Preparation of Phosphoglycerides by Phosphoramidite Chemistry

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Phosphoglycerides have been prepared in high yield by a three-step procedure utilising phosphoramidite intermediates. 2-Chloro-3-methyl-1,3,2-oxazaphosphospholidine **5** reacts with diacylglycerols to give cyclic phosphoramidites in near-quantitative yield. These are oxidised to the corresponding phosphates in very high yield with N_2O_4. The phosphates hydrolyse in water at ambient temperature, *via* exclusive P–N cleavage, to yield the target phospholipids. Similarly prepared from 2-chloro-1,3-dimethyl-1,3,2-diazaphospholidine **1** were the phosphoramidate lipid analogues. Spectral data on the intermediates and products are included and discussed.

Phospholipids, well known as major structural components of cell membranes,[1] are implicated in many physiological processes.[2] Common natural phospholipids contain a diacylglycerol moiety attached *via* a phosphate diester to a choline or ethanolamine unit. Such structures largely comprise the fluid bi-layer of the mammalian cell membrane. There is mounting evidence[3] that changes in the lipid bi-layer are intimately involved in the neoplastic state and in viral infection, and that a new, non-genotoxic approach to chemotherapy may be available in the field of phospholipid analogues.

Until recently, the synthesis of phospholipids was achieved using phosphate chemistry. This could be slow, and yields poor, especially for rather bulky diacylglycerols.[4] More recently, phosphite chemistry has been employed, with greatly improved syntheses.[5] However, consistently, the problem of introducing the amino terminus has been a major limitation of most routes. We have developed a new route to phospholipids[6] which entirely removes this problem, whilst retaining the advantages of phosphite reactivity. In particular, the amino group is 'protected' from the start in a phosphoramidite heterocycle. The rationale behind using phosphoramidite intermediates was that final P–N cleavage would be achieved by simple acid hydrolysis of the heterocycle.[6] Indeed, we have recently noted the facile cleavage of the cyclic intermediate, simply using water at room temperature, leads to smooth hydrolysis to the desired product.[7] The route we have introduced is readily adapted to allow the synthesis of entirely novel phospholipid analogues, whose biological properties are unknown and would be eagerly awaited. For example, we have noted that the use of the diamidate versions of the above-mentioned reagents yield entirely novel amino-linked phosphoramidate lipids.[8]

To date we have applied the phosphoramidite methodology only to simple alkyl-containing model compounds. We herein report the successful application of these methods to the preparation of glycerol-based phospholipids. Such materials are more closely related to natural phospholipids, a similarity which may confer more potent biological properties on these products. In one case, the products we report are simply *N*-monomethyl analogues of the natural phosphatidylethanolamine (lecithin) lipids, in the other case we report novel diaza-based systems.

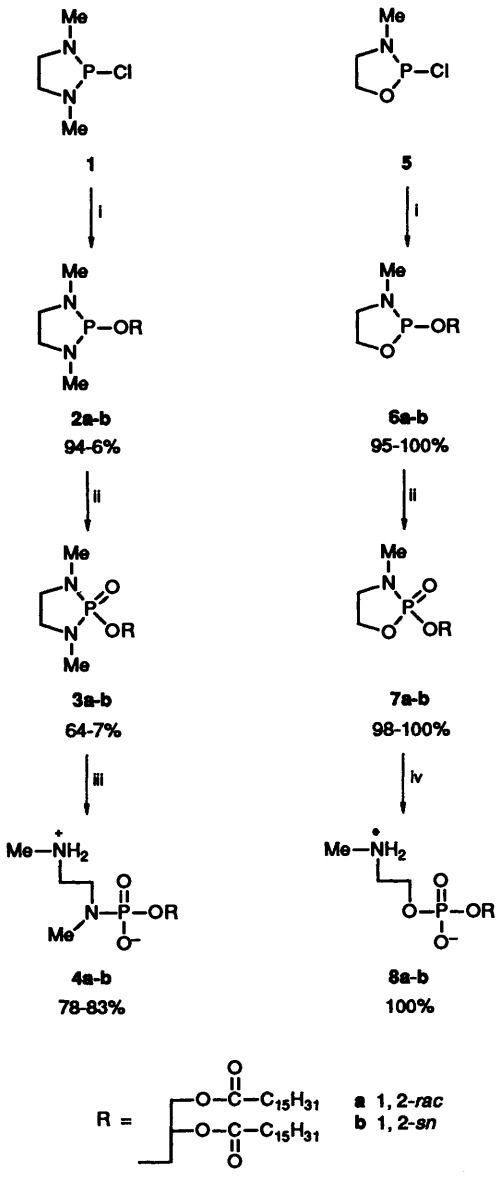
The phosphorochloridite **1** was prepared by the reaction of phosphorus trichloride with *N,N'*-dimethylethylenediamine as we have described.[8]

