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CYCLIC PLATELET-ACTIVATING FACTOR ANALOGUES DERIVED FROM 2-DEOXY-D-*erythro*-PENTOSE

MICHAEL L. PHILLIPS AND ROSANNE BONJOUKLIAN
Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285 (U.S.A.)
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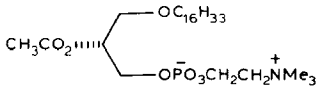
ABSTRACT

A method for the synthesis of chiral cyclic analogues of platelet-activating factor (PAF) is reported. Treatment of suitably substituted derivatives of 2-deoxy-D-*erythro*-pentose with phosphorus oxychloride, followed by choline *p*-toluenesulfonate generates cyclic phospholipids in good yield. Further chemical modification produces other compounds including optically active γ-butyrolactones such as 2-deoxy-5-*O*-hexadecyl-3-*O*-phosphocholyl-D-*erythro*-pentono-1,4-lactone and 2-deoxy-3-*O*-hexadecyl-5-*O*-phosphocholyl-D-*erythro*-pentono-1,4-lactone. All phospholipids were poor antagonists of PAF-induced aggregation of human platelets, and two analogs were poor agonists. The chemistry presented should be useful for the syntheses of other conformationally restricted analogues of PAF.

INTRODUCTION

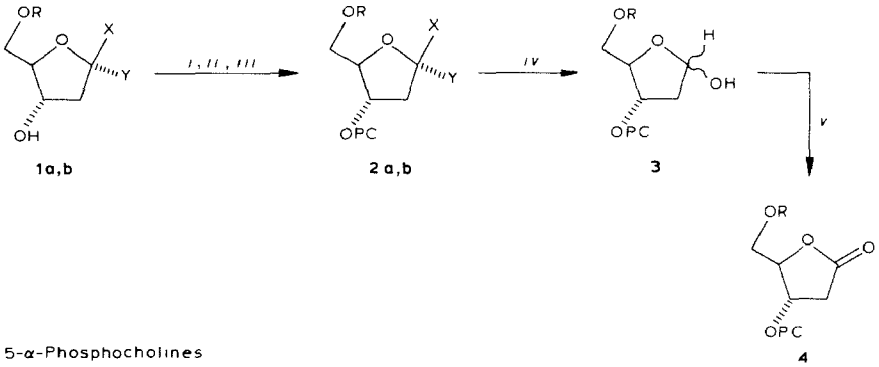
The recent discovery of platelet-activating factor (1-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine, PAF) as a potent cell-derived mediator of allergy, inflammation, and cardiovascular function has provoked scientists of many disciplines to pay increasing attention to phospholipids and their role in cellular function (for comprehensive reviews, see ref. 1). It has also encouraged medicinal chemists to synthesize structural analogues of PAF in order to probe its structure–activity relationship and to generate compounds with varying pharmacology (see ref. 2 for the first specific PAF antagonist).

In this paper, we describe the the synthesis and platelet-aggregation activity of a series of PAF analogues derived from 2-deoxy-D-*erythro*-pentose. These compounds were conceptually generated by connecting the acetate methyl group with

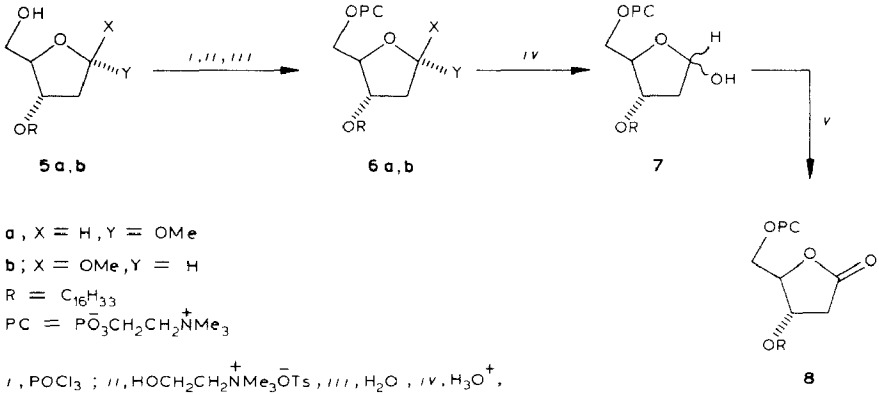


Platelet-activating factor (PAF)

