The Synthesis by Phosphoramidite Methodology of Novel Phospholipids Related to Ethylenediamine

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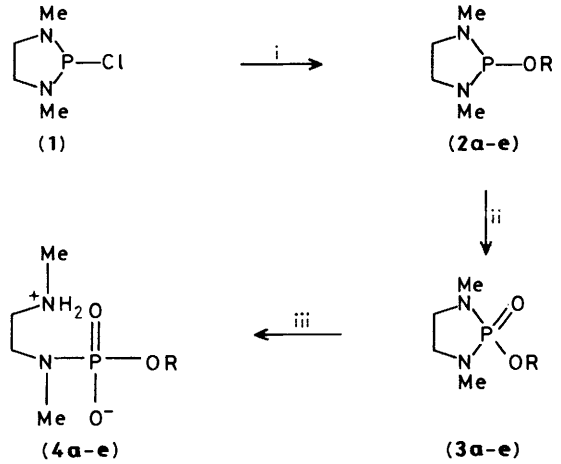
Novel phospholipid analogues related to ethylenediamine have been prepared by a rapid three-step procedure. The diazaphosphacyclopentane (**1**) reacts with alcohols to yield cyclic phosphoramidites in high yield. These are oxidised to the phosphates with N_2O_4. The phosphates undergo a single P–N cleavage under conditions of acid catalysis to yield phospholipid analogues, similar in phosphate structure to natural phospholipids, but with a single substitution of N for O. Full spectroscopic and analytical data are presented and discussed.

Phospholipids, major structural components of cell membranes,[1] are involved in many physiological processes,[2] and modified phospholipids are of great biological interest as enzyme inhibitors[3] and potential drugs.[4] The syntheses of many novel phospholipids have now been reported;[5] frequently however, these syntheses are slow and proceed in low yields. We,[6] and others,[7] have recently reported the application of phosphoramidite methodology to the preparation of novel phospholipids. Here we report the application of such procedures to the preparation of highly novel phospholipid analogues. Based on ethylenediamine, these materials contain the same phosphorus moiety as natural phospholipids, but with a single substitution of N for O. A preliminary account of this work has appeared.[8]

Results and Discussion

The phosphitylating agent 2-chloro-1,3-dimethyl-1,3,2-diazaphosphacyclopentane (**1**) was prepared by the low temperature reaction of phosphorus trichloride with *N,N'*-dimethylethylenediamine.[9] Phosphorus n.m.r.[10] and other spectroscopic data fully support the structure of this product. Of particular interest is the ^{13}C n.m.r. spectrum; this displays two signals, each with two bond phosphorus coupling clearly visible. The methylene carbon resonance is shifted downfield by *ca.* 1 p.p.m. relative to the starting amine, whereas the methyl signal is shifted upfield by over 3 p.p.m.[11]

Compound (**1**) was treated with hexanol and triethylamine at −60 °C to yield the phosphite triester (**2a**). This was fully characterised by spectroscopic data. Interestingly, in the proton n.m.r. spectrum, although the chemical shift of the *N*-methyl moiety is almost unchanged, relative to (**1**), the magnitude of the phosphorus coupling constant is markedly altered. Of course, the phosphorus-31 chemical shift is greatly altered; compound (**2a**) has a resonance at +124 p.p.m., very close to the figure reported for the methoxy analogue,[10] and some 40 p.p.m. upfield of the signal for (**1**). In the electron impact mass spectrum of (**2a**) fragmentation proceeds *via* successive loss of alkyl groups from the molecular ion; loss of the complete alkyloxy chain giving an intense peak. The octyl and octadecyl analogues, (**2b**) and (**2c**), were similarly prepared, although solubility problems necessitated a slightly higher reaction temperature in the latter case. No diminution of yield was noted with increasing chain length in (**2c**) (87%). Spectral data for these phosphites were similar to those for (**2a**). The electron impact mass spectrum of (**2c**) is particularly impressive, displaying a molecular ion peak, and weak peaks corresponding to successive fragmentation along the alkyl chain. Intense peaks correspond to loss of the alkyl (base peak) and alkyloxy chains.



