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

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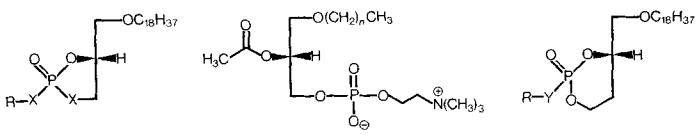
The synthesis of the five-membered cyclic phosphorodiamidic-acid derivatives **10** and **11** as well as the preparation of the six-membered cyclic phosphates **18**, **19**, **22**–**25**, and phosphoramidates **27**–**32** is described. The effects of these conformationally restricted platelet-activating 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].



2 X = O
3 X = NH

1 $n = 15, 17$

4 Y = O
5 Y = NH

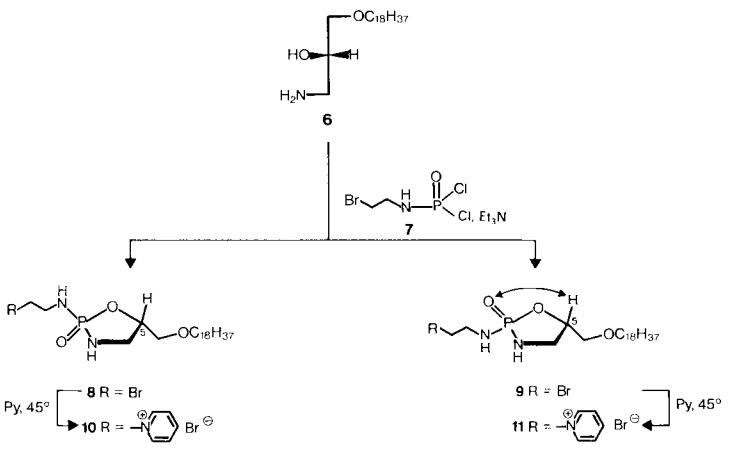
R = –[alkyl, aryl]–$\overset{\oplus}{N}$ $Z^{\ominus}$ with Z = Br, I

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)* NaN_3, DMF; *iii)* H_2, 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 Et_3N 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 ^{1}H-NMR signal for H–C(5) in **9** appears at 4.65 ppm, while the corresponding proton in **8** resonates at 4.53 ppm.

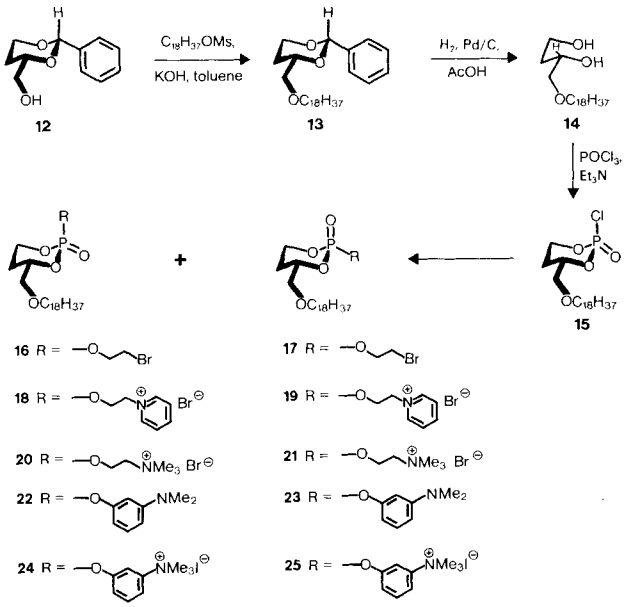
Introduction of a positively charged N-function could be achieved by conversion of each diastereoisomer **8** and **9**, in low yield, to the hygroscopic pyridinium salts **10** and **11**, respectively, which turned out to be quite difficult to isolate. The ^{31}P-NMR spectrum of **11** showed the presence 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 $POCl_3$ and Et_3N 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/Et_3N/4-(dimethylamino)pyridine (Me_2NPy) 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 ^{31}P-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

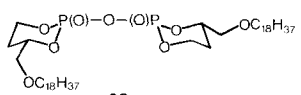
[2]) This compound was available by heating 2-aminoethyl bromide hydrobromide in $POCl_3$ according to a protocol developed for the preparation of the corresponding 2-chloroethyl derivative [29].

