

202. Conformationally Restricted Analogs of Platelet-Activating Factor (PAF)

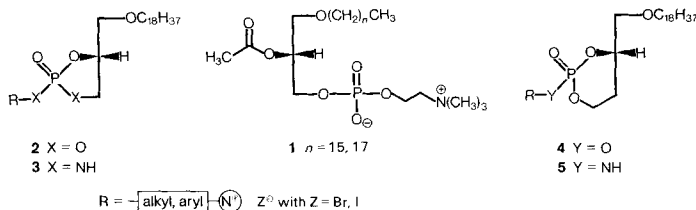
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The synthesis of the five-membered cyclic phosphorodiamidic-acid derivatives **10** and **11** as well as the preparation of the six-membered cyclic phosphates **18**, **19**, **22–25**, and phosphoramidates **27–32** is described. The effects of these conformationally restricted platelet-activating factor analogs on rabbit platelet aggregation are briefly discussed. The 2-oxo-1,3,2-dioxaphosphorinanes **19**, **25**, and **30** were found to be equally potent platelet-activating factor antagonists as the known thiazolium salt **33**.

Introduction. – Platelet-activating factor (PAF, **1**) is an ether phospholipid produced by a variety of different cell types [1] [2]. Recent studies have revealed that PAF is a potent platelet-activating, chemotactic, and hypotensive agent [3]; it also induces bronchoconstriction, increased vascular permeability, and gastric ulceration [4]. In general, PAF is believed to play an important role as mediator in anaphylactic and inflammatory processes. A PAF-specific cell surface receptor has been characterized recently [5]. Considerable efforts have been undertaken in order to *i*) get information about structure-activity relationships [6–10], *ii*) discover compounds with desired, selective physiological effects only, *e.g.* antihypertensive activity [6] [11], *iii*) find inhibitors of the biosynthesis of PAF [12] [13], or *iv*) identify antagonists of PAF [6] [14–25].

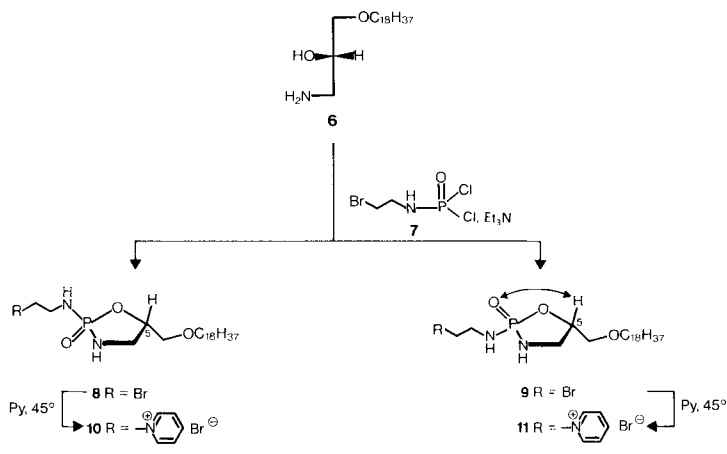


Here, we describe the synthesis and PAF-antagonistic properties of the conformationally restricted analogs **3–5** of PAF.

Syntheses. – *Five-Membered Cyclic Analogs of Type 3.* Because of the intrinsic instability of five-membered cyclic esters of phosphoric acid [26], *e.g.* **2**, towards hydrolysis, we decided to prepare a cyclic phosphorodiamidic-acid derivative of type **3**. Reaction of the (*S*)-amino alcohol **6**¹⁾ (*Scheme 1*) with *N*-(2-bromoethyl)phosphoramidic dichloride

¹⁾ The amino alcohol **6** was prepared from (*S*)-1-*O*-octadecyl-glycerol [27] in three steps: *i*) TsCl, pyridine; *ii*) NaN₃, DMF; *iii*) H₂, Pd/C, THF. We thank Dr. R. Barner and Mr. G. Hirth for providing us with the experimental details of this reaction sequence [28].

Scheme 1



(7)²) in the presence of Et₃N led to the formation of the two diastereoisomers **8** (27%) and **9** (26%), which could be easily separated by chromatography. Assignment of configuration at the P-atom is based on the observation that a P=O bond exhibits a deshielding effect on the protons in a 1,3-*cis*-relationship [30] as indicated in formula **9**. Thus, the ¹H-NMR signal for H-C(5) in **9** appears at 4.65 ppm, while the corresponding proton in **8** resonates at 4.53 ppm.

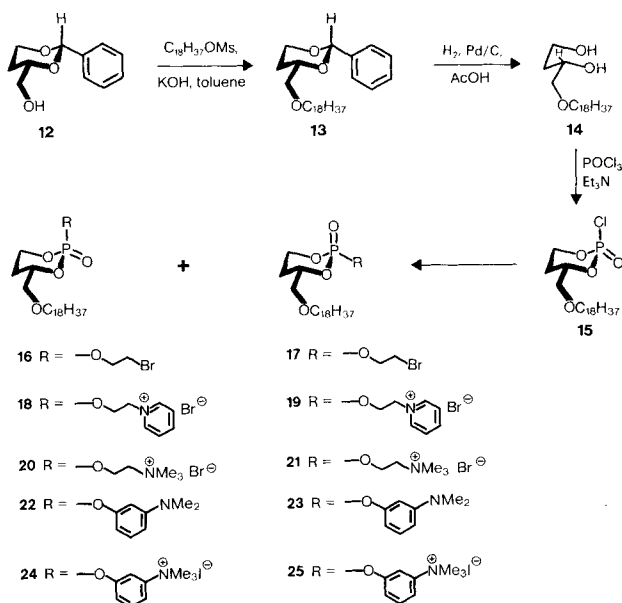
Introduction of a positively charged N-function could be achieved by conversion of each diastereoisomer **8** and **9**, in low yield, to the hygroscopic pyridinium salts **10** and **11**, respectively, which turned out to be quite difficult to isolate. The ³¹P-NMR spectrum of **11** showed the presence of a small amount of the diastereoisomer **10**, which could not be removed by recrystallization.