a: R = C_6H_{13}
b: R = C_8H_{17}
c: R = $C_{18}H_{37}$
d: R = CH_2CO_2Et
e: R = $\Delta^9 - C_{18}H_{35}$

Scheme. *Reagents:* i, ROH, Et_3N, CH_2Cl_2, −40 to −60 °C; ii, N_2O_4, CH_2Cl_2, −60 °C; iii, H_2O, THF, catalytic HCl, room temp., 15 min–2 h

Since natural phospholipids are commonly diacyl glycerols it was of interest to determine the potential for applying this novel route to such structures. To this end, the model hydroxy ester ethyl glycolate was prepared by standard methods[12] and condensed with (**1**) as previously, to give the phosphite (**2d**). It is interesting to note that in its ^{31}P n.m.r. spectrum (**2d**) has a signal 5 p.p.m. downfield of the corresponding signals for (**2a–c**), presumably as a result of the deshielding effect of the ester moiety.

Since natural phospholipids frequently contain an alkenyl group[13] at the 2-position of the glycerol moiety, in order to test the compatibility of our route to unsaturated alcohols, oleyl alcohol was condensed with (**1**) to yield (**2e**), which had similar spectroscopic properties to (**2c**), with the exception of the vinylic resonances in the ^1H n.m.r. spectrum.

The second stage of our synthetic strategy was the oxidation of the cyclic phosphite triesters to their corresponding phosphates. Many reagents have been reported for this type of conversion; in this case the use of dinitrogen tetraoxide[14] was found to be most successful. One concern was the possible addition across the double bond of (**2e**), since this type of

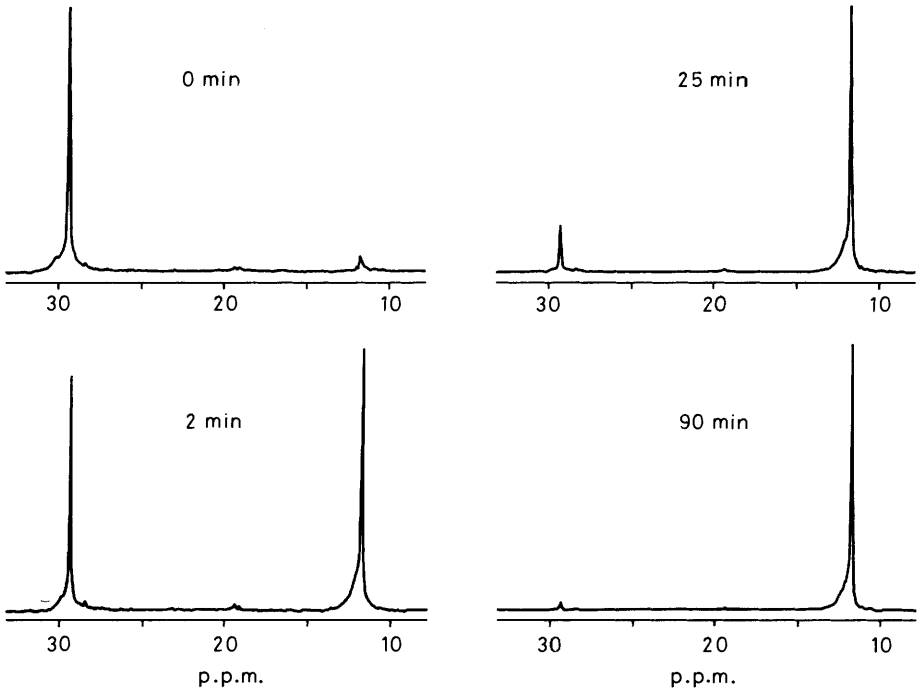


Figure. Phosphorus-31 n.m.r. kinetic study of hydrolysis of (**3b**), in aqueous THF containing HCl (2 molar %)