3-α-Phosphocholines



5-α-Phosphocholines



a, X = H, Y = OMe

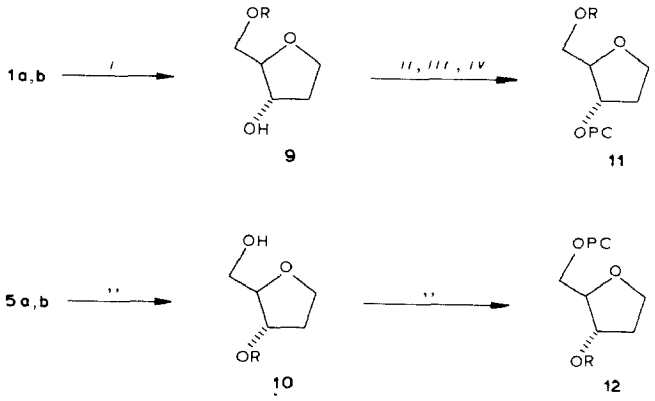
b; X = OMe, Y = H

R = $C_{16}H_{33}$

PC = $PO_3^-CH_2CH_2\overset{+}{N}Me_3$

I, $POCl_3$; II, $HOCH_2CH_2\overset{+}{N}Me_3\bar{O}Ts$, III, H_2O, IV, H_3O^+, V, $Br_2-H_2O-BaCO_3$

Scheme I



I, Et_3SiH, $BF_3 \cdot OEt_2$, II, $POCl_3$; III, $HOCH_2CH_2\overset{+}{N}Me_2\bar{O}Ts$, IV, H_2O

Scheme II

C-1 or C-3 of the glycerol backbone of PAF. The choice of 2-deoxy-D-*erythro*-pentose as starting material leads to optically active, cyclic phospholipids possessing a fixed *trans* orientation of the polar phosphocholine group to the aliphatic ether appendage. The following chemistry should prove general for the syntheses of other conformationally restricted phospholipids, possibly derived from other natural carbohydrates.

RESULTS AND DISCUSSION

As illustrated in Schemes I and II, the chemistry used to generate the various cyclic phospholipids was generally straightforward, and the starting materials **1a,b** and **5a,b** were readily available. For example, the α and β anomers **1a** and **1b** used for the 3-α-phosphocholine series were obtained from the known methyl 2-deoxy-3-*O*-benzyl-α,β-D-*erythro*-pentofuranoside, which was alkylated at O-5 by using sodium hydride–hexadecyl bromide in DMF, and then debenzylated (H_2, 5% Pd–$CaCO_3$, ethanol) to afford **1a** and **1b**, readily separable by column chromatography.

Each alcohol was then transformed into the desired phosphocholine derivative **2a** and **2b** by sequential treatment with phosphorus oxychloride, followed by choline *p*-toluenesulfonate, and then subsequent hydrolysis[3]. The free hemiacetal **3** could be obtained from either glycoside by hydrolysis in M HCl. This compound was found to eliminate readily to the alkoxymethylfuran if acid was not completely removed prior to product isolation. Subsequent oxidation to the target lactone **4** was readily accomplished by using aqueous bromine[4]. Attempted oxidation with Me_2SO–Ac_2O yielded only an anomeric mixture of 1-acetates, while use of pyridinium dichromate led to decomposition.

A similar procedure was followed for generation of the starting materials **5a** and **5b** and the rest of the 5-phosphocholine series, using methyl 2-deoxy-5-*O*-trityl-α,β-D-*erythro*-pentofuranoside as starting material.

To study the effect of removing oxygen functionality at C-1, phospholipids **11** and **12** were synthesized. Thus, as shown in Scheme II, glycosides **1a,b** and **5a,b** could be reduced to the 1,4-anhydroalditols by Et_3SiH–$BF_3 \cdot Et_2O$ to afford alcohols **9** and **10**, respectively[5]. Conversion into the desired products **11** and **12** were then effected in the manner previously described. Direct transformation of the phospholipids **2–8** by this reductive technique failed.

