Chemistry of Natural Compounds, Bioorganic, and Biomolecular Chemistry

Derivatives of dolichyl phosphate with fluorescent label. Analogs of dolichyl phosphate with different lengths of isoprene chain, containing the (1-naphthyl)amino group in the ω-fragment

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A series of fluorescent dolichyl phosphates containing the (1-naphthyl)amino group in the ω-fragment of the chain and possessing a definite distance between fluorophoric and phosphate groups were synthesized for studying the interactions of dolichyl phosphates with enzymes and biological membranes. The corresponding terminal 2,3-dihydrohexadeca-, 2,3-dihydroundeca-, and 2,3-dihydrooctaprenol epoxides were obtained from racemic dolichols (prepared from natural polyprenol mixtures) by van Tamelen epoxidation of their ω-isoprene unit and separated by preparative HPLC. These epoxides were converted to aldehydes, which were subjected to reductive amination with 1-aminonaphthalene and $NaBH_4$ with subsequent phosphorylation of the resulting amino alcohols.

Key words: dolichyl phosphate, (±)-dolichols, fluorescent label, van Tamelen epoxidation, reductive amination of aldehydes, 1-aminonaphthalene, phosphorylation.

In the present work, we continue our previous investigations in the synthesis of dolichyl phosphate derivatives containing fluorophores. Such compounds are of considerable interest for elucidation of the molecular mechanisms of interactions of dolichyl phosphates with biological membrane constituents and enzymes involved in the assembly of carbohydrate chains of glycoproteins.

Earlier,[1] we reported the transformation of a mixture of oligomer-homologs of dolichols into dolichyl phosphates containing fluorescent (2-pyridyl)amino (**1**) and (1-naphthyl)amino (**2**) groups at the ω-isoprene unit of the oligoisoprene chain (Scheme 1). A detailed synthesis of 2-aminopyridine derivatives **1** was published later.[2] The starting compound for the synthesis of phosphates **1** and **2** was a mixture of racemic dolichols **3a** (R = H) prepared from easily accessible polyprenols of pine needles.[3]

Biochemical investigations[1,4] revealed that phosphates **1** and **2** are effective substrates for an enzyme catalyzing the synthesis of dolichyl mannosyl phosphate, an impor-

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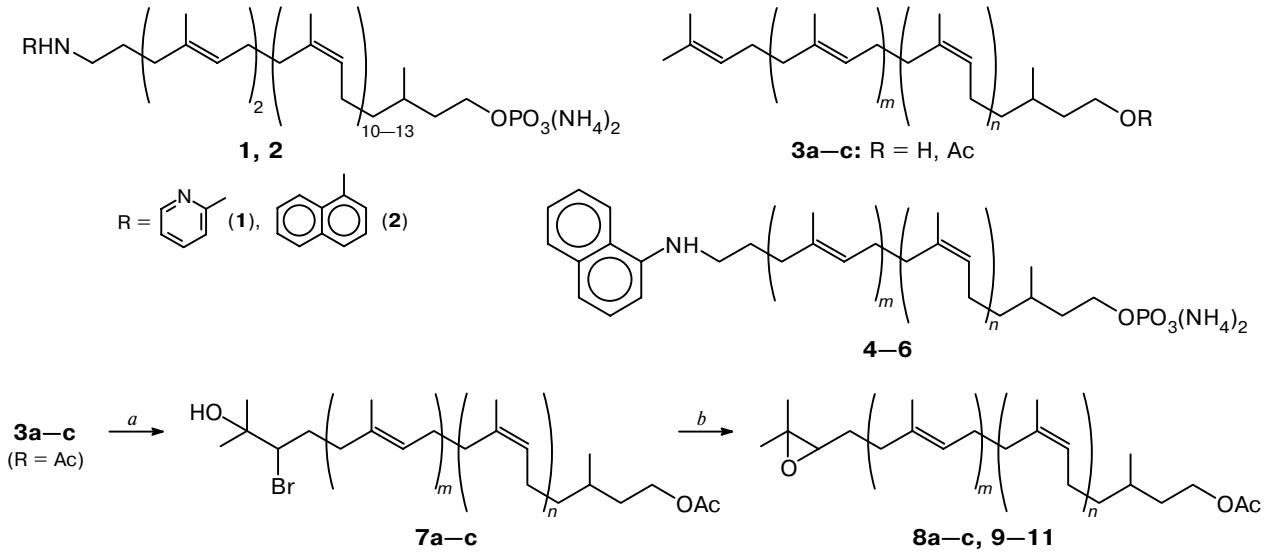
Scheme 1



3, 7, 8: m = 2, n = 10—13 (**a**); m = 3, n = 6, 7 (**b**); m = 2, n = 3, 4 (**c**);
4, 9: m = 2, n = 12; **5, 10:** m = 3, n = 6; **6, 11:** m = 2, n = 4

Reagents and conditions: *a*. NBS/THF—water, 25 °C; *b*. K_2CO_3/MeOH.

tant intermediate in the biosynthesis of carbohydrate chains of glycoproteins. Then, it was demonstrated that these fluorescent analogs of dolichyl phosphate can be used to study the topology of enzyme-substrate complexes *via* a resonance transfer of fluorescence energy. Fluorescent derivatives **2** containing the (1-naphthyl)amino group (fluorescence excitation and emission maxima are at 340 and 410 nm, respectively, in *n*-heptane—propan-2-ol, 4 : 1) were found to be significantly more convenient for such investigations than 2-aminopyridine derivatives **1** (fluorescence excitation and emission maxima are at 315 and 360 nm, respectively, under the same conditions). A series of dolichyl phosphates that contain 1-aminonaphthalene group and are homogeneous in chain length but differ in the number of inner isoprene units were necessary for more detailed studies on the structures of enzyme-substrate complexes.

The present work is devoted to the synthesis of three dolichyl phosphate derivatives **4**—**6** that meet the aforesaid requirements. Some data on the preparation of compound **4** were published earlier.[1]

Phosphates **4**—**6** were synthesized from the aforementioned dolichols **3a** (R = H) and from racemic alcohols **3b** (R = H) and **3c** (R = H) prepared,[5] like a mixture of homologs **3a**,[3] from relatively easily accessible plant polyprenols.