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 Et_3N/Me_2NPy, a 1:1 mixture[4]) of the two diastereoisomers **22** and **23** was formed, together with a small amount of the anhydride **26**. Chromatographic separation



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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-

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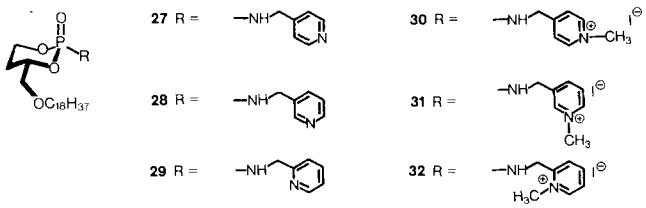
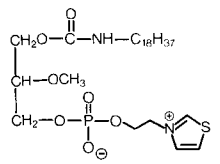
[3]) All attempts to prepare the choline derivatives **20** and **21**, starting either from **16** and **17** or directly from **15**, failed.

[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 prepared[5]). Treatment of **15**, formed *in situ* from diol **14**, with either 2-, 3-, or 4-(aminomethyl)pyridine in the presence of Et_3N/Me_2NPy proceeded with inversion at the P-atom leading almost exclusively to the equatorial intermediates **27–29**. Methylation (CH_3I, 43°) then gave the corresponding pyridinium salts **30–32**, whose ^{31}P-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



33 (CV-3988)

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 IC_{50} 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).

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[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]) IC_{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.* $POCl_3$ *(Fluka)* was destilled 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* F_{254} *(Merck);* detection by UV (254 nm), by I_2 vapor, or by spraying with 50% H_2SO_4/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*. $[\alpha]_D^{20}$: *Perkin Elmer 241* polarimeter, *c* in g/100 ml. IR spectra: *Nicolet-7199-FT-IR* spectrophotometer; in cm^{-1}. ^{1}H-NMR, ^{13}C-NMR, and ^{31}P-NMR spectra: *Bruker AS-250* (^{1}H(250 MHz)), *Bruker HX-270* (^{1}H(270 MHz), ^{13}C(62.9 MHz)), or *Bruker WM-400* (^{1}H(400 MHz), ^{31}P(162.0 MHz), ^{13}C(100.62 MHz)); $CDCl_3$ solns. unless otherwise specified; δ values in ppm relative to tetramethylsilane (^{1}H- and ^{13}C-NMR) as internal standard or H_3PO_4(^{31}P-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: NH_3); *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. Et_3N (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 (CH_2Cl_2/MeOH 49:1→29:1) to give **8** (233 mg, 27%) and **9** (223 mg, 26%).

8: M.p. 98–100° (AcOEt), R_f ($CHCl_3$/MeOH 9:1) 0.55, $[\alpha]_D^{20} = -5.9°$ ($c = 0.51$, THF). IR (KBr): 3226*m* (br.), 2919*s*, 2849*s*, 1468*m*, 1201*m*, 1123*m*, 1102*m*, 1078*m*, 720*w*. ^{1}H-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). ^{31}P-NMR: +28.15. MS: 512 (5, $M^{+\cdot}$ with ^{81}Br), 510 (5, $M^{+\cdot}$ with ^{79}Br), 431 (8), 417 (8), 244 (30), 242 (31), 43 (100). Anal. calc. for $C_{23}H_{48}BrN_2O_3P$ (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 ($CHCl_3$/MeOH 9:1) 0.50, $[\alpha]_D^{20} = -0.9°$ ($c = 0.7$, THF). IR (KBr): 3273*m* (br.), 2917*s*, 2850*s*, 1471*m*, 1214*s*, 1125*s*, 717*w*. ^{1}H-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). ^{31}P-NMR: +29.09. MS: 512 (2, $M^{+\cdot}$ with ^{81}Br), 510 (2, $M^{+\cdot}$ with ^{79}Br), 431 (18), 417 (56), 43 (100).

*1-{2-[((2*R*,5*S*)-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 solide product (82 mg), which was successively washed with hexane, AcOEt, and acetone. The remaining material was then dissolved in CH_2Cl_2, 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 ($CHCl_3$/MeOH/H_2O 60:35:5) 0.45. IR (KBr): 3248*m*, 2918*s*, 2849*s*, 1634*m*, 1488*m*, 1221*m*, 1126*m*, 1070*m*. ^{1}H-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). ^{31}P-NMR: +29.63. FAB-MS: 510 ($M^{+\cdot}$, cation).