Compound **1** was treated with *rac*-1,2-dipalmitoylglycerol in dichloromethane containing triethylamine at 0 °C to yield the phosphorodiamidite **2a** in almost quantitative yield. The reaction temperature used was somewhat higher than that previously used by us for simple alkyl analogues of this glyceride,[8] on account of the poor solubility of the glycerol in dichloromethane at low temperature. However, this is not unusual for the phosphitylation of glycerols, which have commonly been carried out at 0 °C,[9] or at ambient temperature.[10] The order of addition of reagents was also altered in this case, the previously suggested order[8] giving rise to impurities in the ^{31}P NMR. Lastly, the isolation procedure was also altered from that we had previously used,[8] because of difficulties encountered in the organic–aqueous extraction. Thus, the product was isolated by evaporating the reaction mixture to dryness, treating the residue with hexane, and filtering off the salt. The product displayed a single resonance in its ^{31}P NMR spectrum, much further upfield than noted for compound **1** (**2a**, δ 129), but in a very similar position to that previously noted for simple alkyl analogues of this glyceride.[8] The two *N*-methyl groups were non-equivalent in the ^1H NMR spectrum, each appearing as a (phosphorus-coupled) doublet.

In a similar manner, compound **1** was treated with *sn*-1,2-dipalmitoylglycerol to yield the phosphorodiamidite **2b** in very high yield. As expected, this displayed the same spectral data as **2a**. However, additional ^{13}C NMR data were recorded in this case. Extensive 2- and 3-bond phosphorus coupling was noted, and the *N*-methyl groups were again noted to be non-equivalent (doublets). The glycerol carbon signals were fully assigned by reference to the spectrum of tributylglycerol.[11]

Following our established synthetic route,[6–8] the next stage was oxidation of the phosphorodiamidites to the corresponding phosphorodiamidates. This was achieved using a standard solution of dinitrogen tetroxide[12] in anhydrous dichloromethane at low temperature. Thus, the phosphorodiamidites **2a–b** were converted into their corresponding phosphorodiamidates **3a–b** in good yield. Impurities in the ^{31}P NMR spectra of the crude products necessitated mixed-solvent trituration, which led to some diminution of yield by comparison to that noted for the simple alkyl analogues.[8] The ^{31}P NMR data for the phosphorodiamidates were very different from those of the phosphorodiamidite precursors. Thus, a resonance at *ca.* δ 25 was noted for **3a,b**, which is as expected for structures of this type.[8,13] Other spectroscopic data were similar to those for the phosphorodiamidite precursors **2a,b**, although the magnitude of the phosphorus coupling constants in the ^1H NMR spectra were somewhat altered, and the expected P=O stretch was noted in the IR spectrum (ν 1261 cm^{-1}).[14]

The final step in the synthetic route is the hydrolytic cleavage of the P–N bond to yield the acyclic phospholipids **4a,b**. We



Scheme *Reagents and conditions:* i, ROH, CH_2Cl_2, Et_3N, 0 to 20 °C; ii, N_2O_4, CH_2Cl_2, −70 to 20 °C; iii, 4% mol equiv. HCl, THF–H_2O, 20 °C, 2 h; iv, THF–H_2O, 20 °C, 3 h.

originally noted that the oxaza analogues of compounds **3a,b** could be hydrolysed successfully using 2 mol dm^{-3} hydrochloric acid at reflux.[6] Subsequently, the diaza heterocycles were hydrolysed using only catalytic quantities of acid, at ambient temperature.[8] Thus, this method was employed for **3a,b**, although more THF was needed to dissolve the glycerol compounds. A simple isolation procedure, not involving chromatographic purification, gave the target lipids **4a,b** in very good yield. The products displayed one signal in their ^{31}P NMR spectra at *ca.* δ 9, as expected.[8,14] The ^1H NMR data clearly revealed a single P–N cleavage, with one N–Me group retaining phosphorus coupling, and the other (at the cleavage site) not. Carbon-13 NMR data also confirmed the structure and purity of **4a,b**, although signal-broadening restricted an unambiguous assignment of all signals. The lipid analogues **4a,b** gave good Fast Atom Bombardment (FAB) mass spectral data, protonated molecular ion peaks being prominent, and intense diacylglyceryl fragments dominating the spectra. Analytical data also confirmed the purity of **4a,b**.

