N_2 through the mixture. The residue was partitioned between aq HCl (25 mL) and CH_2Cl_2 (4 × 25 mL). The solvent from the combined organic phases were removed under reduced pressure. The white solid obtained (280 mg, 100% conversion of **3**) was used without further purification. A portion of the solid (140 mg) was dissolved in a mixture of CH_2Cl_2 (1 mL), MeCN (1.6 mL), and *i*-PrOH (1.6 mL). Then, Me_3N (45% in H_2O, 2 mL) was added. After 3 h, the solvent was removed under vacuum. The crude product was purified on a silica gel column (eluent: CH_2Cl_2–MeOH–25% NH_4OH, 75:22:3); white solid; yield: 56 mg (42%); R_f = 0.1 (CH_2Cl_2–MeOH–25% NH_4OH, 75:22:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.27 (br, 2 H), 3.86 (br, 2 H), 3.78 (dd, *J* = 13.1, 6.6 Hz, 2 H), 3.41 (s, 9 H), 1.66–1.48 (m, 2 H), 1.25 (s, 26 H), 0.87 (t, *J* = 6.8 Hz, 3 H).

^{31}P NMR (162 MHz, $CDCl_3$): δ = –0.40 (s).

HRMS (ESI+): *m/z* [M + H]$^+$ calcd for $C_{21}H_{47}NO_4P$: 408.3237; found: 408.3232.

1,3-Bis(hexadecyloxy)propan-2-ol (5)

NaH (60% in mineral oil, 525 mg, 13.1 mmol) was added in 3 portions to hexadecan-1-ol (6.63 g, 27.3 mmol) at 100 °C. After stirring for 30 min, epichlorohydrin (250 μL, 3.19 mmol) was added dropwise to the hot mixture and maintained at 100 °C overnight, after which H_2O (2 mL) was added to quench the reaction. CH_2Cl_2 (200 mL) was added, followed by THF to facilitate the solubility of the product, and the organic phase was washed with H_2O (3 × 150 mL). The organic phase was dried (Na_2SO_4), filtered, and the solvent removed under reduced pressure. Purification on a silica gel column (eluent: pentane–EtOAc, 5:95) afforded a white solid; yield: 1.06 g (61%); R_f = 0.16 (pentane–EtOAc, 95:5)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.94 (s, 1 H), 3.60–3.26 (m, 8 H), 2.45 (s, 1 H), 1.57 (s, 4 H), 1.26 (s, 52 H), 0.88 (t, *J* = 5.3 Hz, 6 H).

HRMS (ESI+): *m/z* [M + H]$^+$ calcd for $C_{35}H_{73}O_3$: 541.5554; found: 541.5565.

Benzyl 1,3-Bis(hexadecyloxy)propan-2-yl 2-Bromoethyl Phosphate (6)

A solution of **5** (400 mg, 739 μmol) in anhyd THF (20 mL) was added dropwise to a solution of BODP (**1**; 405 μL, 2.44 mmol) and anhyd Et_3N (722 μL, 5.18 mmol) in anhyd THF (25 mL) over 3 h at 0 °C. The stirring was continued at 20 °C for 12 h. After the consumption of the starting material (TLC: pentane–EtOAc, 9:1), bromoethanol (370 μL, 5.18 mmol) was added dropwise at 0 °C. The ice-bath was removed and the stirring continued for 45 min. MCPBA (829 mg, 3.70 mmol) was added at 0 °C and the mixture was stirred for 1 h at 20 °C. Then, aq 10% $Na_2S_2O_3$ (110 mL) and sat. aq $NaHCO_3$ (50 mL) were added and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The organic solvent was removed under reduced pressure and the product was purified on a silica gel column (eluent: pentane–EtOAc, 5:2) to give a yellowish solid; yield: 536 mg (89%); R_f = 0.35 (pentane–EtOAc, 4:1).