In general, these cyclic phospholipids were stable for several weeks when stored at 5°, and when kept in saline (pH 6–6.5) at the same temperature. However, lactones **4** and **8** readily absorbed water and slowly decomposed upon prolonged warming to 37° (as used in the platelet-aggregation studies).

With regard to their *in vitro* comparison with PAF, the results were very disappointing, but nonetheless valuable. Only at the relatively high concentrations of 50–100μM did these compounds uniformly inhibit human platelet aggregation

induced with 0.1μM PAF*. It is noteworthy, however, that only lactone **4** and ether **11**, of the 3-α-phosphocholine series, induced aggregation at 200μM. These compounds possess the natural chirality of PAF, whereas members of the 5-phosphocholine series are antipodal.

In conclusion, we have demonstrated the syntheses of two *trans* series of five-membered ring analogues of PAF, and have shown that these compounds, for the most part, lack both potent agonist and antagonist activity with regards to platelet aggregation. We will continue to probe various cyclic series to gain more information about the structural requirements of the PAF receptor.

EXPERIMENTAL

Materials. — 2-Deoxy-D-*erythro*-pentose was purchased from Sigma Chemical Company and hexadecyl bromide from Eastman Chemicals. Choline *p*-toluenesulfonate was prepared by the method of Brockerhoff and Ayengar[3]. Solvents were prepared as follows: DMF was stored over 4Å molecular sieves; THF was freshly distilled from sodium; Et_3N and pyridine were stored over KOH; $CHCl_3$ was passed over neutral alumina (activity I). All organic extracts were dried over anhydrous Na_2SO_4.

Methods. — Analytical t.l.c. was performed on EM Merck Silica Gel 60 F-254 plates (5 × 10 cm), that were developed with either 3:1 cyclohexane–EtOAc (solvent *A*) or 10:5:1 $CHCl_3$–MeOH–NH_4OH (solvent *B*). Spots were made visible by using H_2SO_4. Flash-column purifications were performed with EM Merck Silica Gel 60 using eluting solvents as indicated in each experiment. (Compounds were eluted from the columns by using the most polar of the solvent systems indicated.)

I.r. spectra were recorded with Beckman Acculab 3 and Perkin–Elmer 281 spectrophotometers. ^{1}H-N.m.r. spectra were recorded using Varian T-60, JEOL FX-90Q, Bruker WM 270, and Bruker WH360 instruments. Chemical shifts are expressed in p.p.m. downfield from Me_4Si.

F.a.b. (fast-atom bombardment), f.d. (field desorption) and exact-mass determinations were obtained with Varian MAT 731 and VG analytical ZAB-3F spectrometers. Elemental analyses were performed at Lilly Research Laboratories facilities.

Specific rotations were determined with a Perkin–Elmer 241 polarimeter.

Methyl 2-deoxy-5-O-hexadecyl-α and β-D-erythro-*pentofuranoside* (**1a** *and* **1b**). — To hexane-washed sodium hydride (60% dispersion, 0.446 g, 1.5 eq.) in a three-necked, 25-mL round-bottom flask under N_2 atmosphere was added a

*Human platelet-aggregation experiments were performed using the method of Born[6]. Citrated platelet-rich plasma (2.5–4.0 × 10^5 platelets/mL) was used and platelet aggregation was monitored at 37° with a Payton Aggregometer by the conventional absorbance method. Platelets were treated with drug for 2 min prior to addition of PAF, and absorbance was measured 4 min later.