*1-{2-[((2*S*,5*S*)-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 ($CHCl_3$/MeOH/H_2O 60:35:5) 0.3. IR (KBr): 3238*m*, 2918*s*, 2849*s*, 1635*m*, 1488*m*, 1468*m*, 1219*m*, 1128*m*, 1069*m*. ^{1}H-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). ^{31}P-NMR: +29.48, +29.64 (small peak). FAB-MS: 510 ($M^{+\cdot}$, cation).

*(2*S*,4*S*)-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 H_2O 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 Et_2O/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 Na_2SO_4, and evaporated. Purification by FC (250 g SiO_2, 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, $[\alpha]_D^{20} = +0.67°$ ($c = 0.6$, $CHCl_3$). IR (KBr): 2919*s*, 2849*s*, 1485*w*, 1125*s*, 1108*s*, 757*m*, 695*m*. ^{1}H-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, $M^{+\cdot}$), 253 (10), 163 (100). Anal. calc. for $C_{29}H_{50}O_3$ (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 H_2). 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, $[\alpha]_D^{20} = +1.3$ ($c = 0.15$, $CHCl_3$). IR (KBr): 3410*s*, 2913*s*, 2848*s*, 1463*m*, 1125*s*, 1100*m*. ^{1}H-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, $M^{+\cdot}$), 283 (18), 252 (5), 75 (100). Anal. calc. for $C_{22}H_{46}O_3$ (358.61): C 73.69, H 12.93; found: C 73.63, H 12.78.

*(2*R*,4*S*)- and (2*S*,4*S*)-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 Et_3N (1.46 ml, 10.5 mmol) in dry toluene (50 ml) was added $POCl_3$ (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 Et_3N (0.93 ml, 6.67 mmol), 2-bromoethanol (0.49 ml, 7 mmol), and Me_2NPy (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): 2918*s*, 2849*s*, 1299*m*, 1127*m*, 1065*m*, 720*w*. ^{1}H-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). ^{13}C-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, $M^{+\cdot}$ + 1 with ^{81}Br), 527 (1, $M^{+\cdot}$ + 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): 2918*s*, 2850*s*, 1272*s*, 1121*m*, 1069*s*, 1018*s*, 968*s*, 723*w*. ^{1}H-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, $M^{+\cdot}$ + 1 with ^{81}Br), 527 (< 1, $M^{+\cdot}$ + 1 with ^{79}Br), 447 (4), 277 (10), 275 (10), 71 (100). Anal. calc. for $C_{24}H_{48}BrO_5P$ (527.52)·0.1 C_6H_{14}: C 55.11, H 9.29, Br 14.90; found: C 55.33, H 9.06, Br 15.07.

The intermediate *(2R,4S)-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): 1301*m*, 1142*m*, 994*m*, 720*w*. ^{1}H-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, $M^{+\cdot}$ with ^{37}Cl), 438 (2, $M^{+\cdot}$ with ^{35}Cl), 189 (22), 187 (63), 71 (100).

(2S,4S)- and (2R,4S)-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° (*c* = 0.5, $CHCl_3$). IR (KBr): 2805*w*, 1606*s*, 1574*m*, 1503*s*, 1291*s*, 1145*s*, 997*s*, 986*s*. ^{1}H-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*(P,C) = 6.4); 129.9 (*d*); 109.0 (*d*); 106.8 (*d*, *J*(P,C) = 4.9); 103.4 (*d*, *J*(P,C) = 5.8); 79.4 (*d*, *J*(P,C) = 7.2); 72.7 (*t*, *J*(P,C) = 9.4); 72.0 (*t*); 68.3 (*t*, *J*(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, $M^{+\cdot}$). Anal. calc. for $C_{30}H_{54}NO_5P$ (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° (*c* = 1, $CHCl_3$). IR (KBr): 2817*w*, 1606*s*, 1572*m*, 1507*m*, 1294*s*, 1073*s*, 998*s*. ^{1}H-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*(P,C) = 7.1); 129.7 (*d*); 109.2 (*d*); 107.5 (*d*, *J*(P,C) = 4); 104.1 (*d*, *J*(P,C) = 5.5); 78.3 (*d*, *J*(P,C) = 6.9); 71.9 (*t*); 71.8 (*t*, *J*(P,C) = 6.7); 66.9 (*t*, *J*(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, $M^{+\cdot}$). Anal. calc. for $C_{30}H_{54}NO_5P$ (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): 1313*s*, 1302*s*, 1142*m*, 1067*s*, 976*s*. ^{1}H-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 ($M^{+\cdot}$ + 1).