Thus, the lipid analogues **4a,b** had been prepared in *ca.* 50% overall yield from the parent glycerol, in three-steps, each of which was rapid, and proceeded under mild conditions. The products were pure without recourse to chromatography, which can be troublesome in the case of such compounds.[15]

It was of interest to establish whether such procedures could also be applied to the oxaza analogues, more related to natural lipids. Thus, compound **5** was prepared from methylaminoethanol by the procedure reported.[7] As above, this was treated first with *rac*-, and subsequently *sn*-1,2-dipalmitoylglycerol to give the phosphoramidite triesters **6a,b** in near-quantitative yield. Again, the products displayed resonances in the ^{31}P NMR, much further upfield than noted for compound **5** (**6a–b**, *ca.* δ 138), but in a very similar position to that previously noted for simple alkyl analogues of this glyceride.[7] Interestingly, in both cases **6a,b** displayed two closely spaced ^{31}P resonances, corresponding to the multiple chiral centres, and the mixed stereochemistry at the phosphorus (and the glyceryl C-2 in **6a**) leading to two diastereoisomers. The ratios were not 1:1, and indeed differed for each case **6a,b**.

The oxidation of **6a,b** was conducted entirely as noted for **2a,b** above. Again, ^{31}P NMR data for the crude products indicated significant quantities of impurity, as had been noted above for the diaza series. However, the position of this impurity in the phosphorus NMR (*ca.* δ −2) suggested that it might be the intended hydrolysed product **8a,b**, and the crude products were, therefore, used direct in the hydrolysis without purification. Interestingly, the diastereoisomers of **7a,b**, presumed to be retained in the oxidation, are not resolved in the ^{31}P NMR spectrum, unlike the phosphoramidite precursors **6a,b**.

Although the hydrolysis was originally carried out under acidic conditions, and catalytic acid does appear to be necessary for the diaza heterocycles, such as **3a,b**, we have recently noted[7] that hydrolysis of oxaza heterocycles could be conducted simply in water (often mixed with a co-solvent), in the absence of added acid. Thus, **7a,b** were hydrolysed to the target acyclic lipids **8a,b**, in quantitative yield, simply by stirring in aqueous THF at ambient temperature. The materials were fully characterised by spectroscopy and microanalysis. Thus, one signal close to the reference in ^{31}P NMR, a N–Me singlet in ^1H NMR and molecular ion peaks in the FAB mass spectra are amongst the data confirming the structure of **8a,b**.

Thus, the phosphoramidite method is successful for glycerol-based lipids, for both oxaza and diaza systems. The reactions proceed in high yield, under mild conditions, and the products are isolated without recourse to chromatography. We are currently applying such methodology to glycerol ethers of interest as anti-neoplastic agents.

Experimental

Phosphorus-31 NMR spectra were recorded on a Varian XL-200 spectrometer operating at 82 MHz or a Varian CFT20 instrument operating at 32 MHz and shifts are reported in units of δ relative to 85% phosphoric acid as external standard, positive shifts are downfield. Carbon-13 NMR spectra were recorded on a Varian XL-200 spectrometer operating at 50 MHz, or a Varian VXR-400 spectrometer operating at 100 MHz and shifts are in units of δ relative to TMS; in the alkyl chains carbon atoms are numbered from the terminus. Both phosphorus-31 and carbon-13 NMR spectra were proton noise decoupled and all signals were singlets unless otherwise stated. ^1H NMR spectra were recorded on a Varian XL-200 spectrometer operating at 200 MHz and are reported in units of δ relative to internal TMS. All NMR spectra were recorded in $CDCl_3$ unless otherwise stated, and all coupling constants are reported in Hz. IR spectra were recorded on a Perkin-Elmer 983 spectrometer. Mass spectra were recorded on a VG7070H spectrometer, courtesy of Dr. M. Mruzek (EIMS) or on a VG Zab 1F spectrometer courtesy of the University of London