reaction is well known.[15] Schechter[16] reports optimum temperatures in the range −10 to +25 °C for such additions, with the use of oxygen-containing solvents reported to facilitate the reaction.[16,17] Thus, oxidation of the phosphites (**2a—e**) was conducted in dry dichloromethane at low temperature, using a standard solution of dinitrogen tetraoxide. Certain spectral properties characterise the phosphates (**3a—e**) as a group. Thus, a dramatic shift in the phosphorus-31 n.m.r. resonance is noted; from *ca.* 125 p.p.m. for the phosphites to *ca.* 25 p.p.m. for the phosphates. This compares closely to data reported on similar compounds, such as $OP(NMe_2)_2(OEt)$.[18] As previously, the coupling constant from phosphorus to NMe in the ^1H n.m.r. spectrum is highly receptive to changes in the phosphorus environment, and diminished from *ca.* 12 to *ca.* 10 Hz on oxidation. As expected, the presence of a phosphoryl function was clearly visible in the i.r. spectra of (**3a—e**), with a single strong band in each case, in the range 1 224—1 257 cm^{-1}. Corbridge[19] reports that most phosphates display a phosphoryl stretch in the range 1 200—1 320 cm^{-1}.

Thus, having synthesized the cyclic phosphates (**3 a—e**) the final step in the synthesis was their acid-catalysed hydrolysis. Although the P–N bond is well known to be acid labile,[20] it was unclear whether hydrolysis could be restricted to a single phosphoramide bond in (**3 a—e**). Indeed, initial attempts, using an excess of acid,[6] led to mixtures of mono- and di-cleaved products. However, kinetic studies by phosphorus-31 n.m.r. established conditions which gave only a single cleavage of the heterocycle (Figure). Ideal conditions varied with the individual case from 2—5 molar %; (**3d**) hydrolysed rather more easily than (**3a—c**), and (**3e**) rather less. Thus, by n.m.r., yields of (**4a—e**) were quantitative. However, isolated yields were not so great (65—90%), probably due to the physical properties of the phospholipid-like (amphipathic) products. Phosphate diesters (**4a—e**) were fully characterised by spectroscopic and analytical data. Thus, the ^1H n.m.r. spectra provide strong evidence of a single P–N cleavage; one *N*-methyl signal remains phosphorus coupled ($\delta \sim 2.7$) whilst the other, at the cleavage site, loses this coupling ($\delta \sim 3.0$). Again, phosphorus n.m.r. chemical shifts change markedly on proceeding from the cyclic phosphate triesters (**3a—e**) to the cleaved materials (**4a—e**). The final products are observed at *ca.* 9 p.p.m.; which compares closely to +11 p.p.m. reported for $OP(NMe_2)(OEt)_2$.[21] The highly polar nature of the diesters lead to poor electron impact mass spectra. However, using fast atom bombardment, intense [>50%, excluding (**4e**)] protonated molecular ion peaks were noted in each case, as were typical M_2H^+ peaks and fragments corresponding to loss of water, and of alkyl groups.

Thus, in conclusion, novel phospholipids based on ethylenediamine can be prepared by a rapid three-step procedure based on phosphoramidite intermediates. The synthesis is entirely compatible with the presence of olefinic and ester functionalities in the side chain, which suggests that it should be applicable to more complex phospholipids of biological interest. Such studies are currently under way.

Experimental

^1H N.m.r. spectra were recorded on a Varian XL200 spectrometer with $SiMe_4$ as internal standard. ^{31}P N.m.r. spectra were recorded on this instrument with 85% H_3PO_4 as external standard; positive chemical shifts are downfield of this reference. I.r. spectra were obtained on a Perkin-Elmer 983 spectrophotometer. Mass spectra were recorded at U.C.L. on a VG 7070H spectrometer courtesy of Dr. M. Mruzek (e.i.) or on a VG Zab 1F courtesy of the University of London Mass Spectrometry Service (f.a.b.). Microanalyses were performed in this department courtesy of Mr. A. T. T. Stones. All reactions, excluding hydrolyses, were carried out under scrupulously dry conditions. Light petroleum refers to the fraction boiling 40—60 °C.