(2R,4S)-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 (CH_2Cl_2/MeOH 19:1), **27** (5.65 g, 56%). M.p. 70–72° (hexane), R_f (CH_2Cl_2/MeOH 9:1) 0.46. $[\alpha]_D^{20}$ = –3.8° (*c* = 1, $CHCl_3$). IR (KBr): 3196*m*, 1604*m*, 1563*m*, 1232*s*, 1126*m*, 1081*s*. ^{1}H-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 ($M^{+\cdot}$ + 1). Anal. calc. for $C_{28}H_{51}N_2O_4P$ (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.

(2R,4S)-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 (CH_2Cl_2/MeOH 10:1), **28** (709 mg, 69%). M.p. 60–62°, R_f (CH_2Cl_2/MeOH 9:1) 0.48. IR (KBr): 3212*m*, 1577*w*, 1242*s*, 1077*s*, 1055*s*. ^{1}H-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*(P,C) = 5); 72.8 (*t*, *J*(P,C) = 10); 71.9 (*t*); 65.9 (*t*, *J*(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, $M^{+\cdot}$), 242 (80), 43 (100). Anal. calc. for $C_{28}H_{51}N_2O_4P$ (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.

(2R,4S)-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 (CH_2Cl_2/MeOH 49:1), **29** (325 mg, 32%). M.p. 82–83°, R_f (CH_2Cl_2/MeOH 9:1) 0.14, $[\alpha]_D^{20}$ = +6.0° (*c* = 1, $CHCl_3$). IR (KBr): 3207*m*, 1591*w*, 1223*s*, 1122*s*, 1064*s*. ^{1}H-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, $M^{+\cdot}$), 242 (54), 70 (100). Anal. calc. for $C_{28}H_{51}N_2O_4P$ (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-[(2R,4S)-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×) and recrystallized from acetone (2×) to give **18** (63 mg, 37%). M.p. 75° (dec. > 85°), R_f ($CHCl_3$/MeOH/H_2O 60:35:5) 0.50. IR (KBr): 1634*m*, 1580*m*, 1292*s*, 995*s*, 965*s*. ^{1}H-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 ($M^{+\cdot}$, cation). Anal. calc. for $C_{29}H_{53}BrNO_5P$ (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*. ^{1}H-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 ($M^{+\cdot}$, cation).

Trimethyl{3-[(2S,4S)-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° unter 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*, 1224*m*, 968*s*. ^{1}H-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*(P,C) = 5); 148.0 (*s*); 132.0 (*d*); 122.1 (*d*); 116.5 (*d*); 113.4 (*d*, *J*(P,C) = 7); 80.7 (*d*, *J*(P,C) = 7); 72.4 (*t*, *J*(P,C) = 10); 72.1 (*t*); 69.6 (*t*, *J*(P,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 ($M^{+\cdot}$, cation). Anal. calc. for $C_{31}H_{57}INO_5P$ (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°. ^{1}H-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 ($M^{+\cdot}$, cation). Anal. calc. for $C_{31}H_{57}INO_5P$ (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]methyl}-pyridinium 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*. ^{1}H-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 ($M^{+\cdot}$, cation). Anal. calc. for $C_{29}H_{54}IN_2O_4P$ (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]methyl}-pyridinium 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 (CH_2Cl_2/MeOH 9:1) 0.17, $[\alpha]_D^{20}$ = +6° (*c* = 1, $CHCl_3$). IR (KBr): 3244*m*, 1636*m*, 1507*m*, 1241*s*, 1066*s*. ^{1}H-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*(P,C) = 5); 72.9 (*t*, *J*(P,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 ($M^{+\cdot}$, cation). Anal. calc. for $C_{29}H_{54}IN_2O_4P$ (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): 3181*m*, 1631*m*, 1514*w*, 1245*s*, 1067*s*. ^{1}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}P-NMR: +5.14, +2.54 (very small peak). FAB-MS: 525 ($M^{+\cdot}$, cation).

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