IR (ATR): 2922, 2853, 1462, 1378, 1278, 1117, 1013, 734, 697 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.47–7.31 (m, 5 H), 5.14 (d, *J* = 7.6 Hz, 2 H), 4.70–4.59 (m, 1 H), 4.30 (dd, *J* = 14.8, 6.6 Hz, 2 H), 3.65–3.53 (m, 4 H), 3.53–3.35 (m, 6 H), 1.54 (tt, *J* = 13.7, 6.7 Hz, 4 H), 1.26 (s, 52 H), 0.89 (t, *J* = 7.0 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 181.1, 175.2, 148.1, 135.9, 128.6, 128.5, 127.9, 71.7, 70.2, 69.4, 66.5, 62.8, 31.9, 29.7, 29.7, 29.6, 29.5, 29.5, 29.4, 29.3, 29.2, 26.1, 22.7, 14.1.

HRMS (Turbo Spray): *m/z* [M + H]$^+$ calcd for $C_{44}H_{83}BrO_6P$: 817.5105; found: 817.5113.

Pet-PC-Pet (7)

To a solution of **6** (503 mg, 615 μmol) in CH_2Cl_2 (7 mL) was added TFA (98%, 7.00 mL, 93.3 mmol). After stirring the mixture for 24 h, the TFA was removed by bubbling N_2 through the solution. The residual crude oil was partitioned between aq 1 M HCl (25 mL) and CH_2Cl_2 (4 × 25 mL). The solvent from the combined organic phases was removed under reduced pressure to give 315 mg (70% conver-

sion of **6**) of a white solid, which was used without further purification. A portion of the crude solid (285 mg) was dissolved in a mixture of $CHCl_3$ (8 mL), MeCN (5 mL), and *i*-PrOH (8 mL). Then, Me_3N (45% in H_2O, 4 mL) was added. After stirring for 48 h, the solvents were removed under reduced pressure and the crude product was purified on a silica gel column (eluent: CH_2Cl_2–MeOH–25% NH_4OH, 75:22:3); white solid; yield: 213 mg (54%); R_f = 0.27 (CH_2Cl_2–MeOH–25% NH_4OH, 75:22:3).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.33 (s, 3 H), 3.81 (s, 2 H), 3.55 (d, *J* = 5.1 Hz, 4 H), 3.39 (s, 13 H), 1.61–1.43 (m, 4 H), 1.25 (s, 52 H), 0.87 (t, *J* = 6.8 Hz, 6 H).

HRMS (Turbo Spray): *m*/*z* [M + H]$^+$ calcd for $C_{40}H_{85}NO_6P$: 706.6109; found: 706.6126.

2-Hydroxypropane-1,3-diyl Dipalmitate (8)[18]

A solution of palmitoyl chloride (1.70 mL, 5.45 mmol) in anhyd THF (12 mL) was added dropwise to a solution of glycerol (200 μL, 2.72 mmol) and pyridine (900 μL, 11.1 mmol) in anhyd THF (18 mL) at 0 °C under N_2 over 90 min. The stirring was continued at 20 °C for 1 h. Then, the solution was partitioned between aq 1 M HCl (100 mL) and Et_2O (3 × 150 mL). The product was recrystallized from Et_2O at 6 °C overnight. The white powder was filtered, dried, and used without further purification; yield: 540 mg (35%); R_f = 0.7 (CH_2Cl_2–MeOH, 49:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.20–4.11 (m, 5 H), 2.41 (s, 1 H), 2.34 (t, *J* = 7.3 Hz, 2 H), 1.63–1.61 (m, 4 H), 1.25 (s, 48 H), 0.88 (t, *J* = 8.0 Hz, 6 H).