Six-membered Cyclic Analogs of Type 4 and 5. The enantiomerically pure diol **14**, key intermediate in the synthesis of the six-membered cyclic PAF-analogs of types **4** and **5**, was synthesized as shown in Scheme 2. Reaction of the benzylidene acetal **12** (prepared from (*S*)-1,2,4-butanetriol [31]) with octadecyl mesylate in the presence of solid KOH [32] produced the ether derivative **13**. Removal of the protecting group to give **14** was accomplished by catalytic hydrogenation in AcOH. Treatment of the diol **14** with POCl₃ and Et₃N gave a single phosphochloridate **15**. The known axial preference of the P-Cl bond in six-membered cyclic phosphates [33] [34] supports the structural assignment expressed in formula **15**.

Exposure of **15** to 2-bromoethanol/Et₃N/4-(dimethylamino)pyridine (Me₂NPy) gave a 1:4 mixture of the two diastereoisomeric cyclic phosphates **16** and **17**, separable by chromatography. The configuration of **16** and **17** was assigned using ³¹P-NMR spectroscopy, since it is well documented that the signals of 2-oxo-1,3,2-dioxaphosphorinanes with an axial P=O bond appear at lower field when compared to those of the isomers with an equatorial P=O bond [35]. Upon heating **16** in pyridine, the corresponding salt **18** was

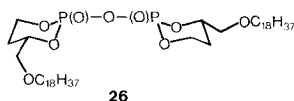
²) This compound was available by heating 2-aminoethyl bromide hydrobromide in POCl₃ according to a protocol developed for the preparation of the corresponding 2-chloroethyl derivative [29].

Scheme 2



produced in diastereoisomerically pure form. However, when **17** was subjected to the same reaction conditions, a 3:2 mixture of the pyridinium salts **19** and **18** was obtained, reflecting the axial preference of alkoxy substituents in six-membered cyclic phosphates under thermodynamic control [33] [34].

Because of the structural similarity of choline and 3-(trimethylammonio)phenol [36]³⁾, the reaction of **15** with 3-(dimethylamino)phenol was briefly investigated (Scheme 2): in the presence of $\text{Et}_3\text{N}/\text{Me}_2\text{NPy}$, a 1:1 mixture⁴⁾ of the two diastereoisomers **22** and **23** was formed, together with a small amount of the anhydride **26**. Chromatographic separation

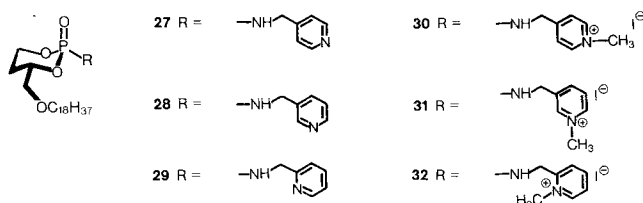


was followed by methylation of **22** and **23**, affording the quaternary ammonium salts **24** and **25**. In the case of **23**, the salt formation was again accompanied by isomerization yielding a 3:1 mixture of **25** and **24**. The thermodynamically more stable isomer **22**, on the other hand, could be converted to the single diastereoisomer **24**.

To circumvent the isomerization problem just mentioned as well as to arrive at compounds of higher stability than the pyridinium salts **10**, **11**, **18**, and **19**, the phosphor-

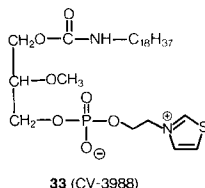
³⁾ All attempts to prepare the choline derivatives **20** and **21**, starting either from **16** and **17** or directly from **15**, failed.

⁴⁾ In the absence of Me_2NPy , only **23** was observed, i.e. Me_2NPy accelerates the isomerization to the thermodynamically more stable diastereoisomer **22**.



amidates **27–32** were prepared⁵). Treatment of **15**, formed *in situ* from diol **14**, with either 2-, 3-, or 4-(aminomethyl)pyridine in the presence of Et₃N/Me₂NPy proceeded with inversion at the P-atom leading almost exclusively to the equatorial intermediates **27–29**. Methylation (CH₃I, 43°) then gave the corresponding pyridinium salts **30–32**, whose ³¹P-NMR spectra revealed at most traces of the axial isomers.

Results. – To determine the PAF-antagonistic activity of **10**, **11**, **18**, **19**, **22–25**, and **30–32**, their ability to inhibit PAF-induced platelet aggregation in rabbit platelet-rich plasma (PRP) was examined. The same assay was used to measure eventual PAF-agonistic activity. The thiazolium salt **33** (CV-3988), shown to be a specific PAF-antagonist



by Terashita *et al.* [37], served as reference substance. From the results summarized in the Table, the following conclusions can be drawn:

- i) With the exception of **22** and **32** at high concentrations, all compounds tested are devoid of proaggregatory activity.
- ii) The five-membered cyclic phosphorodiamidic-acid derivatives **10** and **11** were found to be inactive as PAF-antagonists.
- iii) In the series of the six-membered cyclic phosphates, the representatives with an equatorial side chain, *e.g.* **19** and **25**, exhibited PAF-antagonistic activity at significantly lower concentrations than the axial diastereoisomers **18** and **24**, respectively.
- iv) A positively charged functional group seems to be a characteristic feature of an antagonist in this series, since the uncharged members **22** and **23** did not block PAF-induced platelet aggregation.
- v) Comparison of the IC₅₀ values of **30–32** demonstrates that PAF-antagonistic potency can be enhanced by increasing the distance between the P-atom and the positively charged, quaternary N-function.
- vi) The conformationally restricted analogs **19**, **25**, and **30** were shown to be equipotent to the open-chain PAF-antagonist **33** (CV-3988).

⁵) In contrast to alkoxy groups, the alkylamino substituents show a strong preference for the equatorial position in 2-oxo-1,3,2-dioxaphosphorinanes [33] [34].

Table. Effects of Conformationally Restricted PAF Analogs on Platelet Aggregation in Rabbit Platelet-Rich Plasma (PRP)

Compound	Inhibition of PAF ^{a)} <i>IC</i> ₅₀ [μM] ^{b)}	Proaggregation	
		Highest dose [μM]	Effect ^{c)}
10	≫ 30	30	–
11	> 10	10	–
18	17	30	–
19 ^{d)}	2.1	30	–
22	≫ 30	30	aggregation followed by desaggregation
23	≫ 30	30	–
24	30	30	–
25 ^{e)}	3.2	30	–
30	4.0	30	–
31	6.5	30	–
32	12.0	30	shape change of the platelets
33	3.2	30	–

^{a)} Platelet aggregation was induced by 4 nM of PAF [38].