2-*Chloro*-1,3-*dimethyl*-1,3,2-*diazaphosphacyclopentane* (**1**).—Dry *N,N'*-dimethylethylenediamine (17.63 g, 0.2 mol) and triethylamine (32 ml, 0.23 mol) in dichloromethane (30 ml) were added dropwise with vigorous stirring to dichloromethane (80 ml) at −40 °C under an atmosphere of nitrogen. Separately, but

simultaneously, phosphorus trichloride (20 ml, 0.23 mol) in dichloromethane (50 ml) was added dropwise. After warming to −30 °C, a further portion of triethylamine (32 ml, 0.23 mol) in dichloromethane (20 ml) was added dropwise with vigorous stirring. The solution was allowed to warm to ambient temperature, with stirring for 2 h. The solvent was then removed under reduced pressure and the residue extracted with diethyl ether (3 × 100 ml). The extract was filtered and the filtrate was concentrated under reduced pressure to give a yellow oil which was vacuum distilled. The product was collected as a clear, colourless oil (22 g, 72%), b.p. 34—44 °C, 0.1 mmHg; $\delta_H(CDCl_3)$ 3.34 (d, 2 H, NCH_2, *J* 7.5 Hz) and 2.80 (d, 3 H, NMe, *J* 15 Hz); $\delta_P(C_6D_6)$ +165; $\delta_C(C_6D_6)$ 52.80 (d, NCH_2, *J* 10.7 Hz) and 33.16 (d, NMe, *J* 18.8 Hz); m/z (e.i.) 154 (M^+, ^{37}Cl) 152.0275, (M^+, ^{35}Cl; calc. for $C_4H_{10}ClN_2P$: 152.0270), 117 (M^+ − Cl, base peak), 74 (24%), 60 (20), 42 (15), and 28 (14); $\nu_{max.}$(liquid film) 2 998, 2 444, and 1 020 cm^{-1}.

2-*Hexyloxy*-1,3-*dimethyl*-1,3,2-*diazaphosphacyclopentane* (**2a**).—Anhydrous hexan-1-ol (1.00 g, 9.84 mmol) and triethylamine (0.996 g, 9.84 mmol) in dichloromethane (30 ml) were added dropwise with vigorous stirring to compound (**1**) (1.5 g, 9.84 mmol) in dichloromethane (30 ml) at −60 °C under an atmosphere of dry nitrogen. The solution was warmed to ambient temperature, with stirring for 40 min, and then extracted with saturated aqueous hydrogen carbonate (60 ml), followed by saturated brine (60 ml). The mixture was then dried ($MgSO_4$) and evaporated under reduced pressure. The residue was treated with anhydrous diethyl ether (100 ml), and the extract filtered, and concentrated under reduced pressure to yield the product as a clear oil (1.86 g, 87%); $\delta_H(CDCl_3)$ 3.60 (m, 2 H, OCH_2), 3.10 (m, 4 H, NCH_2CH_2), 2.72 (d, 6 H, NMe, *J* 12 Hz), 1.50 (m, 2 H, OCH_2CH_2), 1.27 (m, 6 H, $CH_2CH_2CH_2Me$), and 0.89 (m, 3 H, CH_2Me); $\delta_P(C_6D_6)$ +124; m/z (e.i.) 218.1550 (M^+, calc. for $C_{10}H_{23}N_2OP$: 218.1548, 7%), 189 (M^+ − Et, 0.1), 175 (M^+ − Pr, 4), 161 (M^+ − Bu, 0.1), 133 (M^+ − Hex, 34%), 117 (M^+ − OHex, 87), and 44 (Me_2N, base peak); $\nu_{max.}$(liquid film) 2 995, 2 858, and 1 027 cm^{-1}.