Mass spectrometry group (FAB). Microanalyses were performed at University College London courtesy of the Group of Mr. A. T. T. Stones. Phospholipids were noted to be hygroscopic, and analytical data are presented appropriately. All experiments involving water-sensitive reagents were carried out under scrupulously dry conditions. Where needed, anhydrous solvents and reagents were obtained in the following ways. Triethylamine, hexane, diethyl ether and dichloromethane were refluxed over CaH_2 for several hours and distilled. All but triethylamine were further dried over activated 4 Å molecular sieves. Dipalmitoylglycerols were dried by repeated co-evaporation with toluene under reduced pressure and/or desiccation under vacuum for several hours.

3-O-(1,3-*Dimethyl*-1,3,2-*diazaphospholidin*-2-*yloxy*)-1,2-*di*-O-*palmitoyl*-rac-*glycerol* **2a**.—Compound **1** (0.05 g, 0.31 mmol) in dry dichloromethane (10 cm^3) was added dropwise with vigorous stirring to 1,2-di-*O*-palmitoyl-*rac*-glycerol (0.17 g, 0.30 mmol) and triethylamine (0.03 g, 0.31 mmol) in dichloromethane (10 cm^3) at 0 °C under an atmosphere of nitrogen. The stirred solution was allowed to warm to ambient temperature, for 1 h and then evaporated under reduced pressure. The residue was treated with dry hexane (100 cm^3), filtered, and the filtrate evaporated under reduced pressure to yield the product as a white wax (0.20 g, 96%); δ_H 5.0 (1 H, m, CH), 4.2 (2 H, m, $POCH_2CH$), 3.6 [2 H, m, $CH_2OC(O)$], 3.1 (4 H, m, CH_2N), 2.64 (3 H, d, NMe, *J* 12.5), 2.63 (3 H, d, NMe, *J* 12.5), 2.2 [4 H, m, $C(O)CH_2$], 1.5 [4 H, m, $C(O)CH_2CH_2$], 1.2 [48 H, m, $(CH_2)_{12}$] and 0.8 (6 H, t, CH_3CH_2); δ_P 129.4; ν_{max}(liquid film)/cm^{-1} 2919, 2845, 1725, 1468 and 1034.

3-O-(1,3-*Dimethyl*-1,3,2-*diazaphospholidin*-2-*yloxy*)-1,2-*di*-O-*palmitoyl*-sn-*glycerol* **2b**. This compound was prepared as described for **2a** above. Thus, from 1,2-di-*O*-palmitoyl-*sn*-glycerol (0.2 g) was isolated **2b** (0.23 g, 94%); δ_H 5.0 (1 H, m, CH), 4.2 (2 H, m, $POCH_2CH$), 3.6 [2 H, m, $CH_2OC(O)$], 3.1 (4 H, m, CH_2N), 2.65 (3 H, d, NMe, *J* 12.5), 2.64 (3 H, d, NMe, *J* 12.5), 2.2 [4 H, m, $C(O)CH_2$], 1.5 [4 H, m, $C(O)CH_2CH_2$], 1.2 [48 H, m, $(CH_2)_{12}$] and 0.8 (6 H, t, CH_3CH_2); δ_C 172.5 (C=O), 172.1 (C=O), 70.1 (CH), 61.6 [$CH_2OC(O)$], 60.1 (d, $POCH_2$, *J* 7), 52.2 (d, NCH_2, *J* 10), 33.4 [$C(O)CH_2$], 33.3 (d, NMe, *J* 7), 33.2 [$C(O)CH_2$], 33.0 (d, NMe, *J* 7), 30.9 (C-3), 28.4 [m, $(CH_2)_{10}$], 24.0 (C-14), 23.9 (C-14), 21.7 (C-2) and 13.1 (C-1); δ_P 129.4; ν_{max}(liquid film)/cm^{-1} 2919, 2845, 1725, 1468 and 1034.