^{b)} Determined from dose-response curves: Usually, PRP was preincubated with the test compound for 2 min at 37°.

^{c)} No effect observed: is indicated by a dash.

^{d)} A 3:2 mixture of **19** and **18** was used.

^{e)} A 3:1 mixture of **25** and **24** was used.

The skillful technical assistance of Mr. D. Cousot, Miss V. Schmid, Mr. D. Sprenger, and Mr. F. Gruber is gratefully acknowledged. We also thank our colleagues from the Central Research Department for determination of physical and analytical data: Dr. W. Arnold (NMR), Dr. L. Chopard (IR), Dr. A. Dirscherl (microanalyses), Dr. G. Englert (NMR), Dr. M. Grosjean (IR), Mr. W. Meister (MS), and Dr. M. Vecchi (GC).

Experimental Part

General. Reagent grade solvents (Fluka, Merck) were dried by passing through alumina Woelm B-Super I. POCl₃ (Fluka) was distilled before use. Evaporation means removal of solvent by use of a Büchi rotary evaporator at 40–50°C/in vacuo. High vacuum (h.v.): 10^{–2} Torr. TLC: TLC plates coated with silica gel 60 F₂₅₄ (Merck); detection by UV (254 nm), by I₂ vapor, or by spraying with 50% H₂SO₄/EtOH followed by heating or with Zinzadze reagent [39] (for P-containing compounds). Flash chromatography (FC) [40]: silica gel 60 (Merck, 230–400 mesh ASTM). Medium pressure liquid chromatography (MPLC): Lobar columns, LiChroprep Si 60 (40–63 μm, Merck), 1–4.5 bar (CfG Pro Minent pump). GC: Varian 3700, SE 54 column (20 m). M.p.: uncorrected; Büchi 510. [α]_D²⁰: Perkin Elmer 241 polarimeter, c in g/100 ml. IR spectra: Nicolet-7199-FT-IR spectrophotometer; in cm^{–1}. ¹H-NMR, ¹³C-NMR, and ³¹P-NMR spectra: Bruker AS-250 (¹H(250 MHz)), Bruker HX-270 (¹H(270 MHz), ¹³C(62.9 MHz)), or Bruker WM-400 (¹H(400 MHz), ³¹P(162.0 MHz), ¹³C(100.62 MHz)); CDCl₃ solns. unless otherwise specified; δ values in ppm relative to tetramethylsilane (¹H- and ¹³C-NMR) as internal standard or H₃PO₄ (³¹P-NMR) as external reference; coupling constants (*J*) in Hz. MS: MS 9 updated with a Finnigan ZAB console, data system SS 200, VG Altrincham (EI: 70 eV); MM 7070 F, data system 2050, VG Altrincham (CI: NH₃); MS 902, fast-atom gun Kratos, data system 2050, VG Altrincham (FAB, Xe-atom 6 keV, thioglycerol matrix (Fluka)); *m/z* (intensity in % of base peak (100%)).

(2R,5S)- and (2S,5S)-2-(2-Bromoethylamino)-5-(octadecyloxymethyl)-1,3,2-oxazaphospholidin-2-ones (**8** and **9**, resp.). To a suspension of **6**¹⁾ (576 mg, 1.68 mmol) in abs. THF (17 ml) under Ar was added at r.t. abs. Et₃N (492 μl) followed by **7**²⁾ (404 mg, 1.68 mmol). After 4 h at r.t., the white precipitates were removed by filtration through a sintered glass funnel. Evaporation of the filtrate afforded a solid crude product (725 mg), which was purified by MPLC (CH₂Cl₂/MeOH 49:1→29:1) to give **8** (233 mg, 27%) and **9** (223 mg, 26%).

8: M.p. 98–100° (AcOEt), R_f (CHCl₃/MeOH 9:1) 0.55, $[\alpha]_D^{20} = -5.9^\circ$ ($c = 0.51$, THF). IR (KBr): 3226m (br.), 2919s, 2849s, 1468m, 1201m, 1123m, 1102m, 1078m, 720w. ¹H-NMR (400 MHz): 4.53 (m, 1 H); 3.67 (dd, $J = 10.5$, 6, 1 H); 3.55 (dd, $J = 10.5$, 5.5, 1 H); 3.51–3.31 (m, 9 H); 2.95 (m, 1 H); 1.56 (m, 2 H); 1.25 (m, 30 H); 0.88 (t, $J = 7$, 3 H). ³¹P-NMR: +28.15. MS: 512 (5, M^{++} with ⁸¹Br), 510 (5, M^{++} with ⁷⁹Br), 431 (8), 417 (8), 244 (30), 242 (31), 43 (100). Anal. calc. for C₂₃H₄₈BrN₂O₃P (511.53): C 54.01, H 9.46, Br 15.62, N 5.48; found: C 54.35, H 9.71, Br 15.56, N 5.28.

9: M.p. 106–108°, R_f (CHCl₃/MeOH 9:1) 0.50, $[\alpha]_D^{20} = -0.9^\circ$ ($c = 0.7$, THF). IR (KBr): 3273m (br.), 2917s, 2850s, 1471m, 1214s, 1125s, 717w. ¹H-NMR (400 MHz): 4.65 (m, 1 H); 3.67–3.32 (m, 11 H); 2.92 (m, 1 H); 1.58 (m, 2 H); 1.26 (m, 30 H); 0.88 (t, $J = 7$, 3 H). ³¹P-NMR: +29.09. MS: 512 (2, M^{++} with ⁸¹Br), 510 (2, M^{++} with ⁷⁹Br), 431 (18), 417 (56), 43 (100).

1-[2-[(2R,5S)-5-(Octadecyloxymethyl)-2-oxo-1,3,2-oxazaphospholidin-2-yl]amino]ethyl]pyridinium Bromide (10). A soln. of **8** (100 mg, 0.19 mmol) in pyridine (2 ml) was kept under Ar at 45°. After 30 h, the solvents were azeotropically evaporated with cyclohexane to give a tan solid product (82 mg), which was successively washed with hexane, AcOEt, and acetone. The remaining material was then dissolved in CH₂Cl₂, filtered, and the filtrate evaporated to give, after drying under h.v., **10** (19 mg, 16%) as a tan, hygroscopic powder. M.p. 145° (dec.), R_f (CHCl₃/MeOH/H₂O 60:35:5) 0.45. IR (KBr): 3248m, 2918s, 2849s, 1634m, 1488m, 1221m, 1126m, 1070m. ¹H-NMR (270 MHz): 9.43 (m, 2 H); 8.47 (m, 1 H); 8.13 (m, 2 H); 5.29 (m, 1 H); 4.98 (m, 2 H); 4.40 (m, 2 H); 3.76–3.0 (m, 8 H); 1.52 (m, 2 H); 1.25 (m, 30 H); 0.88 (t, $J = 7$, 3 H). ³¹P-NMR: +29.63. FAB-MS: 510 (M^{++} , cation).