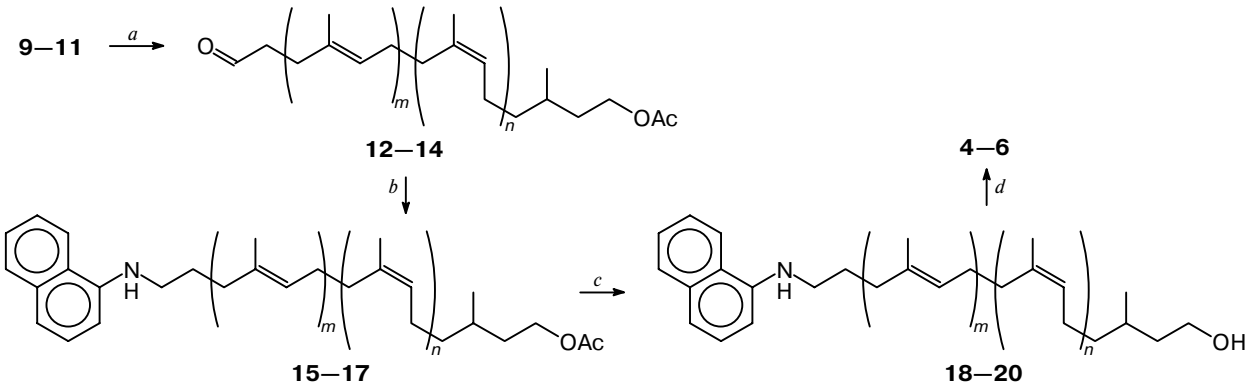
Oligoolefins **3b,c** (R = Ac)[5] were subjected to van Tamelen epoxidation[6]—as was described previously for a mixture of (±)-dolichyl acetates **3a** (R = Ac),[1,2]—to give, through labile bromohydrins **7b,c**, mixtures of the corresponding terminal epoxides **8b,c** in preparatively acceptable yields. According to HPLC data, they are virtually identical in the content of homologs to the starting alcohols **3a**—**c** (and to natural polyprenols used for their preparation[3,5]), as was noted before for racemic epoxides **8a**.[1,2]

Preparative HPLC separation of these mixtures and an earlier described[1,2] mixture of epoxides **8a** proved to be convenient for isolation of individual epoxides. The major components of the mixtures (**9**—**11**, respectively) were used for subsequent synthesis of target derivatives of homogeneous dolichyl phosphates **4**—**6** (Scheme 2). Under the conditions described earlier[1,2] for related epoxides, compounds **9**—**11** were converted by the action of $HIO_4 \cdot 2H_2O$ to the corresponding terminal aldehydes **12**—**14**. For the conversion of the latter into aminoacetates **15**—**17**, a two-step procedure was found to be optimal. First, aldehydes were treated with 1-aminonaphthalene and then, after keeping them for a period of time sufficient for the quantitative formation of very labile α-naphthylimines, treated with $NaBH_4$ *in situ* (*cf.* Ref. 1).

At the final stage of the synthesis of the target products, acetates **15**—**17** were hydrolyzed to alcohols **18**—**20**. The latter were phosphorylated with $(Bu_4N)H_2PO_4/CCl_3CN$, *i.e.*, a highly efficient procedure well known for the synthesis of polyprenyl and dolichyl phosphates was used.[7,8] As shown in our previous studies,[1,2] it is also applicable to the synthesis of amino alcohol phosphates. Phosphates **4**—**6** were isolated as ammonium salts after anion-exchange chromatography on DEAE cellulose (AcO^-) with elution by methanolic $AcONH_4$ and removal of an excess of $AcONH_4$ by its precipitation with toluene.

The structures of new compounds **4**—**6**, **7b,c**, **8b,c**, and **9**—**20** were confirmed by an aggregate of physico-

Scheme 2



12, 15, 18: $m = 2$, $n = 12$; **13, 16, 19:** $m = 3$, $n = 6$; **14, 17, 20:** $m = 2$, $n = 4$

Reagents and conditions: *a*. $HIO_4 \cdot 2H_2O$/THF, 20 °C; *b*. 1) 1-aminonaphthalene, 3 Å molecular sieves/Et_2O, 20 °C, 2) $NaBH_4/Et_2O$—MeOH, 20 °C; *c*. K_2CO_3/MeOH—PhH, 20 °C; *d*. $(Bu_4N)H_2PO_4/CCl_3CN/CH_2Cl_2$, 20 °C.

chemical data. Their ^1H and ^{13}C NMR spectra show signals characteristic of linear oligomeric isoprenoids containing (*E*)- and (*Z*)-isoprene fragments and an α-dihydroisoprene unit and signals corresponding to the functional groups in the ω- and α-fragments of the chain. IR data correspond to the structures suggested for these compounds. The final products, phosphates **4**—**6**, were also characterized by electrospray ionization (ESI) mass spectra; the main peaks in the spectra correspond to the molecular ions of the respective acids.

The fluorescent derivatives of dolichyl phosphates with differently spaced phosphate group and fluorophore, which were synthesized in the present work, and dolichyl phosphates with the (1-naphthyl)amino group attached to the γ-isoprene monomer of the chain, which were obtained in a parallel study,[9,10] are of considerable interest while elucidating the mechanisms of interaction of dolichyl phosphates with biological membrane constituents and enzymes involved in the assembly of the carbohydrate chains of glycoproteins.

Experimental

IR spectra were recorded on a Specord M-80 instrument. UV spectra were recorded on a Specord UV-VIS spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 and Bruker DRX-500 spectrometers in $CDCl_3$. ^{31}P NMR spectra were recorded on the latter instrument with 85% H_3PO_4 as the external standard. ESI mass spectra were obtained on a triple quadrupole API III mass spectrometer (PE-Sciex, Canada).

The R_f values are given for a fixed SiO_2 layer (Silufol) for nonphosphorylated compounds or on a fixed Silica gel 60 layer (Merck, Germany) for phosphates. Column chromatography used Silica gel 60 (≤0.063 mm, Fluka). Preparative HPLC resolution was performed in a column 240×24 mm on Silasorb C-8 (10 μm) in acetone—MeCN (1 : 1 for racemic epoxides **8a** and 3 : 7 for racemic epoxides **8b,c**; 7 mL min^{-1}) with refractometric detection.

Anion-exchange column chromatography of the phosphates was carried out on DEAE cellulose DE-52 (Whatman, England). The methods for detection and quantitative determination of phosphates were described earlier.[2]

Fluka reagents were used (NBS, $HIO_4 \cdot 2H_2O$, $NaBH_4$, and $(Bu_4N)H_2PO_4$). All solvents were purified according to standard procedures before use.