HRMS (ESI–): *m*/*z* calcd [M + $MeCOO^-$]$^-$ for $C_{37}H_{71}O_7$: 627.5205; found: 627.5205

2-[Benzyloxy(2-bromoethoxy)phosphoryloxy]propane-1,3-diyl Dipalmitate (9)

A solution of **8** (365 mg, 0.64 mmol) in anhyd THF (20 mL) was added dropwise to a solution of BODP (**1**; 460 μL, 2.76 mmol) and anhyd Et_3N (820 μL, 5.90 mmol) in anhyd THF (10 mL) over 90 min at 0 °C. The stirring continued at 20 °C for 5 h. After the consumption of the starting material (TLC: pentane–EtOAc, 5:2), bromoethanol (420 μL, 5.90 mmol) was added dropwise at 0 °C. Then the ice-bath was removed and the stirring continued for 45 min. MCPBA (733 mg, 3.27 mmol) was added at 0 °C and the solution was stirred for 1 h at 20 °C. Aq 10% $Na_2S_2O_3$ (110 mL) was added followed by sat. aq $NaHCO_3$ (50 mL). The aqueous phases were extracted with CH_2Cl_2 (4 × 100 mL). The solvents were removed from the combined organic phases and the crude product was purified on a silica gel column (eluent: pentane–EtOAc, 5:2) to give a yellow solid; yield: 275 mg (51%); R_f = 0.5 (pentane–EtOAc, 4:1).

IR (ATR): 2922, 2853, 1743, 1457, 1379, 1276, 1163, 1011, 735, 697 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45–7.31 (m, 5 H), 5.11 (dd, *J* = 8.1, 1.7 Hz, 2 H), 4.81–4.74 (m, 1 H), 4.35–4.24 (m, 4 H), 4.18 (ddd, *J* = 12.1, 7.7, 5.9 Hz, 2 H), 3.47 (tdd, *J* = 6.4, 1.7, 0.5 Hz, 2 H), 2.37–2.29 (m, 2 H), 2.26 (td, *J* = 7.4, 1.6 Hz, 2 H), 1.78–1.40 (m, 4 H), 1.25 (s, 48 H), 0.88 (t, *J* = 7.0 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.2, 135.4, 128.7, 128.7, 128.0, 74.2, 69.7, 66.8, 62.7, 34.0, 33.9, 31.9, 29.6, 29.3, 29.1, 24.7, 22.7, 14.1.

^{31}P NMR (121 MHz, $CDCl_3$): δ = –2.60 (s).

HRMS (ESI+): *m*/*z* = [M + H]$^+$ calcd for $C_{44}H_{79}BrO_8P$: 845.469; found: 845.4682.

Pes-PC-Pes (10)

To a solution of the phosphate triester **9** (55.0 mg, 65.0 μmol) in CH_2Cl_2 (3 mL) was added TFA (98%, 3.00 mL, 40.0 mmol). After 36 h, the solvent was removed by bubbling N_2 through the vial and the crude oil obtained was used directly in the next step. The oil was dissolved in a mixture of $CHCl_3$ (1.5 mL), *i*-PrOH, MeCN (1.5 mL), and Me_3N (45% in H_2O, 3 mL; 2 mL of additional Me_3N were added after 24 h) and the mixture was stirred for 36 h. The solvents were removed under reduced pressure and the crude product was purified on a silica gel column (eluent: CH_2Cl_2–MeOH–25% NH_4OH, 175:22:3, then CH_2Cl_2–MeOH–25% NH_4OH, 75:22:3) to give the product as a white powder; yield: 24 mg (50%); R_f = 0.2 (CH_2Cl_2–MeOH–25% NH_4OH, 75:22:3).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.49 (br s, 1 H), 4.33 (br s, 2 H), 4.24 (d, *J* = 4.9 Hz, 4 H), 3.80 (s, 2 H), 3.34 (s, 9 H), 2.29 (t, *J* = 7.6 Hz, 4 H), 1.71–1.46 (m, 4 H), 1.25 (s, 48 H), 0.88 (t, *J* = 6.7 Hz, 6 H).

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{40}H_{81}O_8NP$: 734.5694; found: 734.5728.

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