1-[2-[(2S,5S)-5-(Octadecyloxymethyl)-2-oxo-1,3,2-oxazaphospholidin-2-yl]amino]ethyl]pyridinium Bromide (11). Treatment of **9** (227 mg, 0.44 mmol) in pyridine (5 ml) according to the procedure described above afforded **11** (88 mg, 33%) contaminated with traces of **10**. M.p. 120–125° (dec.), R_f (CHCl₃/MeOH/H₂O 60:35:5) 0.3. IR (KBr): 3238m, 2918s, 2849s, 1635m, 1488m, 1468m, 1219m, 1128m, 1069m. ¹H-NMR (400 MHz): 9.54–9.40 (m, 2 H); 8.49 (m, 1 H); 8.12 (m, 2 H); 5.23 (m, 1 H); 5.0–4.8 (m, 2 H); 4.6–4.3 (m, 2 H); 3.65–2.9 (m, 8 H); 1.52 (m, 2 H); 1.25 (m, 30 H); 0.88 (t, $J = 7$, 3 H). ³¹P-NMR: +29.48, +29.64 (small peak). FAB-MS: 510 (M^{++} , cation).

(2S,4S)-4-(Octadecyloxymethyl)-2-phenyl-1,3-dioxane (13). A soln. of **12** (8.2 g, 42.2 mmol) in xylene (130 ml) was heated to reflux in the presence of powdered KOH (4.74 g, 84.4 mmol). During 2 h, the H₂O was collected in a Dean-Stark trap. After cooling to 90°, a soln. of octadecyl methanesulfonate (15.0 g, 43.1 mmol) in xylene (90 ml) was added dropwise. The resulting mixture was stirred at 90° for 46 h, then cooled to r.t., partitioned between Et₂O/AcOEt 2:1 and 10% aq. NaCl soln. and extracted (4 × 100 ml). The combined org. extracts were washed with 10% aq. NaCl soln., dried over Na₂SO₄, and evaporated. Purification by FC (250 g SiO₂, hexane/AcOEt 9:1) gave **13** (12.8 g, 68%) as a white solid. M.p. 58–59°, R_f (hexane/AcOEt 4:1) 0.56, $[\alpha]_D^{20} = +0.67^\circ$ ($c = 0.6$, CHCl₃). IR (KBr): 2919s, 2849s, 1485w, 1125s, 1108s, 757m, 695m. ¹H-NMR (80 MHz): 7.55–7.2 (m, 5 H); 5.50 (br. s, 1 H); 4.3–3.3 (m, 7 H); 1.95–1.20 (m, 34 H); 0.88 (t, $J = 6$, 3 H). MS: 446 (24, M^{++}), 253 (10), 163 (100). Anal. calc. for C₂₉H₅₀O₃ (446.72): C 77.97, H 11.28; found: C 77.90, H 11.55.

(S)-4-(Octadecyloxy)butane-1,3-diol (14). A suspension of **13** (12.8 g, 28.7 mmol) in AcOH (560 ml) was warmed to 50° for 20 min. To the resulting soln. was added 10% Pd/C (0.6 g). Hydrogenation at 50° and normal pressure was complete within 20 min (1270 ml H₂). The catalyst was removed by filtration and the soln. evaporated. The residue was taken up in toluene (2 × 100 ml) and concentrated again to give 10.7 g of a colourless oil, which crystallized rapidly on standing. Recrystallization (AcOEt) afforded **14** (8.0 g, 78%). M.p. 60–61°, R_f (hexane/AcOEt) 0.11, $[\alpha]_D^{20} = +1.3^\circ$ ($c = 0.15$, CHCl₃). IR (KBr): 3410s, 2913s, 2848s, 1463m, 1125s, 1100m. ¹H-NMR (80 MHz): 3.82 (m, 3 H); 3.42 (m, 4 H); 2.25 (br. s, 2 H); 1.88–1.50 (m, 4 H); 1.25 (m, 30 H); 0.85 (t, $J = 6$, 3 H). MS: 358 (0, M^{++}), 283 (18), 252 (5), 75 (100). Anal. calc. for C₂₂H₄₆O₃ (358.61): C 73.69, H 12.93; found: C 73.63, H 12.78.

(2R,4S)- and (2S,4S)-2-(2-Bromoethoxy)-4-(octadecyloxymethyl)-1,3,2-dioxaphosphorinane 2-Oxides (16 and 17, resp.). General Procedure 1 (GP 1). To a soln. of **14** (1.80 g, 5 mmol) and Et₃N (1.46 ml, 10.5 mmol) in dry toluene (50 ml) was added POCl₃ (0.48 ml, 5.25 mmol). After stirring for 45 h at 50° under Ar, TLC showed a single new spot of **15**. The precipitates were removed by filtration under Ar. To the filtrate was added Et₃N (0.93 ml, 6.67 mmol), 2-bromoethanol (0.49 ml, 7 mmol), and Me₂NPy (6 mg). The resulting mixture was stirred at 50° under Ar for 48 h. The precipitates were filtered off, the filtrate evaporated, and the residue purified by chromatography (hexane/AcOEt 1:1) to give **16** (0.21 g, 8%) and **17** (0.93 g, 35%).