Bromohydrins 7b. NBS (0.8 g, 4.49 mmol) was added portionwise at 10 °C over 20 min to a stirred solution of a mixture of acetates **3b** (R = Ac) (2.65 g, ~3.3 mmol) in 33 mL of THF and 6 mL of water. The reaction mixture was kept for 2.5 h and then diluted with 100 mL of $MeOBu^t$. The organic layer was separated, washed with water and brine, dried with Na_2SO_4, and concentrated *in vacuo*. The residue (~3 g) was chromatographed on SiO_2 (70 g) eluting with CH_2Cl_2—$MeOBu^t$ (4 : 1). The yield of a mixture of bromohydrins **7b** was 1.23 g (41.5%), colorless oil, R_f 0.38 (hexane—Et_2O, 4 : 1). IR, ν/cm^{-1}: 850, 1050, 1260, 1340, 1380, 1450, 1730, 2740—3040, 3550. ^1H NMR, δ: 0.92 (d, MeC(3), J = 6.0 Hz); 1.10—1.90 (m, $C(2)H_2$, C(3)H, $C(4)H_2$, CH_2CBr); 1.30 and 1.31 (both s, Me_2CO); 1.61 (br.s, *cis*-MeC=C); 1.70 (br.s, *trans*-MeC=C); 1.90—2.30 (m, CH_2C=C); 2.10 (s, MeCOO); 3.96 (br.d, HCBr, J = 10.8 Hz); 4.10 (br.t, CH_2O, J = 7.1 Hz); 5.00—5.25 (m, HC=).

Bromohydrins 7c. Compound **7c** (~4 g) was obtained analogously from a mixture of acetates **3c** (R = Ac) (3.9 g, ~6.4 mmol) in 55 mL of THF and 9 mL of water and NBS (1.2 g, 6.74 mmol). The product was chromatographed on SiO_2 (100 g) with gradient elution ($CH_2Cl_2 \rightarrow MeOBu^t$, up to 20% of the latter) to give a mixture of the starting acetates **2b** (1 g) and a mixture of bromohydrins **7c** (1.65 g, 49%) as colorless oil, R_f 0.25 (hexane—Et_2O, 4 : 1). IR, ν/cm^{-1}: 840, 960, 1050, 1110, 1170, 1250, 1340, 1370, 1450, 1620, 1730, 2740—3040, 3550. ^1H NMR, δ: 0.91 (d, MeC(3), J = 6.1 Hz); 1.10—1.85 (m, $C(2)H_2$, C(3)H, $C(4)H_2$, CH_2CBr); 1.31 and 1.32 (both s, Me_2CO); 1.60 (br.s, *cis*-MeC=C); 1.68 (br.s, *trans*-MeC=C); 1.90—2.35 (m, CH_2C=C); 2.11 (s, MeCOO); 3.92 (br.d, HCBr, J = 11.1 Hz); 4.10 (br.t, CH_2O, J = 7.2 Hz); 5.00—5.20 (m, HC=).

Epoxides (8b) and 3,7,11,15,19,23,27,31,35,39,43-undecamethyl-42,43-epoxytetratetraconta-6*Z*,10*Z*,14*Z*,18*Z*,22*Z*,26*Z*,30*E*,34*E*,38*E*-nonaen-1-yl acetate (10). Potassium carbonate (0.05 g, 0.36 mmol) was added at 20 °C to a stirred (Ar) solution of a mixture of bromohydrins **7b** (0.3 g, ~0.3 mmol) in 4 mL of benzene and 2 mL of MeOH. The reaction mixture was kept for 20 min, diluted with 10 mL of

MeOBu^t, washed with water and brine, dried with Na_2SO_4, and concentrated *in vacuo*. The residue (~0.3 g) was chromatographed on SiO_2 (10 g) with gradient elution (hexane→Et_2O, up to 20% of the latter) to give a mixture of epoxides **8b** (0.23 g, ~85%) (homolog ratio of C_{55} : C_{60} ≈ 2 : 1, HPLC data) as colorless oil, R_f 0.33 (hexane—Et_2O, 9 : 1). IR, ν/cm^{-1}: 980, 1050, 1250, 1380, 1450, 1670, 1730, 2800—3020. ^{1}H NMR, δ: 0.92 (d, MeC(3), J = 6.1 Hz); 1.10—1.70 (m, C(2)H$_2$, C(3)H, C(4)H$_2$, C(O)C—CH$_2$); 1.28 and 1.31 (both s, Me$_2$CO); 1.61 (br.s, *cis*-MeC=C); 1.69 (br.s, *trans*-MeC=C); 1.85—2.30 (m, CH$_2$C=, MeCO); 2.67 (t, HCO, J = 6.0 Hz); 4.09 (br.t, H$_2$CO, J = 6.7 Hz); 5.00—5.20 (m, HC=).

A mixture of **8b** (0.15 g) was chromatographed in ~30 mg portions under the above HPLC conditions to give individual epoxide **10** (90 mg) as colorless oil, R_f 0.34 (hexane—Et_2O, 9 : 1). ^{1}H NMR, δ: 0.92 (d, 3 H, MeC(3), J = 6.3 Hz); 1.10—1.70 (m, 7 H, C(2)H$_2$, C(3)H, C(4)H$_2$, C(41)H$_2$); 1.26 and 1.30 (both s, 6 H, Me$_2$C(43)); 1.63 (br.s, 9 H, 3 *cis*-MeC=C); 1.69 (br.s, 18 H, 6 *trans*-MeC=C); 1.90—2.20 (m, 39 H, 18 CH$_2$C=, MeCOO); 2.70 (t, 1 H, HCO, J = 6.4 Hz); 4.09 (br.t, 2 H, C(1)H$_2$, J = 7.0 Hz); 5.14 (m, 9 H, 9 HC=). ^{13}C NMR, δ: 16.0 (*cis*-MeC=C); 18.8 (MeCOO); 19.4 (MeC(3)); 21.0, 24.9 (Me$_2$C(43)); 23.4 (*trans*-MeC=C); 25.2, 26.4, 26.7, 27.5 (C=CHCH$_2$); 29.6 (C(3)); 32.0, 32.2 (*cis*-CH$_2$(Me)C=C); 35.5, 36.3, 37.3 (C(2), C(4), C(41)); 39.6, 39.8, 40.0 (*trans*-CH$_2$(Me)C=C); 58.2 (Me$_2$CO); 63.0 (CH$_2$O); 64.2 (CHO); 124.2, 124.3, 124.9, 125.0, 125.3 (C=CH); 134.0, 134.8, 135.0, 135.2, 135.3 (C=CH); 171.1 (C=O).