solution of methyl 2-deoxy-3-*O*-benzyl-α-D-*erythro*-pentofuranoside (1.772 g, 7.4 mmol) in 15 mL of DMF. After 30 min at 20°, hexadecyl bromide (3.4 mL, 11.2 mmol) was then introduced and reaction was allowed to proceed for 2 h, after which time 5 mL of H_2O was carefully added. After stirring for 5 min, all volatiles were removed under high vacuum and the residue partitioned between $CHCl_3$ and H_2O and transferred to a separatory funnel. The organic phase was then washed with brine, dried, filtered, and the filtrate evaporated under diminished pressure to afford the crude product (4.2 g). Purification was achieved by flash column-chromatography over 130 g of silica gel, using a gradient of cyclohexane→ 10:1 cyclohexane–Et_2O to afford 1.96 g of methyl 2-deoxy-3-*O*-benzyl-5-*O*-hexadecyl-α-D-*erythro*-pentofuranoside. This material was then redissolved in 30 mL of abs. EtOH and transferred to a Parr shaker bottle. Ethanol-treated 5% Pd on $CaCO_3$ (0.92 g, Engelhard) was then added, and hydrogenolysis was allowed to proceed (H_2, 40 lb.in^{-2}) for 1 h at 20°. The reaction was monitored by t.l.c. The suspension was then filtered through Celite and the filtrate evaporated to afford **1a** (1.4 g, 100%); R_F 0.25 (*A*); $[\alpha]_D$ +57.8° (*c* 1.0, MeOH); n.m.r. ($CDCl_3$): δ 2.1 (m, 2 H), 2.8 (d, *J* 10 Hz, 1 H), 3.4 (s, 3 H), 3.45 (m, 4 H, -CH_2OCH_2-), 4.2 (m, 2 H, H-3, H-4), and 5.1 (dd, 1 H, H-1); *m/z* (rel. intensity) 373 (M^+ + 1, 0.5), 371 (M^+ − 1, 0.4), 341 (6), 255 (3), and 117 (100).

Anal. Calc. for $C_{22}H_{44}O_4$: C, 70.90; H, 11.91. Found: C, 70.95; H, 11.96.

Anomer **1b** was prepared as just described from the β anomer of the starting material; R_F 0.15 (*A*); $[\alpha]_D$ −32.6° (*c* 1.0, MeOH); n.m.r. ($CDCl_3$): δ 2.1 (m, 2 H), 2.6 (br s, 1 H), 3.35 (s, 3 H), 3.4 and 3.5 (overlapping m, 4 H), 3.95 (m, 1 H), 4.35 (m, 1 H), and 5.05 (dd, 1 H); *m/z* (rel. intensity) 341 (20), 255 (2), and 117 (100).

*Methyl 2-deoxy-3-*O*-hexadecyl-α- and β-*D-erythro-*pentofuranoside* (**5a** *and* **5b**). — Methyl 2-deoxy-5-*O*-trityl-α,β-D-*erythro*-pentofuranoside (2.48 g, 6.34 mmol) was alkylated as in the previous series by using sodium hydride (2 eq.) in DMF (13 mL), followed by hexadecyl bromide (2.91 mL, 9.51 mmol) to afford the anomeric 3-ethers (1.51 g, 36%) after chromatographic purification. This material was then dissolved in 1:1 CH_2Cl_2–MeOH (25 mL). *p*-Toluenesulfonic acid (0.42 g, 0.1 eq.) was then added and the mixture was stirred for 4 h at 20°. The mixture was diluted with CH_2Cl_2, washed with 0.1M NaOH (pH 11), and then transferred to a separatory funnel. The aqueous phase was then washed with CH_2Cl_2, and the combined organic phases were treated with brine, dried, filtered, and the filtrate evaporated to afford 1.465 g of crude material. Chromatographic purification over silica gel was accomplished with a cyclohexane→ 5:1 cyclohexane–EtOAc gradient and yielded **5a** (0.3 g) and **5b** (0.37 g) (combined yield of 76%); **5a**: R_F 0.15 (*A*); $[\alpha]_D$ +90.4° (*c* 1.0, MeOH); n.m.r. ($CDCl_3$): δ 2.05 and 2.1 (overlapping m, 3 H), 3.4 (s, 3 H), 3.8 (m, 2 H), 4.0 (m, 2 H), and 5.0 (dd, 1 H); *m/z* (relative intensity) 371 (M^+ − 1, 8), 341 (100) and 312 (38).

Anal. Calc. for $C_{22}H_{44}O_4$: C, 70.90; H, 11.91. Found: C, 70.89; H, 11.93.