16: M.p. 43°, R_f (hexane/AcOEt 1:1) 0.36. IR (KBr): 2918s, 2849s, 1299m, 1127m, 1065m, 720w. ¹H-NMR (400 MHz): 4.65 (m, 1 H); 4.49–4.33 (m, 4 H); 3.61 (m, 1 H); 3.59 (t, $J = 6$, 2 H); 3.51 (m, 1 H); 3.48 (t, $J = 6.5$, 2 H); 2.09 (m, 1 H); 1.86 (m, 1 H); 1.56 (m, 2 H); 1.25 (m, 30 H); 0.88 (t, $J = 7$, 3 H). ¹³C-NMR (100.6 MHz): 79.1 (d, $J(P,C) = 7$); 72.6 (t, $J(P,C) = 11.7$); 72.1 (t); 68.1 (t, $J(P,C) = 7$); 66.4 (t, $J(P,C) = 5.3$); 31.9 (t); 30.2 (t); 30.1 (t);

29.7 (t); 29.6 (t); 29.5 (t); 29.4 (t); 29.3 (t); 28.6 (t); 26.0 (t); 22.7 (t); 14.1 (q). ^{31}P -NMR: -7.41 . MS: 529 (1, $M^{++} + 1$ with ^{81}Br), 527 (1, $M^{++} + 1$ with ^{79}Br), 447 (3), 277 (8), 275 (8), 54 (100).

17: M.p. 69° (hexane), R_f (hexane/AcOEt 1:1) 0.16. IR (KBr): 2918s, 2850s, 1272s, 1121m, 1069s, 1018s, 968s, 723w. ^1H -NMR (270 MHz): 4.73 (m, 1 H); 4.52–4.32 (m, 4 H); 3.61 (m, 2 H); 3.54 (t, $J = 6.5$, 2 H); 3.48 (t, $J = 6.5$, 2 H); 2.16 (m, 1 H); 2.03 (m, 1 H); 1.56 (m, 2 H); 1.25 (m, 30 H); 0.88 (t, $J = 7$, 3 H). ^{31}P -NMR: -5.66 . MS: 529 (< 1 , $M^{++} + 1$ with ^{81}Br), 527 (< 1 , $M^{++} + 1$ with ^{79}Br), 447 (4), 277 (10), 275 (10), 71 (100). Anal. calc. for $\text{C}_{24}\text{H}_{46}\text{BrO}_5\text{P}$ (527.52): C 55.11, H 9.29, Br 14.90; found: C 55.33, H 9.06, Br 15.07.

The intermediate (2*R*,4*S*)-2-chloro-4-(octadecyloxymethyl)-1,3,2-dioxaphosphorinane 2-oxide (**15**) might be isolated as a pale yellow foam upon simple concentration of a small part of the filtrate before addition of 2-bromoethanol. IR (KBr): 1301m, 1142m, 994m, 720w. ^1H -NMR (270 MHz): 4.68 (m, 1 H); 4.63–4.45 (m, 2 H); 3.65 (ddd, $J = 11$, 5, 2, 1 H); 3.55 (ddd, $J = 11$, 5.5, 2, 1 H); 3.48 (t, $J = 7$, 2 H); 2.31–1.88 (m, 2 H); 1.55 (m, 2 H); 1.25 (m, 30 H); 0.88 (t, $J = 6.5$, 3 H). MS: 440 (1, M^{++} with ^{37}Cl), 438 (2, M^{++} with ^{35}Cl), 189 (22), 187 (63), 71 (100).

(2*S*,4*S*)- and (2*R*,4*S*)-2-[3-(Dimethylamino)-phenoxy]-4-(octadecyloxymethyl)-1,3,2-dioxaphosphorinane 2-Oxides (**22** and **23**, resp.). The conversion of **14** (1.80 g, 5 mmol), POCl_3 (0.48 ml, 5.25 mmol), Et_3N (total amount 2.3 ml, 16.5 mmol), 3-(dimethylamino)phenol (686 mg, 5 mmol) and Me_2NPy (6 mg) in dry toluene (50 ml, then 75 ml) according to *GP 1* afforded, after chromatography with hexane/AcOEt 1:1, **22** (811 mg, 30%) and **23** (945 mg, 35%) as well as **26** (107 mg, 5%).

22: M.p. 63 – 64° (hexane), R_f (hexane/AcOEt 1:1) 0.43, $[\alpha]_D^{20} = -8.4^\circ$ ($c = 0.5$, CHCl_3). IR (KBr): 2805w, 1606s, 1574m, 1503s, 1291s, 1145s, 997s, 986s. ^1H -NMR (400 MHz): 7.16 (m, 1 H); 6.59 (m, 2 H); 6.51 (m, 1 H); 4.70 (m, 1 H); 4.53–4.40 (m, 2 H); 3.64 (ddd, $J = 10.5$, 5, 1.5, 1 H); 3.52 (ddd, $J = 10.5$, 5.5, 2, 1 H); 3.47 (t, $J = 6.5$, 2 H); 2.94 (br. s, 6 H); 2.15 (m, 1 H); 1.91 (m, 1 H); 1.55 (m, 2 H); 1.25 (m, 30 H); 0.88 (t, $J = 7$, 3 H). ^{13}C -NMR: 151.9 (s); 151.5 (s, $J(\text{P,C}) = 6.4$); 129.9 (d); 109.0 (d); 106.8 (d, $J(\text{P,C}) = 4.9$); 103.4 (d, $J(\text{P,C}) = 5.8$); 79.4 (d, $J(\text{P,C}) = 7.2$); 72.7 (t, $J(\text{P,C}) = 9.4$); 72.0 (t); 68.3 (t, $J(\text{P,C}) = 7.2$); 40.3 (q); 31.9 (t); 29.7 (t); 29.6 (t); 29.5 (t); 29.4 (t); 28.6 (t); 28.5 (t); 26.1 (t); 22.7 (t); 14.1 (q). ^{31}P -NMR: -12.95 . MS: 539 (100, M^{++}). Anal. calc. for $\text{C}_{30}\text{H}_{54}\text{NO}_5\text{P}$ (539.74): C 66.76, H 10.08, N 2.60; found: C 66.77, H 10.02, N 2.61.