1,3-*Dimethyl*-2-*octyloxy*-1,3,2-*diazaphosphacyclopentane* (**2b**).—Anhydrous octan-1-ol (1.28 g, 9.84 mmol) and triethylamine (0.996 g, 9.84 mmol) in dichloromethane (30 ml) were added dropwise with vigorous stirring to compound (**1**) (1.5 g, 9.84 mmol) in dichloromethane (30 ml) at −60 °C under an atmosphere of dry nitrogen. The solution was warmed to ambient temperature, with stirring for 1 h, and then extracted with saturated aqueous sodium hydrogen carbonate (2 × 60 ml), followed by saturated brine (30 ml). The mixture was then dried ($MgSO_4$) and evaporated under reduced pressure. The residue was treated with light petroleum (100 ml), filtered, and concentrated under reduced pressure to yield the product as a clear oil (1.88 g, 75%); $\delta_H(CDCl_3)$ 3.60 (m, 2 H, OCH_2), 3.12 (m, 4 H, NCH_2CH_2), 2.72 (d, 6 H, NMe, *J* 12 Hz), 1.3 [m, 12 H, $(CH_2)_6$], and 0.86 (m, 3 H, CH_2Me); $\delta_P(CD_2Cl_2)$ +125.5; m/z (e.i.) 246.1844 (M^+, calc. for $C_{12}H_{27}N_2O_2$: 246.1861, 14%), 203 (M^+ − Pr, 7), 189 (M^+ − Bu, 0.6), 161 (M^+ − hexyl, 0.4), 147 (M^+ − heptyl, 0.3), 133 (M^+ − octyl, 54), 117 (M^+ − Ooctyl, base peak), and 44 (Me_2N, 92); $\nu_{max.}$(liquid film) 2 918, 2 851, 2 798, and 1 020 cm^{-1}

1,3-*Dimethyl*-2-*octadecyloxy*-1,3,2-*diazaphosphacyclopentane* (**2c**).—Anhydrous octadecan-1-ol (2.66 g, 9.84 mmol) and triethylamine (0.996 g, 9.84 mmol) in dichloromethane (80 ml) were added dropwise with vigorous stirring to compound (**1**) (1.5 g, 9.84 mmol) in dichloromethane (40 ml) at −40 °C under an atmosphere of dry nitrogen. The solution was warmed to ambient temperature, with stirring for 1 h, and then extracted with saturated aqueous sodium hydrogen carbonate (2 × 150 ml), followed by saturated brine (100 ml). The mixture was then dried ($MgSO_4$) and evaporated under reduced pressure to yield the product as a white wax (3.20 g, 84%); $\delta_H(CDCl_3)$ 3.60 (m, 2 H, OCH_2), 3.12 (m, 4 H, NCH_2CH_2), 2.70 (d, 6 H, NMe, *J* 12 Hz), 1.60 (m, 2 H, OCH_2CH_2), 1.2 [m, 30 H, $(CH_2)_{15}$], and 0.88 (m, 3 H, CH_2Me); $\delta_P(C_6D_6)$ +123.9; *m/z* (e.i.) 386.3416 (M^+, calc. for $C_{22}H_{47}N_2OP$: 386.3426, 8%), 358 (MH^+ − Et, 0.1), 343 (M^+ − Pr, 3), 330 (MH^+ − Bu, 0.1), 315 (M^+ − pentyl, 0.2), 301 (M^+ − hexyl, 0.3), 287 (M^+ − heptyl, 0.3) 273 (M^+ − octyl, 0.3), 259 (M^+ − nonyl, 0.4), 245 (M^+ − decyl, 0.4), 231 (M^+ − undecyl, 0.4), 217 (M^+ − dodecyl, 0.3), 203 (M^+ − tridecyl, 1), 189 (M^+ − tetradecyl, 0.9), 175 (M^+ − pentadecyl, 0.1), 161 (M^+ − hexadecyl, 0.6), 147 (M^+ − heptadecyl, 0.4), 135 (MH^+ − octadecyl, base peak), 133 (M^+ − octadecyl, 30), 117 (M^+ − Ooctadecyl, 95), and 44 (Me_2N, 97); $\nu_{max.}$(liquid film) 2 919, 2 845, and 1 020 cm^{-1}.