Epoxides (8c) and 3,7,11,15,19,23,27,31-octamethyl-30,31-epoxidotriaconta-6*Z*,10*Z*,14*Z*,18*Z*,22*E*,26*E*-hexaen-1-yl acetate (11). A mixture of epoxides **8c** (1.08 g, ~76%) (homolog ratio of C_{35} : C_{40} ≈ 1 : 1, HPLC data) as colorless oil was obtained analogously from a mixture of bromohydrins **7c** (1.6 g, ~2.3 mmol) and K_2CO_3 (0.5 g, 3.61 mmol) in 20 mL of benzene and 10 mL of MeOH, R_f 0.50 (hexane—Et_2O, 4 : 1). IR, ν/cm^{-1}: 840, 900, 970, 1050, 1160, 1250, 1380, 1450, 1670, 2740—3040. ^{1}H NMR, δ: 0.90 (d, MeC(3), J = 5.8 Hz); 1.10—1.70 (m, C(2)H$_2$, C(3)H, C(4)H$_2$, C(O)C—CH$_2$); 1.24 and 1.27 (both s, Me$_2$CO); 1.61 (br.s, *cis*-MeC=C); 1.68 (br.s, *trans*-MeC=C); 1.90—2.20 (m, CH$_2$C=, MeCO); 2.65 (t, HCO, J = 6.3 Hz); 4.09 (br.t, H$_2$CO, J = 7.2 Hz); 5.00—5.20 (m, HC=).

A mixture of **8c** (0.56 g) was chromatographed in ~30 mg portions under the above HPLC conditions to give individual epoxide **11** (0.21 g) as colorless oil, R_f 0.51 (hexane—Et_2O, 4 : 1). ^{1}H NMR, δ: 0.91 (d, 3 H, MeC(3), J = 6.1 Hz); 1.10—1.70 (m, 7 H, C(2)H$_2$, C(3)H, C(4)H$_2$, C(29)H$_2$); 1.25 and 1.30 (both s, 6 H, Me$_2$C(31)); 1.63 (br.s, 6 H, 2 *cis*-MeC=C); 1.68 (br.s, 12 H, 4 *trans*-MeC=C); 1.90—2.20 (m, 27 H, 12 CH$_2$C=, MeCOO); 2.67 (t, 1 H, HCO, J = 6.5 Hz); 4.09 (br.t, 2 H, C(1)H$_2$, J = 7.1 Hz); 5.14 (m, 6 H, 6 HC=). ^{13}C NMR, δ: 15.9 (*cis*-MeC=C); 18.7 (MeCOO); 19.3 (MeC(3)); 20.9, 24.8 Me$_2$C(31); 23.4 (*trans*-MeC=C); 25.1, 26.3, 26.5, 27.4 (C=CHCH$_2$); 29.4 (C(3)); 31.9, 32.1 (*cis*-CH$_2$(Me)C=C); 35.4, 36.2, 37.2 (C(2), C(4), C(29)); 39.6 (*trans*-CH$_2$(Me)C=C); 58.2 (Me$_2$CO); 62.9 (CH$_2$O); 64.1 (CHO); 124.2, 124.8, 124.9, 125.0, 125.2 (C=CH); 133.9, 134.9, 135.1, 135.2 (C=CH); 171.0 (C=O).

3,7,11,15,19,23,27,31,35,39,43,47,51,55,59,63-Hexadecamethyl-62,63-epoxytetrahexaconta-6*Z*,10*Z*,14*Z*,18*Z*,22*Z*,26*Z*,30*Z*,34*Z*,38*Z*,42*Z*,46*Z*,50*Z*,54*E*,58*E*-tetradecaen-1-yl acetate (9). A mixture of epoxides **8a** (0.9 g, homolog ratio of C_{70} : C_{75} : C_{80} : C_{85} ≈ 6 : 13 : 14 : 7, HPLC data) obtained as described earlier[1,2] was chromatographed in ~30 mg portions under the above HPLC conditions to give individual epoxide **9** (0.28 g) as colorless oil, R_f 0.36 (hexane—Et_2O, 9 : 1). IR, ν/cm^{-1}: 840, 940, 970, 1050, 1140, 1250, 1330, 1380, 1450, 1730, 2740—3040. ^{1}H NMR, δ: 0.92 (d, 3 H, MeC(3), J = 6.2 Hz); 1.10—1.70 (m, 7 H, C(2)H$_2$, C(3)H, C(4)H$_2$, C(61)H$_2$); 1.27 and 1.31 (both s, 6 H, Me$_2$C(63)); 1.62 (br.s, 6 H, 2 *cis*-MeC=C); 1.70 (br.s, 36 H, 12 *trans*-MeC=C); 1.90—2.20 (m, 59 H, 28 CH$_2$C=, MeCOO); 2.70 (t, 1 H, HCO, J = 6.4 Hz); 4.09 (br.t, 2 H, C(1)H$_2$, J = 7.1 Hz); 5.16 (m, 14 H, 14 HC=). ^{13}C NMR, δ: 16.0 (*cis*-MeC=C); 18.7 (MeCOO); 19.4 (MeC(3)); 21.0, 24.9 (Me$_2$C(63)); 23.4 (*trans*-MeC=C); 25.2, 26.4, 26.6, 27.5 (C=CHCH$_2$); 29.5 (C(3)); 32.0, 32.2 (*cis*-CH$_2$(Me)C=C); 35.5, 36.3, 37.3 (C(2), C(4), C(61)); 39.7 (*trans*-CH$_2$(Me)C=C); 58.2 (Me$_2$CO); 63.0 (CH$_2$O); 64.1 (CHO); 124.3, 124.6, 124.9, 125.0, 125.3, 125.7 (C=CH); 134.0, 134.8, 135.0, 135.2, 135.3, 135.6 (C=CH); 171.1 (C=O).

62-Acetoxy-4,8,12,16,20,24,28,32,36,40,44,48,52,56,60-pentadecamethyldohexaconta-4*E*,8*E*,12*Z*,16*Z*,20*Z*,24*Z*,28*Z*,32*Z*,36*Z*,40*Z*,44*Z*,48*Z*,52*Z*,56*Z*-tetradecaenal (12). A solution of $HIO_4 \cdot 2H_2O$ (0.1 g, 0.44 mmol) in 2 mL of THF was added at 20 °C over 5 min to a stirred (Ar) solution of epoxide **9** (0.28 g, 0.25 mmol) in 3 mL of Et_2O. The reaction mixture was kept for 20 min, diluted with Et_2O (10 mL), washed with water and brine, dried with Na_2SO_4, and concentrated *in vacuo*. The residue (0.3 g) was chromatographed at 0 °C on SiO_2 (30 g) eluting with hexane—Et_2O (4 : 1) to give aldehyde **12** (0.25 g, 85%) as colorless oil, R_f 0.40 (hexane—Et_2O, 9 : 1). IR ($CHCl_3$), ν/cm^{-1}: 840, 980, 1040, 1080, 1130, 1250, 1380, 1450, 1730, 2740—3020. ^{1}H NMR, δ: 0.91 (d, 3 H, MeC(60), J = 6.3 Hz); 1.10—1.70 (m, 5 H, C(59)H$_2$, C(60)H, C(61)H$_2$); 1.61 (br.s, 6 H, 2 *cis*-MeC=C); 1.69 (br.s, 36 H, 12 *trans*-MeC=C); 1.90—2.20 (m, 57 H, 27 CH$_2$C=, MeCO); 2.25—2.55 (m, 4 H, CH$_2$CH$_2$CHO); 4.11 (br.t, 2 H, C(62)H$_2$, J = 7.2 Hz); 5.12 (m, 14 H, 14 HC=); 9.76 (m, 1 H, HCO). ^{13}C NMR, δ: 15.9, 16.0 (*cis*-MeC=C); 18.8 (MeCOO); 20.9 (MeC(60)); 23.4 (*trans*-MeC=C); 25.2, 26.4, 26.5, 26.9 (C=CHCH$_2$); 29.5 (C(60)); 31.8, 31.9, 32.2 (*cis*-CH$_2$(Me)C=C); 35.4, 37.2, (C(61), C(4)); 39.5 (*trans*-CH$_2$(Me)C=C); 42.1 (C(2)); 62.9 (CH$_2$O); 124.3, 124.9, 125.0, 125.2, 125.3 (C=CH); 132.8, 134.8, 135.0, 135.1, 135.2 (C=CH); 171.1 (OC=O); 202.5 (C=O).