Compound **5b** had R_F 0.25 (*A*); $[\alpha]_D$ −43.4° (*c* 1.0, MeOH); n.m.r. ($CDCl_3$): δ 2.1 (br t, 2 H), 2.6 (m, 1 H), 3.4 (s, 3 H), 3.65 (m, 2 H), 4.1 (m, 2 H), and 5.05

(dd, 1 H); *m/z* (rel. intensity) 373 ($M^+ + 1$, 4), 341 (100) and 312 (56).

Anal. Calc. for $C_{22}H_{44}O_4$: C, 70.90; H, 11.91. Found: C, 70.93; H, 11.95.

*Methyl 2-deoxy-5-O-hexadecyl-3-O-phosphocholyl-β-*D-erythro-*pentofuranoside** (**2b**). — To a solution of $POCl_3$ (0.14 mL, 1.5 mmol) in dry THF (1 mL) was added dropwise a solution of **1b** (0.372 mg, 1 mmol) and Et_3N (0.28 mL, 2 mmol) in THF (5 mL). After 45 min, the resulting suspension was quickly filtered, the filtrate evaporated, and the residue redissolved in a solution of pyridine (0.62 mL, 7.7 mmol) in 6 mL of $CHCl_3$. Choline *p*-toluenesulfonate (0.606 g, 2.2 mmol) was then added, and after 5 h, 0.2 mL of H_2O was introduced. After 30 min, the mixture was diluted with $CHCl_3$, H_2O, and MeOH (9:3:4). The organic layer was washed with 5% aq. $NaHCO_3$, dried, concentrated, and then chromatographed ($CHCl_3 \rightarrow$ 1:2 $CHCl_3$–MeOH) to yield **2b** (0.357 mg, 66.5%); R_F 0.25 (*B*); $[\alpha]_D$ −12.0° (*c* 1.0, $CHCl_3$); n.m.r. ($CDCl_3$): δ 2.28 (m, 2 H, H-2), 3.34 (s, 3 H, OCH_3), 3.39 (s, 9 H, NMe_3), 4.20 (m, 1 H, H-4), 4.73 (m, 1 H, H-3), and 5.10 (dd, 1 H, *J* 3.0 and 4.9 Hz, H-1); *m/z* (rel. intensity) 538 ($M^+ + 1$, 1), 184 (32), and 73 (100).

Anal. Calc. for $C_{27}H_{57}NO_7P$: mol. wt. 538.3873. Found: mol. wt. 538.3877. *Anal.* Calc. for $C_{27}H_{56}NO_7P \cdot 2\,H_2O$: C, 56.52; H, 10.54; N, 2.44. Found: C, 56.98; H, 10.49; N, 2.85.

*Methyl 2-deoxy-5-O-hexadecyl-3-O-phosphocholyl-α-*D-erythro-*pentofuranoside* (**2a**). — This compound had R_F 0.25 (*B*); $[\alpha]_D$ +52.6° (*c* 1.0, $CHCl_3$); n.m.r. ($CDCl_3$): δ 2.07 (br m, 2 H, H-2), 4.27 (m, 1 H, H-4), 4.65 (m, 1 H, H-3), and 5.05 (dd, 1 H, *J* 1.0 and 6.1 Hz, H-1); *m/z* (rel. intensity) 538 ($M^+ + 1$, 0.3) and 184 (100).

Anal. Calc. for $C_{27}H_{57}NO_7P$: mol. wt. 538.3873. Found: mol. wt. 538.3866.

*Methyl 2-deoxy-3-O-hexadecyl-5-O-phosphocholyl-α-*D-erythro-*pentofuranoside* (**6a**). — This compound had R_F 0.19 (*B*); $[\alpha]_D$ +59.4° (*c* 1.0, MeOH); n.m.r. ($CDCl_3$): δ 1.95 and 2.22 (d of m, 2 H, H-2), 3.36 (s, 3 H, OCH_3), 3.4 (s, 9 H, NMe_3), 3.8–4.2 (m, 6 H) and 5.0 (d, 1 H, *J* 2.0 Hz, H-1); *m/z* (rel. intensity) 538 ($M^+ + 1$, 40), 264 (70), and 184 (100).