23: M.p. 57 – 58° (hexane), R_f (hexane/AcOEt 1:1) 0.18, $[\alpha]_D^{20} = +13.0^\circ$ ($c = 1$, CHCl_3). IR (KBr): 2817w, 1606s, 1572m, 1507m, 1294s, 1073s, 998s. ^1H -NMR (400 MHz): 7.14 (m, 1 H); 6.57–6.48 (m, 3 H); 4.77 (m, 1 H); 4.57–4.43 (m, 2 H); 3.64 (ddd, $J = 10.5$, 5, 2, 1 H); 3.57 (ddd, $J = 10.5$, 6.5, 1, 1 H); 3.44 (t, $J = 7$, 2 H); 2.94 (br. s, 6 H); 2.18–2.02 (m, 2 H); 1.53 (m, 2 H); 1.25 (m, 30 H); 0.88 (t, $J = 7$, 3 H). ^{13}C -NMR (100.6 MHz): 151.8 (s); 151.7 (s, $J(\text{P,C}) = 7.1$); 129.7 (d); 109.2 (d); 107.5 (d, $J(\text{P,C}) = 4$); 104.1 (d, $J(\text{P,C}) = 5.5$); 78.3 (d, $J(\text{P,C}) = 6.9$); 71.9 (t); 71.8 (t, $J(\text{P,C}) = 6.7$); 66.9 (t, $J(\text{P,C}) = 8.2$); 40.4 (q); 31.9 (t); 29.7 (t); 29.6 (t); 29.5 (t); 29.4 (t); 27.7 (t); 27.6 (t); 26.1 (t); 22.7 (t); 14.1 (q). ^{31}P -NMR: -11.31 . MS: 539 (100, M^{++}). Anal. calc. for $\text{C}_{30}\text{H}_{54}\text{NO}_5\text{P}$ (539.74): C 66.76, H 10.08, N 2.60; found: C 66.74, H 10.16, N 2.60.

2,2'-Oxybis[4-(octadecyloxymethyl)-1,3,2-dioxaphosphorinane 2-Oxide] (**26**). M.p. 87 – 89° (Et_2O), R_f (hexane/AcOEt 1:1) 0.25. IR (KBr): 1313s, 1302s, 1142m, 1067s, 976s. ^1H -NMR (270 MHz): 4.88 (m, 2 H); 4.75 (m, 2 H); 4.52 (m, 2 H); 3.67–3.42 (m, 8 H); 2.20 (m, 2 H); 1.90 (m, 2 H); 1.55 (m, 4 H); 1.25 (m, 60 H); 0.88 (t, $J = 7$, 6 H). FAB-MS: 823 ($M^{++} + 1$).

(2*R*,4*S*)-4-(Octadecyloxymethyl)-2-[4-(pyridylmethyl)amino]-1,3,2-dioxaphosphorinane 2-Oxide (**27**). Treatment of **14** (7.0 g, 19.5 mmol) in toluene (2×200 ml) with POCl_3 (1.9 ml, 21 mmol), Et_3N (5.9 and 2.9 ml, 63 mmol), and 4-(aminomethyl)pyridine (2 ml, 20 mmol) according to *GP 1* gave, after FC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 19:1), **27** (5.65 g, 56%). M.p. 70 – 72° (hexane), R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) 0.46. $[\alpha]_D^{20} = -3.8^\circ$ ($c = 1$, CHCl_3). IR (KBr): 3196m, 1604m, 1563m, 1232s, 1126m, 1081s. ^1H -NMR (400 MHz): 8.55 (m, 2 H); 7.28 (m, 2 H); 4.75 (m, 1 H); 4.57 (m, 1 H); 4.32 (m, 1 H); 4.28 (m, 2 H); 3.54 (ddd, $J = 10.5$, 4.5, 2, 1 H); 3.48 (ddd, $J = 10.5$, 5, 1, 1 H); 3.43 (t, $J = 6.5$, 2 H); 3.40 (m, 1 H); 2.05 (m, 1 H); 1.80 (m, 1 H); 1.52 (m, 2 H); 1.25 (m, 30 H); 0.88 (t, $J = 7$, 3 H). ^{31}P -NMR: $+5.93$, $+3.24$ (very small peak). FAB-MS: 511 ($M^{++} + 1$). Anal. calc. for $\text{C}_{28}\text{H}_{51}\text{N}_3\text{O}_4\text{P}$ (510.70): C 65.85, H 10.07, N 5.49, P 6.07; found: C 65.58, H 10.14, N 5.32, P 5.91.

(2*R*,4*S*)-4-(Octadecyloxymethyl)-2-[3-(pyridylmethyl)amino]-1,3,2-dioxaphosphorinane 2-Oxide (**28**). Conversion of **14** (717 mg, 2 mmol), POCl_3 (0.19 ml, 2.1 mmol), Et_3N (0.59 and 0.29 ml, 6.3 mmol), and 3-(aminomethyl)pyridine (0.20 ml, 2 mmol) in toluene (total amount 35 ml) according to *GP 1* yielded, after MPLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1), **28** (709 mg, 69%). M.p. 60 – 62° , R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) 0.48. IR (KBr): 3212m, 1577w, 1242s, 1077s, 1055s. ^1H -NMR (270 MHz): 8.56 (m, 1 H); 8.52 (m, 1 H); 7.75 (m, 1 H); 7.28 (m, 1 H); 4.73 (m, 1 H); 4.56 (m, 1 H); 4.30 (m, 1 H); 4.18 (m, 2 H); 3.56 (ddd, $J = 10.5$, 4.5, 2, 1 H); 3.48 (m, 1 H); 3.44 (t, $J = 7$, 2 H); 3.42 (m, 1 H); 2.02 (m, 1 H); 1.81 (m, 1 H); 1.53 (m, 2 H); 1.25 (m, 30 H); 0.88 (t, $J = 7$, 3 H). ^{13}C -NMR (100.6 MHz): 148.9 (d); 148.8 (d); 135.2 (d); 134.9 (s); 123.4 (d); 76.4 (d, $J(\text{P,C}) = 5$); 72.8 (t, $J(\text{P,C}) = 10$); 71.9 (t); 65.9 (t, $J(\text{P,C}) = 6$); 41.9 (t); 31.9 (t); 29.7 (t); 29.6 (t); 29.5 (t); 29.4 (t); 28.6 (t); 28.5 (t); 26.1 (t); 22.7 (t); 14.1 (q).

^{31}P -NMR: +5.87, +3.25 (very small peak). MS: 510 (64, M^+), 242 (80), 43 (100). Anal. calc. for $\text{C}_{28}\text{H}_{51}\text{N}_2\text{O}_4\text{P}$ (510.70): C 65.85, H 10.07, N 5.49, P 6.07; found: C 65.92, H 10.62, N 5.47, P 6.18.