42-Acetoxy-4,8,12,16,20,24,28,32,36,40-decamethyldotetraconta-4*E*,8*E*,12*E*,16*Z*,20*Z*,24*Z*,28*Z*,32*Z*,36*Z*-nonaenal (13). Aldehyde **13** (66 mg, 82%) as colorless oil was obtained analogously from epoxide **10** (85 mg, 0.1 mmol), R_f 0.45 (hexane—Et_2O, 9 : 1). IR ($CHCl_3$), ν/cm^{-1}: 840, 970, 1050, 1250, 1330, 1450, 1660, 1730, 2740—3040. ^{1}H NMR, δ: 0.92 (d, 3 H, MeC(40), J = 5.9 Hz); 1.10—1.80 (m, 5 H, C(39)H$_2$, C(40)H, C(41)H$_2$); 1.61 (br.s, 9 H, 3 *cis*-MeC=C); 1.70 (br.s, 18 H, 6 *trans*-MeC=C); 1.80—2.20 (m, 37 H, 17 CH$_2$C=, MeCO); 2.25—2.60 (m, 4 H, CH$_2$CH$_2$CHO); 4.11 (br.t, 2 H, C(42)H$_2$, J = 6.7 Hz); 5.12 (m, 9 H, 9 HC=); 9.75 (m, 1 H, HCO).

30-Acetoxy-4,8,12,16,20,24,28-heptamethyltriaconta-4*E*,8*E*,12*Z*,16*Z*,20*Z*,24*Z*-hexaenal (14). Aldehyde **14** (0.18 g, 90%) as colorless oil was obtained analogously from epoxide **11** (0.28 g, 0.25 mmol), R_f 0.33 (hexane—Et_2O, 9 : 1). IR ($CHCl_3$), ν/cm^{-1}: 840, 970, 1060, 1250, 1330, 1450, 1650, 1730, 2730—3020. ^{1}H NMR, δ: 0.92 (d, 3 H, MeC(28), J = 6.0 Hz); 1.10—1.80 (m, 5 H, C(27)H$_2$, C(28)H, C(29)H$_2$); 1.61 (br.s, 6 H, 2 *cis*-MeC=C); 1.70 (br.s, 12 H, 4 *trans*-MeC=C); 1.90—2.20 (m, 25 H, 11 CH$_2$C=, MeCO); 2.27—2.55 (m, 4 H, CH$_2$CH$_2$CHO); 4.11 (br.t, 2 H, C(30)H$_2$, J = 6.9 Hz); 5.14 (m, 6 H, 6 HC=); 9.75 (br.s, 1 H, HCO).

3,7,11,15,19,23,27,31,35,39,43,47,51,55,59-Pentadecamethyl-62-(1-naphthyl)aminodohexaconta-6*Z*,10*Z*,14*Z*,18*Z*,22*Z*,26*Z*,30*Z*,34*Z*,38*Z*,42*Z*,46*Z*,50*Z*,54*E*,58*E*-tetra-

decaen-1-yl acetate (15). A solution of aldehyde **12** (0.23 g, 0.20 mmol) and 1-aminonaphthalene (0.07 g, 0.49 mmol) in 4 mL of Et_2O was stirred at 20 °C (Ar) for 6 h in the presence of 3 Å molecular sieves (0.1 g) and cooled to 0 °C. MeOH (2 mL) and $NaBH_4$ (100 mg, 2.6 mmol) were added, and the reaction mixture was heated to 20 °C over 5 min, kept at this temperature for 30 min, diluted with 10 mL of Et_2O, washed with water and brine, dried with Na_2SO_4, and concentrated *in vacuo*. The residue (0.3 g) was chromatographed on SiO_2 (20 g) eluting with hexane—Et_2O (9 : 1) to give amine **15** (0.18 g, ~71%) as colorless oil, R_f 0.63 (hexane—Et_2O, 9 : 1). IR ($CHCl_3$), ν/cm^{-1}: 840, 970, 1040, 1080, 1130, 1250, 1380, 1410, 1450, 1530, 1580, 1670, 1730, 2740—3020, 3420. ^{1}H NMR, δ: 0.96 (d, 3 H, MeC(3), J = 5.9 Hz); 1.10—1.70 (m, 5 H, C(2)H_2, C(3)H, C(4)H_2); 1.64 (br.s, 6 H, 2 *cis*-MeC=C); 1.72 (br.s, 36 H, 12 *trans*-MeC=C); 1.90 (m, 2 H, HC(61)); 1.95—2.30 (m, 59 H, 28 CH_2C=, MeCO); 3.33 (br.t, 2 H, CH_2N, J = 6.5 Hz); 4.15 (br.t, 2 H, C(1)H_2, J = 6.4 Hz); 4.41 (br.s, 1 H, NH); 5.20 (m, 14 H, 14 HC=); 6.65 (d, 1 H, C(2′)H-naphthyl, J = 7.0 Hz); 7.20—7.85 (m, 6 H, H-naphthyl). ^{13}C NMR, δ: 16.0 (*cis*-MeC=C); 19.4 (MeCOO); 20.9 (MeC(3)); 23.5 (*trans*-MeC=C); 25.2, 26.5, 26.7, 27.0 (C=CHCH_2); 27.4 (C(61)); 29.5 (C(3)); 31.8, 32.0, 32.2 (*cis*-CH_2(Me)C=C); 35.5, 37.3 (C(2), C(4)); 37.4, 39.7 (*trans*-CH_2(Me)C=C); 43.9 (CH_2N); 63.0 (CH_2O); 104.1, 117.1, 119.8, 123.4, 124.4, 124.5, 126.7, 128.7, 134.4, 143.6 (C-naphthyl); 124.3, 125.0, 125.3, 125.6 (C=CH); 134.8, 135.0, 135.2, 135.3 (C=CH); 171.1 (OC=O).