Ethyl 1,3-*Dimethyl*-1,3,2-*diazaphosphacyclopentan*-2-*yloxy*-*acetate* (**2d**).—Anhydrous ethyl glycolate (0.819 g, 7.87 mmol) and triethylamine (0.879, 8.65 mmol) in dichloromethane (30 ml) were added dropwise with vigorous stirring to compound (**1**) (1.32 g, 8.65 mmol) in dichloromethane (30 ml) at −60 °C under an atmosphere of dry nitrogen. The solution was warmed to ambient temperature, with stirring for 40 min, and then extracted with saturated aqueous sodium hydrogen carbonate (80 ml), followed by water (60 ml). The mixture was then dried ($MgSO_4$) and evaporated under reduced pressure. The residue was treated with diethyl ether (100 ml) and the extract filtered and concentrated under reduced pressure, to yield the product as a clear oil (1.21 g, 70%); $\delta_H(CDCl_3)$ 4.20 (q, 2 H, OCH_2Me), 4.12 (d, 2 H, $POCH_2$, *J* 12 Hz), 3.20 (m, 4 H, NCH_2CH_2), 2.74 (d, 6 H, NMe, *J* 12 Hz), and 1.28 (t, 3 H, CH_2Me); $\delta_P(CDCl_3)$ +129.6; *m/z* (e.i.) 220.0972 (M^+, calc. for $C_8H_{17}N_2O_3P$: 220.0977, 1%), 205 (M^+ − Me, <1), 191 (M^+ − Et, <1), 175, 133 (M^+ − CH_2CO_2Et, 82), 117 (M^+ − OCH_2CO_2Et, base peak), 90, 74, 60, and 42; $\nu_{max.}$(liquid film) 2 972, 2 891, 2 805, 1 751, and 1 027 cm^{-1}.

1,3-*Dimethyl*-2-*oleyloxy*-1,3,2-*diazaphosphacyclopentane* (**2e**).—Anhydrous oleyl alcohol (1.408 g, 5.25 mmol) and triethylamine (0.584 g, 5.77 mmol) in dichloromethane (40 ml) were added dropwise with vigorous stirring to compound (**1**) (0.88 g, 5.77 mmol) in dichloromethane (30 ml) at −60 °C under an atmosphere of dry nitrogen. The solution was warmed to ambient temperature, with stirring for 1 h, and then extracted with saturated aqueous sodium hydrogen carbonate (100 ml), followed by saturated brine (100 ml). The mixture was then dried ($MgSO_4$) and evaporated under reduced pressure. The residue was treated with hexane (100 ml), and the extract filtered and concentrated under reduced pressure, to yield the product as a clear oil (1.44 g, 72%); $\delta_H(CDCl_3)$ 5.28 (m, 2 H, CH=CH), 3.36 (m, 2 H, OCH_2), 3.12 (m, 4 H, NCH_2CH_2), 2.66 (d, 6 H, NMe, *J* 12 Hz), 2.00 (m, 4 H, 2 × CH_2C=), 1.60 (m, 2 H, OCH_2CH_2), 1.08 (m, 22 H, $(CH_2)_{12}$), and 0.88 (m, 3 H, CH_2Me); $\delta_P(CDCl_3)$ +126.0; *m/z* (e.i.) 384.3271 (M^+, calc. for $C_{22}H_{45}N_2OP$: 384.3270, 4%), 369 (M^+ − Me, <1), 341 (M^+ − Pr, 0.6), 327 (M^+ − Bu, 0.5), 313 (M^+ − pentyl, 0.7), 299 (M^+ − hexyl, 1), 285 (M^+ − heptyl, 3), 271 (M^+ − octyl, 1), 258 (M^+ − nonenyl, 0.1), 245 (M^+ − decenyl, 0.2), 231 (M^+ − undecenyl, 0.9), 217 (M^+ − dodecenyl, 0.3), 203 (M^+ − tridecenyl, 0.9), 189 (M^+ − tetradecenyl, 0.7) 175 (M^+ − pentadecenyl, 0.2), 161 (M^+ − hexadecenyl, 1), 135 (MH_2^+ − oleyl, base peak), 133 (M^+ − oleyl, 27), 117 (M^+ − Ooleyl, 68), 89, 87, 74, 60, 57, and 44 (Me_2N, 66); $\nu_{max.}$(liquid film) 2 918, 2 851, and 1 017 cm^{-1}.