(2*R*,4*S*)-4-((Octadecyloxymethyl)-2-[(2-pyridylmethyl)amino]-1,3,2-dioxaphosphorinane 2-Oxide (29). Reaction of **14** (717 mg, 2 mmol) with POCl_3 (0.19 ml, 2.1 mmol), Et_3N (0.59 and 0.29 ml, 6.3 mmol), and 2-(aminomethyl)pyridine (0.20 ml, 2 mmol) in toluene (total amount 35 ml) according to GP 1 gave, after MPLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 49:1), **29** (325 mg, 32%). M.p. 82–83°, R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) 0.14, $[\alpha]_D^{20} = +6.0^\circ$ ($c = 1$, CHCl_3). IR (KBr): 3207*m*, 1591*w*, 1223*s*, 1122*s*, 1064*s*. ^1H -NMR (270 MHz): 8.54 (*m*, 1 H); 7.65 (*m*, 1 H); 7.36 (*m*, 1 H); 7.15 (*m*, 1 H); 4.74 (*m*, 1 H); 4.58 (*m*, 1 H); 4.38–4.23 (*m*, 3 H); 4.16 (*m*, 1 H); 3.57 (*ddd*, $J = 10.5, 4.5, 2, 1$ H); 3.48 (*m*, 1 H); 3.43 (*t*, $J = 6.5, 2$ H); 2.05 (*m*, 1 H); 1.82 (*m*, 1 H); 1.53 (*m*, 2 H); 1.25 (*m*, 30 H); 0.88 (*t*, $J = 7, 3$ H). ^{31}P -NMR: +6.04. MS: 510 (18, M^+), 242 (54), 70 (100). Anal. calc. for $\text{C}_{28}\text{H}_{51}\text{N}_2\text{O}_4\text{P}$ (510.70): C 65.85, H 10.07, N 5.49, P 6.07; found: C 65.55, H 10.16, N 5.25, P 5.63.

1-{2-[(2*R*,4*S*)-4-((Octadecyloxymethyl)-2-oxo-1,3,2-dioxaphosphorinan-2-yl)oxy]ethyl}pyridinium Bromide (18). A soln. of **16** (150 mg, 0.28 mmol) in pyridine (3 ml) was stirred at 50° under Ar. After 26 h, the solvents were evaporated. The residue was washed with AcOEt (2 $\times$) and recrystallized from acetone (2 $\times$) to give **18** (63 mg, 37%). M.p. 75° (dec. > 85°), R_f ($\text{CHCl}_3/\text{MeOH}/\text{H}_2\text{O}$ 60:35:5) 0.50. IR (KBr): 1634*m*, 1580*m*, 1292*s*, 995*s*, 965*s*. ^1H -NMR (270 MHz): 9.76 (*m*, 2 H); 8.48 (*m*, 1 H); 8.07 (*m*, 2 H); 5.55 (*m*, 2 H); 4.81–4.32 (*m*, 5 H); 3.62–3.42 (*m*, 4 H); 2.14 (*m*, 1 H); 1.85 (*m*, 1 H); 1.52 (*m*, 2 H); 1.25 (*m*, 30 H); 0.88 (*t*, $J = 7, 3$ H). FAB-MS: 526 (M^+ , cation). Anal. calc. for $\text{C}_{29}\text{H}_{53}\text{BrNO}_3\text{P}$ (606.62): C 57.42, H 8.81, N 2.31; found: C 57.24, H 8.72, N 2.06.

Treatment of **17** (150 mg, 0.28 mmol) in pyridine/ CH_3CN 1:1 (5 ml) with 4 Å-molecular sieves (0.5 g) in the same way as described above led to **19/18** 3:2 (35 mg, 20%). M.p. 25–30°. IR (KBr): 1634*m*, 1580*m*, 1289*s*, 965*s*. ^1H -NMR (270 MHz): 9.76, 9.62 (2*m*, ratio 2:3, 2 H); 8.50 (*m*, 1 H); 8.08 (*m*, 2 H); 5.60–5.38 (*m*, 2 H); 4.80–4.30 (*m*, 5 H); 3.63–3.41 (*m*, 4 H); 2.13 (*m*, 1 H); 1.90 (*m*, 1 H); 1.55 (*m*, 2 H); 1.25 (*m*, 30 H); 0.88 (*t*, $J = 7, 3$ H). FAB-MS: 526 (M^+ , cation).

Trimethyl-3-[(2*S*,4*S*)-4-((octadecyloxymethyl)-2-oxo-1,3,2-dioxaphosphorinan-2-yl)oxy]phenyl ammonium Iodide (24): General Procedure 2 (GP 2). A soln. of **22** (100 mg, 0.19 mmol) in CH_3I (5 ml) was kept at 50° under Ar for 96 h. The solvents were then evaporated. The solid residue was washed with hot hexane and dried under h.v. to give **24** (115 mg, 91%). M.p. 110° (> 129°, dec.). IR (KBr): 1604*m*, 1490*m*, 1236*m*, 968*s*. ^1H -NMR (400 MHz): 8.20 (br. *s*, 1 H); 7.79 (*m*, 1 H); 7.64 (*m*, 2 H); 5.10 (*m*, 1 H); 4.90 (*m*, 1 H); 4.53 (*m*, 1 H); 4.02 (br. *s*, 9 H); 3.63 (*m*, 2 H); 3.51 (*m*, 2 H); 2.24 (*m*, 1 H); 2.01 (*m*, 1 H); 1.55 (*m*, 2 H); 1.25 (*m*, 30 H); 0.88 (*t*, $J = 7, 3$ H). ^{13}C -NMR (100.6 MHz): 151.7 (*s*, $J(\text{P},\text{C}) = 5$); 148.0 (*s*); 132.0 (*d*); 122.1 (*d*); 116.5 (*d*); 113.4 (*d*, $J(\text{P},\text{C}) = 7$); 80.7 (*d*, $J(\text{P},\text{C}) = 7$); 72.4 (*t*, $J(\text{P},\text{C}) = 10$); 72.1 (*t*); 69.6 (*t*, $J(\text{P},\text{C}) = 7$); 57.9 (*q*); 31.9 (*t*); 29.7 (*t*); 29.6 (*t*); 29.5 (*t*); 29.4 (*t*); 27.9 (*t*); 27.8 (*t*); 26.1 (*t*); 22.7 (*t*); 14.1 (*q*). FAB-MS: 554 (M^+ , cation). Anal. calc. for $\text{C}_{31}\text{H}_{57}\text{INO}_3\text{P}$ (681.67): C 54.62, H 8.43, I 18.62, N 2.05; found: C 54.25, H 8.66, I 18.74, N 2.09.