Anal. Calc. for $C_{27}H_{56}NO_7P \cdot H_2O$: C, 58.35; H, 10.52; N, 2.52. Found: C, 58.15; H, 10.21; N, 2.31.

*Methyl 2-deoxy-3-O-hexadecyl-5-O-phosphocholyl-β-*D-erythro-*pentofuranoside* (**6b**). — This compound had R_F 0.19 (*B*); $[\alpha]_D^{25}$ −23.2° (*c* 1.0, MeOH); n.m.r. ($CDCl_3$): δ 2.1 (m, 2 H, H-2), 3.33 (s, 3 H, OCH_3), 3.4 (s, 9 H, NMe_3), 3.8–4.2 (m, 6 H), and 5.1 (d of d, 1 H, *J* 1.0 Hz, H-1); *m/z* (rel. intensity) 264 (M-OCH_3-$OC_{16}H_{33}$, 86) and 184 (100). An analytical sample was prepared by recrystallization from CH_2Cl_2–Me_2CO.

Anal. Calc. for $C_{27}H_{56}NO_7P$: C, 60.31; H, 10.50; N, 2.60. Found: C, 60.58; H, 10.49; N, 2.49.

*2-Deoxy-5-O-hexadecyl-3-O-phosphocholyl-*D-erythro-*pentofuranoside* (**3**). — A solution of **2b** (0.25 g, 0.48 mmol) in 0.55M HCl (5.2 mL) was heated for 1.5

*The term "phosphocholyl" is used for the group $-P\bar{O}_3CH_2CH_2\overset{+}{N}Me_3$.

h to 70° with stirring. After cooling, the solution was made neutral and lyophilized. The residue was then extracted with $CHCl_3$, the mixture filtered, the filtrate evaporated, and the residue chromatographed ($CHCl_3$ → 1:1 $CHCl_3$–MeOH) to give **3** (0.247 g, 99%); R_F 0.12 (*B*); $[\alpha]_D^{25}$ +17.0° (*c* 1.0, MeOH); n.m.r. ($CDCl_3$): δ 2.2 (m, 2 H, H-2), 3.35 (s, 9 H, NMe_3), and 5.55 (m, 1 H, H-1); *m/z* (rel. intensity) 524 (M^+ + 1, 1) and 184 (100).

Anal. Calc. for $C_{26}H_{55}NO_7P$: mol. wt. 524.3716. Found: mol. wt. 524.3688.

2-Deoxy-3-O-hexadecyl-5-O-phosphocholyl-D-erythro-*pentofuranose* (**7**). — This compound had R_F 0.14 (*B*); $[\alpha]_D^{25}$ +13.2° (*c* 1.0, MeOH); n.m.r. ($CDCl_3$): δ 2.1 (m, 2 H, H-2), 5.48 and 5.57 (2 m, 1 H, H-1 anomers in 3:7 ratio); *m/z* (rel. intensity) 524 (M^+ + 1, 15), 264 (100), and 184 (100).

Anal. Calc. for $C_{26}H_{55}NO_7P$: mol. wt. 524.3716. Found: mol. wt. 524.3748.

2-Deoxy-5-O-hexadecyl-3-O-phosphocholyl-D-erythro-*pentono-1,4-lactone* (**4**). — Barium carbonate (0.033 g, 0.17 mmol) was added to a solution of **3** (0.063 g, 0.12 mmol) in 1.8 mL of H_2O. The resulting solution was cooled to 0°, and then Br_2 (7.4 μL, 0.145 mmol) was added. After 5.5 h, the material was lyophilized, extracted into $CHCl_3$, the extract concentrated and then chromatographed ($CHCl_3$ → 1:1 $CHCl_3$–MeOH) to afford **4** (0.028 g, 45%); R_F 0.25 (*B*); ν_{max}^{film} 1770 cm^{-1}; n.m.r. ($CDCl_3$): δ 2.2–3.0 (m, 2 H, H-2), 3.35 (s, 9 H, NMe_3), and 3.4–5.0 (m, 10 H); *m/z* (rel. intensity) 522 (M^+ + 1, 1), 184 (100).