3,7,11,15,19,23,27,31,34,39-Decamethyl-42-(1-naphthyl)aminodotetraconta-6*Z*,10*Z*,14*Z*,18*Z*,22*Z*,26*Z*,30*E*,34*E*,38*E*-nonaen-1-yl acetate (16). Amine **16** (47 mg, 68%) as colorless oil was obtained analogously from aldehyde **13** (60 mg, 0.076 mmol), R_f 0.57 (hexane—Et_2O, 9 : 1). IR ($CHCl_3$), ν/cm^{-1}: 845, 1040, 1250, 1370, 1430, 1450, 1575, 1730, 2730—3020, 3430. ^{1}H NMR, δ: 0.94 (d, 3 H, MeC(3), J = 5.6 Hz); 1.10—1.70 (m, 5 H, C(2)H_2, C(3)H, C(4)H_2); 1.63 (br.s, 9 H, 3 *cis*-MeC=C); 1.71 (br.s, 18 H, 6 *trans*-MeC=C); 1.80—2.20 (m, 41 H, 18 CH_2C=, MeCO, C(41)H_2); 3.30 (br.t, 2 H, CH_2N, J = 6.3 Hz); 4.11 (br.t, 2 H, C(1)H_2, J = 5.9 Hz); 4.35 (br.s, 1 H, NH); 5.05—5.30 (m, 9 H, 9 HC=); 6.60 (d, 1 H, C(2′)H-naphthyl, J = 6.5 Hz); 7.20—7.85 (m, 6 H, H-naphthyl).

3,7,11,15,19,23,27-Heptamethyl-30-(1-naphthyl)aminotriaconta-6*Z*,10*Z*,14*Z*,18*Z*,22*E*,26*E*-hexaen-1-yl acetate (17). Amine **17** (0.10 g, 70%) as colorless oil was obtained analogously from aldehyde **14** (0.12 g, 0.21 mmol), R_f 0.53 (hexane—Et_2O, 9 : 1). IR ($CHCl_3$), ν/cm^{-1}: 840, 1050, 1250, 1370, 1420, 1450, 1580, 1730, 2740—3040, 3420. ^{1}H NMR, δ: 0.93 (d, 3 H, MeC(3), J = 5.4 Hz); 1.10—1.70 (m, 5 H, C(2)H_2, C(3)H, C(4)H_2); 1.64 (br.s, 6 H, 2 *cis*-MeC=C); 1.71 (br.s, 12 H, 4 *trans*-MeC=C); 1.80—2.20 (m, 29 H, 12 CH_2C=, MeCO, C(29)H_2); 3.28 (br.t, 2 H, CH_2N, J = 6.3 Hz); 4.11 (br.t, 2 H, C(1)H_2, J = 6.0 Hz); 4.35 (br.s, 1 H, NH); 5.05—5.25 (m, 6 H, 6 HC=); 6.60 (d, 1 H, C(2′)H-naphthyl, J = 6.9 Hz); 7.20—7.85 (m, 6 H, H-naphthyl).

3,7,11,15,19,23,27,31,35,39,43,47,51,55,59-Pentadecamethyl-62-(1-naphthyl)aminodohexaconta-6*Z*,10*Z*,14*Z*,18*Z*,22*Z*,26*Z*,30*Z*,34*Z*,38*Z*,42*Z*,46*Z*,50*Z*,54*E*,58*E*-tetradecaen-1-ol (18). Potassium carbonate (0.05 g, 0.36 mmol) was added to a solution of acetate **15** (0.17 g, 0.14 mmol) in a mixture of MeOH (2 mL) and benzene (2 mL). The reaction mixture was stirred at 20 °C (Ar) for 2 h, diluted with 10 mL of Et_2O, washed with water and brine, dried with Na_2SO_4, and concentrated *in vacuo*. The residue (0.2 g) was chromatographed on SiO_2 (5 g) eluting with hexane—Et_2O (4 : 1) to give amino alcohol **18** (0.16 g, 98%) as colorless oil, R_f 0.20 (hexane—Et_2O, 9 : 1). IR ($CHCl_3$), ν/cm^{-1}: 840, 1050, 1130, 1280, 1380, 1410, 1450, 1530, 1580, 1660, 2740—3040, 3430, 3640. ^{1}H NMR, δ: 0.94 (d, 3 H, MeC(3), J = 5.5 Hz); 1.10—1.70 (m, 5 H, C(2)H_2, C(3)H, C(4)H_2); 1.64 (br.s, 6 H, 2 *cis*-MeC=C); 1.71 (br.s, 36 H, 12 *trans*-MeC=C); 1.90 (m, 2 H, C(61)H_2); 1.95—2.30 (m, 56 H, 28 CH_2C=); 3.30 (br.t, 2 H, CH_2N, J = 6.1 Hz); 3.70 (m, 2 H, C(1)H_2); 5.20 (m, 14 H, 14 HC=); 6.64 (d, 1 H, C(2′)H-naphthyl, J = 6.6 Hz); 7.21—7.87 (m, 6 H, H-naphthyl). ^{13}C NMR, δ: 16.0 (*cis*-MeC=C); 19.6 (MeC(3)); 23.5 (*trans*-MeC=C); 25.3, 26.5, 26.7, 27.0 (C=CHCH_2); 27.4 (C(61)); 29.3 (C(3)); 31.8, 32.0, 32.2 (*cis*-CH_2(Me)C=C); 37.4 (C(4)); 37.6, 39.7 (*trans*-CH_2(Me)C=C); 40.0 (C(2)); 43.9 (CH_2N); 61.2 (CH_2O); 104.2, 117.1, 119.8, 123.4, 124.6, 125.6, 126.7, 128.7, 134.3, 143.6 (C-naphthyl); 124.3, 125.1, 125.3, 125.5 (C=CH); 134.8, 135.0, 135.2 (C=CH).