Preparation of Standard Dinitrogen Tetraoxide Solutions.—Dinitrogen tetraoxide was condensed at 0 °C and treated with

dry oxygen gas for 15 min. Phosphorus pentaoxide was added, and the oxidant distilled by slight warming and collected in an acetone–solid CO_2 cooling bath. Purified dinitrogen tetraoxide could be stored for prolonged periods in the deep freeze. To prepare a standard solution, it was allowed to warm to ambient temperature and a small volume (*ca.* 1 ml) was added to an accurately weighed volume of dry dichloromethane (*ca.* 100 ml). Accurate re-weighing allowed calculation of the concentration of oxidant (*ca.* 0.1 M). Such solutions could be stored, firmly stoppered, in the fridge for several weeks, without appreciable deterioration.

2-*Hexyloxy*-1,3-*dimethyl*-1,3,2-*diazaphosphacyclopentane* 2-*Oxide* (**3a**).—A portion of standard dinitrogen tetraoxide solution (9.6 ml, contains 1.06 mmol oxidant) was added dropwise with vigorous stirring to a solution of 2-hexyloxy-1,3-dimethyl-1,3,2-diazaphosphacyclopentane (0.92 g, 4.22 mmol) in dry dichloromethane (15 ml) at −60 °C. The solution was allowed to warm to ambient temperature, when the solvent was removed under reduced pressure. The residue was dissolved in diethyl ether (50 ml) and extracted with water (5 ml). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure, to yield the product as a clear oil (0.79 g, 80%); $\delta_H(CDCl_3)$ 3.86 (m, 2 H, OCH_2), 3.10 (d, 4 H, NCH_2CH_2, *J* 9.6 Hz), 2.60 (d, 6 H, NMe, *J* 9.6 Hz), 1.34 [m, 8 H, $(CH_2)_4$], and 0.88 (m, 3 H, CH_2Me); $\delta_P(CDCl_3)$ +25.0; *m/z* (e.i.) 234.1496 (M^+, calc. for $C_{10}H_{23}N_2O_2P$: 234.1497, 5%), 219 (M^+ − Me, 0.2), 205 (M^+ − Et, 0.7), 191 (M^+ − Pr, 0.1), 178 (MH^+ − Bu, 0.2), 163 (M^+ − pentyl, 0.1), 151 (MH_2^+ − hexyl, McClafferty, 42), 149 (M^+ − hexyl, 8), 133 (M^+ − Ohexyl, 20), 56, and 43 ($MeNCH_2$, base peak); $\nu_{max.}$(liquid film) 2 925, 2 858, 1 257 (P=O), and 1 040 cm^{-1}.