3-O-(1,3-*Dimethyl*-2-*oxo*-1,3,2-*diazaphospholidin*-2-*yloxy*)-1,2-*di*-O-*palmitoyl*-rac-*glycerol* **3a**.—A portion of standard dinitrogen tetroxide solution (1.75 cm^3, containing 0.08 mmol of oxidant, sufficient to oxidise 0.32 mmol of phosphite) was added dropwise with vigorous stirring to compound **2a** (0.22 g, 0.32 mmol) in dry dichloromethane (25 cm^3) at −70 °C. The solution was allowed to warm to ambient temperature and then evaporated under reduced pressure. The residue was treated with a mixture of hexane and diethyl ether (300 cm^3; 35:65) and filtered. The filtrate was evaporated under reduced pressure to yield the product as a white solid (0.15 g, 67%); δ_H 5.1 (1 H, m, CH), 4.2 (2 H, m, $POCH_2CH$), 4.0 [2 H, m, $CH_2OC(O)$], 3.1 (4 H, d, CH_2N, *J* 9.9), 2.64 (3 H, d, NMe, *J* 9.9), 2.56 (3 H, d, NMe, *J* 9.9), 2.2 [4 H, m, $C(O)CH_2$], 1.6 [4 H, m, $C(O)CH_2CH_2$], 1.2 [48 H, m, $(CH_2)_{12}$] and 0.8 (6 H, t, CH_3CH_2); δ_P 25.1; ν_{max}(liquid film)/cm^{-1} 2919, 2845, 1732, 1261, 1064, 800 and 727.

3-O-(1,3-*Dimethyl*-2-*oxo*-1,3,2-*diazaphosphalidin*-2-*yloxy*)-1,2-*di*-O-*palmitoyl*-sn-*glycerol* **3b**. This compound was prepared as described for **3a** above. Thus, from **2b** (0.21 g) was isolated **3b** (0.14 g, 64%); δ_H 5.1 (1 H, m, CH), 4.2 (2 H, m, $POCH_2CH$), 4.0 [2 H, m, $CH_2OC(O)$], 3.1 (4 H, d, CH_2N, *J* 9.9), 2.58 (3 H, d, NMe, *J* 9.9), 2.57 (3 H, d, NMe, *J* 9.9), 2.3 [4 H, m, $C(O)CH_2$], 1.5 [4 H, m, $C(O)CH_2CH_2$], 1.2 [48 H, m, $(CH_2)_{12}$] and 0.8 (6 H, t, CH_3CH_2); δ_P 25.1; ν_{max}(liquid film) 2919, 2845, 1732, 1261, 1064, 800 and 727.

Water-mediated Hydrolyses.—Of **3a**. Dilute hydrochloric acid (0.2 mol dm^3; 0.04 mol) was mixed with water (2 cm^3) and added to a solution of compound **3a** (0.15 g, 0.21 mmol) in tetrahydrofuran (6 cm^3) at ambient temperature. The mixture was stirred for 2 h, and then carefully neutralised by dropwise addition of dilute aqueous sodium hydroxide to give a final pH of 6.94. The mixture was lyophilised, and the residue dissolved in dichloromethane (100 cm^3), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was treated with hexane to yield **4a** as a white solid (0.11 g, 78%); δ_H 5.1 (1 H, m, CH), 4.25 (2 H, m, $POCH_2CH$), 3.8 [2 H, m, $CH_2OC(O)$], 3.2 (2 H, m, CH_2N), 2.9 (2 H, m, CH_2N), 2.7 (3 H, d, NMe, *J* 8.8), 2.6 (3 H, s br, NMe), 2.2 [4 H, m, $C(O)CH_2$], 1.5 [4 H, m, $C(O)CH_2CH_2$], 1.2 [48 H, m, $(CH_2)_{12}$] and 0.8 (6 H, t, CH_3CH_2); δ_P 8.7; δ_C 172.4 (C=O), 172.0 (C=O), 69.5 (d, CH, *J* 7.5), 61.74 (d, $POCH_2$, *J* 5), 61.66 [$CH_2OC(O)$], 46.4 (s br, NCH_2), 45.1 (s br, NCH_2), 33.7 (s br, NMe), 33.3 [$C(O)CH_2$], 33.1 [$C(O)CH_2$], 32.6 (NMe), 30.9 (C-3), 28.5 [m, $(CH_2)_{10}$], 24.0 (C-14), 23.95 (C-14), 23.9 (C-14), 21.7 (C-2) and 13.1 (C-1); *m/z* (FAB) 720 (MH^+, 10%), 552 (dipalmitoylglycerol, 10), 465 (MH^+ − hexadecanoyl, 2), 367 (2), 313 (6), 209 (9), 169 (M^+ − diacylglycerol, 22), 133 (30), 89 (100), 58 (41); ν_{max}(liquid film)/cm^{-1} 3439, 2918, 2845, 1738, 1465, 1198, 1064 and 800 (Found: C, 62.2; H, 11.1; N, 4.0; P, 3.8. $C_{39}H_{79}N_2O_7P{\cdot}2H_2O$ requires C, 62.01; H, 11.09; N, 3.71; P, 4.10%).