3,7,11,15,19,23,27,31,34,39-Decamethyl-42-(1-naphthyl)aminodotetraconta-6*Z*,10*Z*,14*Z*,18*Z*,22*Z*,26*Z*,30*E*,34*E*,38*E*-nonaen-1-ol (19). Amine **19** (44 mg, 98%) as colorless oil was obtained analogously from acetate **16** (47 mg, 0.051 mmol), R_f 0.35 (hexane—Et_2O, 4 : 1). IR ($CHCl_3$), ν/cm^{-1}: 840, 910, 1080, 1380, 1410, 1450, 1520, 1580, 1730, 2800—3020, 3350, 3600. ^{1}H NMR, δ: 0.92 (d, 3 H, MeC(3), J = 4.8 Hz); 1.10—1.70 (m, 5 H, C(2)H_2, C(3)H, C(4)H_2); 1.61 (br.s, 9 H, 3 *cis*-MeC=C); 1.70 (br.s, 18 H, 6 *trans*-MeC=C); 1.80—2.30 (m, 38 H, 36 CH_2C=, C(41)H_2); 3.28 (br.t, 2 H, CH_2N, J = 5.1 Hz); 3.68 (m, 2 H, C(1)H_2); 5.05—5.30 (m, 9 H, HC=); 6.58 (d, 1 H, C(2′)H-naphthyl, J = 6.0 Hz); 7.15—7.80 (m, 6 H, H-naphthyl). ^{13}C NMR, δ: 16.0 (*cis*-MeC=C); 19.5 (MeC(3)); 23.5 (*trans*-MeC=C); 25.3, 26.4, 26.7 27.0 (C=CHCH_2); 27.4 (C(41)); 29.3 (C(3)); 32.0, 32.2 (*cis*-CH_2(Me)C=C); 37.4 (C(4)); 37.5, 39.7, 39.8 (*trans*-CH_2(Me)C=C); 40.0 (C(2)); 43.9 (CH_2N); 61.2 (CH_2O); 104.2, 117.1, 119.8, 123.4, 124.4, 125.6, 126.7, 128.7, 134.4, 143.6 (C-naphthyl); 124.2, 125.0, 125.1, 125.5 (C=CH); 134.8, 135.0, 135.2, 135.4 (C=CH).

3,7,11,15,19,23,27-Heptamethyl-30-(1-naphthyl)aminotriaconta-6*Z*,10*Z*,14*Z*,18*Z*,22*E*,26*E*-hexaen-1-ol (20). Amine **20** (94 mg, 100%) as colorless oil was obtained analogously from acetate **17** (0.10 g, 0.14 mmol), R_f 0.33 (hexane—Et_2O, 4 : 1). IR ($CHCl_3$), ν/cm^{-1}: 850, 1060, 1130, 1250, 1280, 1350, 1380, 1430, 1450, 1530, 1580, 1670, 2740—3060, 3440, 3620. ^{1}H NMR, δ: 0.94 (d, 3 H, MeC(3), J = 5.4 Hz); 1.10—1.70 (m, 5 H, C(2)H_2, C(3)H, C(4)H_2); 1.63 (br.s, 6 H, 2 *cis*-MeC=C); 1.70 (br.s, 12 H, 4 *trans*-MeC=C); 1.80—2.20 (m, 26 H, 12 CH_2C=, C(29)H_2); 3.29 (br.t, 2 H, CH_2N, J = 6.6 Hz); 3.70 (m, 2 H, C(1)H_2); 5.10—5.30 (m, 6 H, 6 HC=); 6.64 (d, 1 H, C(2′)H-naphthyl, J = 6.4 Hz); 7.20—7.85 (m, 6 H, H-naphthyl). ^{13}C NMR, δ: 16.0 (*cis*-MeC=C); 19.5 (MeC(3)); 23.4 (*trans*-MeC=C); 25.2, 26.4, 26.6 (C=CHCH_2); 27.3 (C(29)); 29.2 (C(3)); 31.9, 32.2 (*cis*-CH_2(Me)C=C); 37.3 (C(4)); 37.5, 39.7 (*trans*-CH_2(Me)C=C); 39.9 (C(2)); 43.8 (CH_2N); 61.1 (CH_2O); 104.1, 117.0, 119.8, 123.3, 124.5, 125.6, 126.6, 128.6, 134.3, 143.5 (C-naphthyl); 124.2, 124.9, 125.0, 125.4 (C=CH); 134.9, 135.0, 135.2, 135.3 (C=CH).

3,7,11,15,19,23,27,31,35,39,43,47,51,55,59-Pentadecamethyl-62-(1-naphthyl)aminodohexaconta-6*Z*,10*Z*,14*Z*,18*Z*,22*Z*,26*Z*,30*Z*,34*Z*,38*Z*,42*Z*,46*Z*,50*Z*,54*E*,58*E*-tetradecaenyl phosphate, diammonium salt (4). Trichloroacetonitrile (29.8 mg, 207 μmol) was added to a solution of amino alcohol **18** (93.3 mg, 77.2 μmol) and $(Bu_4N)H_2PO_4$ (63.7 mg, 188 μmol) in 1 mL of CH_2Cl_2. After 18 h, the solvent was evaporated at 20 °C, and the residue was dissolved in 3 mL of the upper (organic) phase of an equilibrium *n*-butanol—water mixture. The solution was washed with the

lower phase of the same mixture (3×1 mL), and MeOH (1 mL), concentrated aqueous ammonia (0.1 mL), and Dowex 50Wx8 cation exchanger (NH_4^+) (1 mL) were added. The reaction mixture was stirred for 1.5 h. The ion-exchanger was filtered off and washed with toluene—MeOH (4 : 1) (3×5 mL), and the combined solution was concentrated *in vacuo*. The residue was dissolved in 50 mL of $CHCl_3$—MeOH (2 : 1), and the solution was passed through a column (1.1×10 cm) filled with DEAE cellulose (AcO^-) equilibrated with the same mixture of solvents. The column was washed with this mixture (50 mL) and MeOH (50 mL), and compound **4** was eluted with 0.03 *M* methanolic $AcONH_4$ (150 mL). The fractions containing the target product (TLC data) were concentrated, and toluene (25 mL) was added. The resulting mixture was left at 0 °C for 18 h. The precipitate that formed was filtered off, and the filtrate was evaporated to dryness. The residue was dissolved in 5 mL of heptane—propan-2-ol (4 : 1). Colorimetric determination showed that the solution contains 46.9 μmol of phosphate, *i.e.*, the product yield was 61%. Phosphate **4**, R_f 0.55 ($CHCl_3$—MeOH—water, 60 : 25 : 4). UV (heptane—propan-2-ol, 4 : 1), λ/nm (ε): 252 (18000), 335 (5600). ^{1}H NMR, δ: 0.85 (d, 3 H, MeC(3), J = 6 Hz); 1.10—1.55 (m, 3 H, C(3)H, C(4)H_2); 1.59, 1.60 (both s, each 3 H, 2 *cis*-MeC=C); 1.66, 1.68 (both s, 3 H and 33 H, 12 *trans*-MeC=C); 1.75—1.90 (m, 6 H, C(2)H_2, C(5)H_2, C(61)H_2); 1.95—2.15 (m, 54 H, 27 CH_2C=); 3.26 (br.t, 2 H, CH_2N, J = 6 Hz); 3.92 (m, 2 H, C(1)H_2); 5.05—5.15 (m, 14 H, 14 HC=); 6.73 (br.s, 1 H, C(2′)H-naphthyl); 7.30—7.82 (m, 6 H, H-naphthyl). ^{13}C NMR, δ: 15.9, 16.0 (*cis*-MeC=C); 19.1 (MeC(3)); 23.4 (*trans*-MeC=C); 25.1 (C(5)); 26.4, 26.6 (C=CHCH_2); 29.2 (C(3)); 31.9, 32.2 (*cis*-CH_2(Me)C=C); 37.2 (C(2)); 37.5 (C(4), C(60)); 39.6 (*trans*-CH_2(Me)C=C); 44.0 (CH_2N); 64.7 (CH_2O); 120.0, 124.2, 124.3, 124.9, 125.0, 125.1, 125.8, 126.4, 128.7 (C-naphthyl and C=CH); 134.7, 135.2, 135.3 (C=CH). ^{31}P NMR, δ: 1.93. MS: m/z 1289, calculated for the monoisotopic ion $C_{87}H_{135}O_4NP$ $[M_{acid} - H]^-$ 1289.