Anal. Calc. for $C_{26}H_{53}NO_7P$: mol. wt. 522.3560. Found: mol. wt. 522.3584. (This compound failed to give satisfactory elemental analyses.)

2-Deoxy-3-O-hexadecyl-5-O-phosphocholyl-D-erythro-*pentono-1,4-lactone* (**8**). — This compound had R_F 0.2 (*B*); $[\alpha]_D^{25}$ +7.3° (*c* 1.0, $CHCl_3$); ν_{max}^{film} 1770 cm^{-1}; n.m.r. ($CDCl_3$): δ 2.5 and 3.0 (ddd, 2 H, H-2) and 3.38 (s, 9 H, NMe_3); *m/z* (rel. intensity) 522 (M^+ + 1, 100) and 184 (100).

Anal. Calc. for $C_{26}H_{53}NO_7P$: mol. wt. 522.3560. Found: mol. wt. 522.3580.

1,4-Anhydro-2-deoxy-3-O-hexadecyl-D-erythro-*pentitol* (**10**). — To a chilled (0°) solution of **5b** (0.288 g, 0.77 mmol) in 10 mL of 2:1 CH_3CN–CH_2Cl_2 was added Et_3SiH (0.12 mL, 0.77 mmol), followed by $BF_3{\cdot}OEt_2$ (0.095 mL, 0.77 mmol). The resulting suspension was rapidly stirred for 20 min, quenched with K_2CO_3 (0.16 g, 1.15 mmol), and then diluted with $CHCl_3$–H_2O. The organic phase was washed with 0.1M HCl, dried, concentrated, and chromatographed (cyclohexane → 10:1 C_6H_{12}–EtOAc) to yield **10** (0.187 g, 71%); R_F 0.13 (*A*); n.m.r. ($CDCl_3$): δ 2.0 (m, 2 H, H-2) and 3.3–4.0 (m, 9 H); *m/z* (rel. intensity) 343 (M^+ + 1, 100), 324 (10), and 311 (35).

Anal. Calc. for $C_{21}H_{42}O_3$: mol. wt. 342.3134. Found: mol. wt. 342.3139.

1,4-Anhydro-2-deoxy-5-O-hexadecyl-D-erythro-*pentitol* (**9**). — This compound had R_F 0.14 (*A*); n.m.r. ($CDCl_3$): δ 1.8–2.3 (m, 2 H, H-2), 2.6 (s, 1 H, OH), and 3.45–4.4 (2 m, 7 H); *m/z* (rel. intensity) 343 (M^+ + 1, 72) and 87 (100).

Anal. Calc. for $C_{21}H_{42}O_3$: mol. wt. 342.3134. Found: mol. wt. 342.3124.

1,4-Anhydro-2-deoxy-5-O-hexadecyl-3-O-phosphocholyl-D-erythro-*pentitol* (**11**). — Compound **11** was synthesized from **9** as shown peviously: R_F 0.15 (*B*);

n.m.r. ($CDCl_3$): δ 2.1 (m, 2 H, H-2), 3.36 (s, 13 H), and 3.7–4.6 (3 m, 8 H); *m/z* (rel. intensity) 508 ($M^+ + 1$, 12) and 184 (100).

Anal. Calc. for $C_{26}H_{55}NO_6P$: mol. wt. 508.3767. Found: mol. wt. 508.3773.

1,4-Anhydro-2-deoxy-3-O-hexadecyl-5-O-phosphocholyl-D-erythro-*pentitol* (**12**). — Compound **12** was synthesized from **10** as shown earlier: R_F 0.16 (*B*); n.m.r. ($CDCl_3$): δ 1.95 (m, 2 H, H-2), 3.36 (s, 11 H), and 3.6–4.4 (m, 10 H); *m/z* (rel. intensity) 508 ($M^+ + 1$, 100) and 184 (95).

Anal. Calc. for $C_{26}H_{54}NO_6P \cdot 0.5\ H_2O$: C, 60.44; H, 10.73; N, 2.71. Found: C, 60.28; H, 10.88; N, 2.55.

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