Of **3b**. This reaction was conducted as described for **3a** above. Thus, from **3b** (0.14 g) was isolated **4b** (0.12 g, 83%); δ_H 5.1 (1 H, m, CH), 4.26 (2 H, m, $POCH_2CH$), 3.8 [2 H, m, $CH_2OC(O)$], 3.2 (2 H, m, CH_2N), 2.9 (2 H, m, CH_2N), 2.7 (3 H, d, NMe, *J* 9.1), 2.6 (3 H, s br, NMe), 2.2 [4 H, m, $C(O)CH_2$], 1.5 [4 H, m, $C(O)CH_2CH_2$], 1.2 [48 H, m, $(CH_2)_{12}$] and 0.8 (6 H, t, CH_3CH_2); δ_P 8.7; δ_C 172.5 (C=O), 172.1 (C=O), 69.5 (d, CH, *J* 7.5), 61.74 (d, $POCH_2$, *J* 5), 61.66 ($CH_2OC(O)$), 46.4 (s br, NCH_2), 45.2 (s br, NCH_2), 33.8 (s br, NMe), 33.3 [$C(O)CH_2$], 33.1 [$C(O)CH_2$], 32.6 (NMe), 30.9 (C-3), 28.4 [m, $(CH_2)_{10}$], 23.94 (C-14), 23.87 (C-14), 21.7 (C-2) and 13.1 (C-1); *m/z* (FAB) 720 (MH^+, 11%), 552 (dipalmitoylglycerol, 26), 508 (1), 464 (M^+ − hexadecanoyl, 2), 424 (2), 367 (4), 339 (1), 313 (6), 209 (3), 169 (26), 151 (16), 133 (5), 89 (100) and 58 (45); ν_{max}(liquid film)/cm^{-1} 3439, 2918, 2845, 1465, 1198 and 800 (Found: C, 62.7; H, 10.9; N, 3.75; P, 3.61. $C_{39}H_{79}N_2O_7P{\cdot}1.5H_2O$ requires C, 62.77; H, 11.09; N, 3.76; P, 4.15%).

3-O-(3-*Methyl*-1,3,2-*oxazaphospholidin*-2-*yloxy*)-1,2-*di*-O-*palmitoyl*-rac-*glycerol* **6a**.—Compound **5** (0.043 g, 0.31 mmol) in dry dichloromethane (8 cm^3) was added dropwise with vigorous stirring to 1,2-di-*O*-palmitoyl-*rac*-glycerol (0.17 g, 0.30 mmol) and triethylamine (0.03 g, 0.31 mmol) in dichloromethane (10 ml) at 0 °C under an atmosphere of nitrogen. The solution was allowed to warm to ambient temperature, with stirring for 2 h, and was then evaporated under reduced pressure. The residue was treated with dry hexane (60 cm^3), filtered, and the filtrate evaporated under reduced pressure to yield the product as a white solid (0.19 g, 95%); $\delta_P(CH_2Cl_2)$ 138.7 and 137.8 (4:3).

3-O-(3-*Methyl*-1,3,2-*oxazaphospholidin*-2-*yloxy*)-1,2-*di*-O-*palmitoyl*-sn-*glycerol* **6b**. This compound was prepared as described for **6a** above. Thus, from 1,2-dipalmitoyl-*sn*-glycerol (0.15 g) was isolated **6b** (0.18 g, 100%); $\delta_P(CH_2Cl_2)$ 138.7 and 137.8 (2:3).

3-O-(3-*Methyl*-2-*oxo*-1,3,2-*oxazaphospholidin*-2-*yloxy*)-1,2-*di*-O-*palmitoyl*-rac-*glycerol* **7a**.—A portion of standard dinitrogen tetroxide solution (0.16 cm^3, containing 0.075 mmol of oxidant, sufficient to oxidise 0.30 mmol of phosphite) was added dropwise with vigorous stirring to compound **6a** (0.19 g, 0.28 mmol) in dry dichloromethane (5 cm^3) at −60 °C. The solution was allowed to warm to ambient temperature and stirring con-

tinued for a further 10 min; the solution was then evaporated under reduced pressure to yield the product as a white solid (0.19 g, 98%); δ_P 19.9 and −1.3 (1:5).