3,7,11,15,19,23,27,31,34,39-Decamethyl-42-(1-naphthyl)aminodotetraconta-6*Z*,10*Z*,14*Z*,18*Z*,22*Z*,26*Z*,30*E*,34*E*,38*E*-nonaenyl phosphate, diammonium salt (5). Phosphate **5** was obtained analogously from amino alcohol **19** (35.3 mg, 40.6 μmol), $(Bu_4N)H_2PO_4$ (44.1 mg, 123 μmol), and CCl_3CN (19.4 mg, 135 μmol) in 1 mL of CH_2Cl_2 (reaction time 24 h). The yield of **5** was 24%, R_f 0.50 ($CHCl_3$—MeOH—water, 60 : 25 : 4). UV (heptane—propan-2-ol, 4 : 1), λ/nm (ε): 252 (19800), 335 (7000). ^{1}H NMR, δ: 0.86 (d, 3 H, MeC(3), J = 6.5 Hz); 1.10—1.55 (m, 3 H, C(3)H, C(4)H_2); 1.59, 1.60, 1.61 (all s, each 3 H, 3 *cis*-MeC=C); 1.66, 1.68 (both s, 3 H and 15 H, 6 *trans*-MeC=C); 1.75—1.90 (m, 6 H, C(2)H_2, C(5)H_2, C(41)H_2); 1.95—2.15 (m, 34 H, 17 CH_2C=); 3.31 (br.t, 2 H, CH_2N, J = 7 Hz); 3.91 (m, 2 H, C(1)H_2); 5.05—5.15 (m, 9 H, 9 HC=); 6.85 (br.s, 1 H, C(2′)H-naphthyl); 7.25—7.85 (m, 6 H, H-naphthyl). ^{13}C NMR, δ: 15.8, 16.0 (*cis*-MeC=C); 19.1 (MeC(3)); 23.4 (*trans*-MeC=C); 25.2 (C(5)); 26.3, 26.4, 26.6, 26.7 (C=CHCH_2); 29.2 (C(3)); 29.7 (C(41)); 31.9, 32.1, 32.2 (*cis*-CH_2(Me)C=C); 37.1 (C(2)); 37.5 (C(4), C(40)); 39.6, 39.7 (*trans*-CH_2(Me)C=C); 46.0 (CH_2N); 64.8 (CH_2O); 120.1, 124.1, 124.3, 125.0, 125.1, 125.2, 125.5, 125.9, 126.3, 128.7 (C-naphthyl and C=CH); 134.4, 134.7, 134.8, 135.0, 135.1, 135.3 (C=CH). MS: m/z 949, calculated for the monoisotopic ion $C_{62}H_{95}O_4NP$ $[M_{acid} - H]^-$ 949.

3,7,11,15,19,23,27-Heptamethyl-30-(1-naphthyl)aminotriaconta-6*Z*,10*Z*,14*Z*,18*Z*,22*E*,26*E*-hexaenyl phosphate, diammonium salt (6). Phosphate **6** was obtained analogously from amino alcohol **20** (39.5 mg, 61.9 μmol), $(Bu_4N)H_2PO_4$ (76.2 mg, 213 μmol), and CCl_3CN (33.8 mg, 235 μmol) in 2 mL of CH_2Cl_2 (reaction time 72 h). The yield of **6** was 37%, R_f 0.42 ($CHCl_3$—MeOH—water, 60 : 25 : 4). UV (heptane—propan-2-ol, 4 : 1), λ/nm (ε): 252 (19300), 335 (6500). ^{1}H NMR, δ: 0.83 (d, 3 H, MeC(3), J = 6.5 Hz); 1.10—1.55 (m, 3 H, C(3)H, C(4)H_2); 1.56, 1.58 (both s, each 3 H, 2 *cis*-MeC=C); 1.66, 1.67 (both s, 3 H and 9 H, 4 *trans*-MeC=C); 1.75—1.90 (m, 6 H, C(2)H_2, C(5)H_2, C(29)H_2); 1.95—2.15 (m, 22 H, 11 CH_2C=); 3.32 (br.t, 2 H, CH_2N, J = 7.3 Hz); 3.88 (br.t, 2 H, C(1)H_2, J = 6.6 Hz); 5.05—5.13 (m, 6 H, 6 HC=); 7.10—7.95 (m, 7 H, H-naphthyl). ^{13}C NMR, δ: 15.7, 15.9 (*cis*-MeC=C); 19.0 (MeC(3)); 22.7, 22.9, 23.4 (*trans*-MeC=C); 25.2 (C(5)); 25.6 (C(25)); 26.3, 26.4 26.5, 26.6 (C=CHCH_2); 29.3 (C(3)); 29.6 (C(29)); 31.9, 32.2 (*cis*-CH_2(Me)C=C); 36.8 (C(2)); 37.5 (C(4), C(28)); 39.6 (*trans*-CH_2(Me)C=C); 47.2 (CH_2N); 64.8 (CH_2O); 120.4, 122.7, 124.2, 124.6, 125.1, 125.3, 125.5, 125.9, 126.2, 128.7 (C-naphthyl and C=CH); 134.3, 134.7, 135.0, 135.2 (C=CH). MS: m/z 744, calculated for the monoisotopic ion $C_{47}H_{71}O_4NP$ $[M_{acid} - H]^-$ 744.

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