Treatment of **23** (100 mg, 0.19 mmol) in CH_3I (5 ml) according to GP 2 led to a 3:1 mixture **25/24** (115 mg, 91%). M.p. 132–133°. ^1H -NMR (270 MHz): 8.20, 7.94 (2*m*, ratio 1:3, 1 H); 7.85, 7.79 (2*m*, ratio 3:1, 1 H); 7.63 (*m*, 1 H); 7.48 (*m*, 1 H); 5.10 (*m*, 0.25 H); 4.95–4.40 (*m*, 2.75 H); 4.02 (br. *s*, 9 H); 3.77–3.60 (*m*, 2 H); 3.47 (*m*, 2 H); 2.42–1.85 (*m*, 2 H); 1.55 (*m*, 2 H); 1.25 (*m*, 30 H); 0.88 (*t*, $J = 7, 3$ H). FAB-MS: 554 (M^+ , cation). Anal. calc. for $\text{C}_{31}\text{H}_{57}\text{INO}_3\text{P}$ (681.67): C 54.62, H 8.43, I 18.62, N 2.05; found: C 54.69, H 8.54, I 18.33, N 1.97.

1-Methyl-4-[(2*R*,4*S*)-4-((octadecyloxymethyl)-2'-oxo-1',3',2'-dioxaphosphorinan-2'-yl)amino]methylpyridinium Iodide (30). Conversion of **27** (1.5 g, 2.94 mmol) in CH_3I (30 ml) according to GP 2 (reaction time 1 h) gave, after recrystallization from acetone, **30** (1.65 g, 86%). M.p. 75° (dec.). IR (KBr): 3188*m*, 1643*m*, 1577*w*, 1519*w*, 1224*m*, 1069*s*. ^1H -NMR (270 MHz): 9.08 (*m*, 2 H); 8.09 (*m*, 2 H); 5.38 (*m*, 1 H); 4.75 (*m*, 1 H); 4.57 (br. *s*, 3 H); 4.50–4.28 (*m*, 4 H); 3.60 (*dd*, $J = 10.5, 5, 1$ H); 3.49 (*m*, 1 H); 3.46 (*t*, $J = 6.5, 2$ H); 2.14–1.78 (*m*, 3 H); 1.55 (*m*, 2 H); 1.25 (*m*, 30 H); 0.88 (*t*, $J = 7, 3$ H). ^{31}P -NMR: +5.44, +3.08 (very small peak). FAB-MS: 525 (M^+ , cation). Anal. calc. for $\text{C}_{29}\text{H}_{54}\text{IN}_2\text{O}_4\text{P}$ (652.64): C 53.37, H 8.34, N 4.29, P 4.75; found: C 52.84, H 8.35, N 4.49, P 4.85.

1-Methyl-3-[(2*R*,4*S*)-4-((octadecyloxymethyl)-2'-oxo-1',3',2'-dioxaphosphorinan-2'-yl)amino]methylpyridinium Iodide (31). From **28** (511 mg, 1 mmol) and CH_3I (5 ml), **31** (580 mg, 89%) was obtained according to GP 2 (reaction time 90 min). M.p. 57° (acetone, dec.). R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) 0.17, $[\alpha]_D^{20} = +6^\circ$ ($c = 1$, CHCl_3). IR (KBr): 3244*m*, 1636*m*, 1507*m*, 1241*s*, 1066*s*. ^1H -NMR (400 MHz): 9.23 (br. *s*, 1 H); 9.00 (*m*, 1 H); 8.55 (*m*, 1 H); 8.06 (*m*, 1 H); 5.42 (*m*, 1 H); 4.74 (*m*, 1 H); 4.54 (br. *s*, 3 H); 4.50–4.32 (*m*, 4 H); 3.61 (*m*, 1 H); 3.52 (*m*, 1 H); 3.47 (*t*, $J = 7, 2$ H); 2.10 (*m*, 1 H); 1.82 (*m*, 1 H); 1.54 (*m*, 2 H); 1.25 (*m*, 30 H); 0.88 (*t*, $J = 7, 3$ H). ^{13}C -NMR (100.6 MHz): 144.7 (*d*); 144.5 (*d*); 143.7 (*d*); 141.6 (*s*); 127.8 (*d*); 76.8 (*d*, $J(\text{P},\text{C}) = 5$); 72.9 (*t*, $J(\text{P},\text{C}) = 10$); 71.9 (*t*); 66.4 (*t*); 49.4 (*q*); 41.7 (*t*); 31.9 (*t*); 29.7 (*t*); 29.5 (*t*); 29.4 (*t*); 26.1 (*t*); 22.7 (*t*); 14.1 (*q*). ^{31}P -NMR: +5.42, +3.09 (very small peak). FAB-MS: 525 (M^+ , cation). Anal. calc. for $\text{C}_{29}\text{H}_{54}\text{IN}_2\text{O}_4\text{P}$ (652.64): C 53.37, H 8.34, I 19.44, N 4.29; found: C 53.26, H 8.69, I 19.15, N 4.15.

1-Methyl-2- $\{[(2'R,4'S)-4'-(octadecyloxymethyl)-2'-oxo-1',3',2'-dioxaphosphorinan-2'-yl]amino\}$ methyl}-pyridinium Iodide (**32**). Reaction of **29** (217 mg, 0.42 mmol) in CH_3I (4 ml) according to GP 2 afforded **32** (153 mg, 55%). M.p. 58° (acetone, dec.). IR (KBr): 3181m, 1631m, 1514w, 1245s, 1067s. $^1\text{H-NMR}$ (270 MHz): 9.09 (m, 1 H); 8.46 (m, 1 H); 8.33 (m, 1 H); 7.95 (m, 1 H); 5.23 (m, 1 H); 4.75 (m, 3 H); 4.58–4.30 (m, 2 H); 4.50 (br. s, 3 H); 3.63 (m, 1 H); 3.50 (m, 1 H); 3.46 (t, $J = 6.5$, 2 H); 2.16 (m, 1 H); 1.88 (m, 1 H); 1.55 (m, 2 H); 1.25 (m, 30 H); 0.88 (t, $J = 7$, 3 H). $^{31}\text{P-NMR}$: +5.14, +2.54 (very small peak). FAB-MS: 525 (M^{++} , cation).

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