3-O-(3-*Methyl*-2-*oxo*-1,3,2-*oxazaphospholidin*-2-*yloxy*)-1,2-*dipalmitoyl*-sn-*glycerol* **7b**. This compound was prepared as described for **7a** above. Thus, from **6b** (0.18 g) was isolated **7b** (0.18 g, 100%); δ_P 19.8 and −2.3 (1:3).

Water-mediated Hydrolyses.—Of **7a**. Compound **7a** (0.19 g, 0.28 mmol) was suspended in tetrahydrofuran (8 cm^3) and water (8 cm^3) at ambient temperature and stirred for 3 h. The mixture was lyophilised to yield **8a** as a white solid (0.19 g, 100%); δ_H 5.2 (1 H, m, CH), 4.1 (6 H, m, CH_2O), 3.1 (2 H, m, CH_2N), 2.3 [7 H, m, NMe, $C(O)CH_2$], 1.6 [4 H, m, $C(O)CH_2CH_2$], 1.3 [48 H, m, $(CH_2)_{12}$] and 0.9 (6 H, t, CH_3CH_2); δ_P 0.3; δ_C 173.3 (C=O) 172.9 (C=O), 69.7 (d, CH_2O, *J* 4.5), 64.5 (CH), 62.1 [$CH_2OC(O)$], 61.6 (d, CH_2O, *J* 1.5), 49.7 (d, NCH_2, *J* 7.2), 34.1 (NMe), 34.04 [$C(O)CH_2$], 33.97 [$C(O)CH_2$], 31.9 (C-3), 29.4 [m, $(CH_2)_{10}$], 24.83 (C-14), 24.80 (C-14), 22.6 (C-2) and 14.1 (C-1); *m/z* (FAB) 729 (MNa^+, 19%), 707 (MH^+, 13), 552 (dipalmitoylglycerol, 91), 415 (6), 361 (15), 313 (31), 223 (9), 156 (62) and 121 (59); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2924, 2852, 1735, 1639, 1511, 1460, 1227, 1167, 1092 and 1065 (Found: C, 63.8; H, 10.9; N, 2.0; P, 4.3. $C_{38}H_{76}NO_8P{\cdot}0.5H_2O$ requires C, 63.8; H, 10.9; N, 1.96; P, 4.33%).

Of **7b**. This reaction was conducted as described for **7a** above. Thus, from **7b** (0.18 g) was isolated **8b** (0.18 g, 100%); δ_H 9.3 (2 H, s br, NH_2), 5.2 (1 H, m, CH), 4.2 (4 H, m, CH_2O), 4.1 (2 H, m, CH_2O), 3.1 (2 H, m, CH_2N), 2.7 (3 H, s br, NMe), 2.3 [4 H, m, $C(O)CH_2$], 1.6 [4 H, m, $C(O)CH_2CH_2$], 1.3 [48 H, m, $(CH_2)_{12}$] and 0.9 (6 H, t, CH_3CH_2); $\delta_P(CH_2Cl_2)$ −0.81; δ_C 173.3 (C=O), 172.9 (C=O), 69.7 (d, CH_2O, *J* 4.6), 64.5 (CH), 62.1 [$CH_2OC(O)$], 61.6 (d, CH_2O, *J* 1.3), 49.7 (d, NCH_2, *J* 7.5), 34.1 (NMe), 34.04 [$C(O)CH_2$], 33.98 [$C(O)CH_2$], 31.9 (C-3), 29.4 [m, $(CH_2)_{10}$], 24.83 (C-14), 24.80 (C-14), 22.6 (C-2) and 14.1 (C-1); *m/z* (FAB) 1411 (2 M^+, 3%), 707 (MH^+, 26), 552 (dipalmitoylglycerol, 54), 468 (1), 367 (7), 313 (15), and 154 (100); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2918, 2852, 1735, 1631, 1511, 1457, 1257, 1230, 1167, 1092, 1065 and 1041 [Found: C, 63.0; H, 10.9; N, 2.0; P, 4.3. $C_{38}H_{76}NO_8P{\cdot}H_2O$ requires C, 63.0; H, 10.9; N, 1.9; P, 4.3%]

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