1,3-*Dimethyl*-2-*octyloxy*-1,3,2-*diazaphosphacyclopentane* 2-*Oxide* (**3b**).—A portion of standard dinitrogen tetraoxide solution (11.2 ml, 0.608 mmol) was added dropwise with vigorous stirring to a solution of 1,3-dimethyl-2-octyloxy-1,3,2-diazaphosphacyclopentane (0.599 g, 2.43 mmol) in dry dichloromethane (25 ml) at −60 °C. The solution was allowed to warm to ambient temperature when the solvent was removed under reduced pressure. The residue was treated with light petroleum (50 ml), filtered, and concentrated under reduced pressure to yield the product as a clear oil (0.51 g, 80%); $\delta_H(CDCl_3)$ 3.84 (m, 2 H, OCH_2), 3.10 (d, 4 H, NCH_2CH_2, *J* 9.6 Hz), 2.60 (d, 6 H, NMe, *J* 9.6 Hz), 1.30 (m, 12 H, $(CH_2)_6$), and 0.88 (m, 3 H, CH_2Me); $\delta_P(CDCl_3)$ +25.0; *m/z* (e.i.) 262.1791 (M^+, calc. for $C_{12}H_{27}N_2O_2P$: 262.1810, 8%), 233 (M^+ − Et, 0.2), 219 (M^+ − Pr, 2), 205 (M^+ − Bu, 1), 191 (M^+ − pentyl, 0.1), 177 (M^+ − hexyl, 0.4), 163 (M^+ − heptyl, 0.1), 151 (MH_2^+ − octyl, McClafferty, 81), 149 (M^+ − octyl, 12), 133 (M^+ − Ooctyl, 24), 57, and 44 (Me_2N, base peak); $\nu_{max.}$(liquid film) 2 918, 2 851, 1 254 (P=O), and 1 027 cm^{-1}.

1,3-*Dimethyl*-2-*octadecyloxy*-1,3,2-*diazaphosphacyclopentane* 2-*Oxide* (**3c**).—A portion of standard dinitrogen tetraoxide solution (6.73 ml, 0.37 mmol) was added dropwise with vigorous stirring to a solution of 1,3-dimethyl-2-octadecyloxy-1,3,2-diazaphosphacyclopentane (0.566 g, 1.46 mmol) in dry dichloromethane (30 ml) at −40 °C. The solution was allowed to warm to ambient temperature when the solvent was removed under reduced pressure. The residue was treated with hexane (100 ml), filtered, and concentrated under reduced pressure to yield the product as a white solid (0.472 g, 80%);$\delta_H(CDCl_3)$ 3.90 (m, 2 H, OCH_2), 3.12 (d, 4 H, NCH_2CH_2, *J* 9.6 Hz), 2.60 (d, 6 H, NMe, *J* 9.6 Hz), 1.64 (m, 2 H, OCH_2CH_2), 1.26 [m, 30 H, $(CH_2)_{15}$], and 0.86 (m, 3 H, CH_2Me); δ_P + 25.0; *m/z* (e.i.) 402.3406 (M^+, calc. for $C_{22}H_{47}N_2O_2P$: 402.3375, 3%), 373 (M^+ − Et, <1), 345 (M^+ − Bu, <1), 331 (M^+ − pentyl, <1), 317 (M^+ − hexyl, <1), 303 (M^+ − heptyl, <1), 289 (M^+ − octyl, <1), 275 (M^+ − nonyl, 0.1), 261 (M^+ − decyl, 0.1), 247 (M^+ − undecyl, <1), 233 (M^+ − dodecyl, <1), 219 (M^+ − tridecyl, 1), 205 (M^+ − tetradecyl, 1), 191 (M^+ − pentadecyl, 0.1), 177 (M^+ − hexadecyl, 0.2), 163 (M^+ − heptadecyl, 0.2), 151 (MH_2^+ − octadecyl, McClafferty, base peak), 149 (M^+ − octadecyl, 5), 133 (M^+ − Ooctadecyl, 9), 57 (59), and 44 (Me_2N, 47); $\nu_{max.}$(liquid film) 2 911, 2 845, 1 244 (P=O), and 1 027 cm^{-1}.

Ethyl 1,3-*Dimethyl*-1,3,2-*diazaphosphacyclopentan*-2-*yloxyacetate* 2-*Oxide* (**3d**).—A portion of standard dinitrogen tetraoxide solution (6.2 ml, 0.486 mmol) was added dropwise with vigorous stirring to a solution of ethyl 1,3-dimethyl-1,3,2-diazaphosphacyclopentan-2-yloxyacetate (0.408 g, 1.85 mmol) in dry dichloromethane (25 ml) at −60 °C. The solution was allowed to warm to ambient temperature when the solvent was removed under reduced pressure. The residue was treated with diethyl ether (50 ml) and the extract filtered and concentrated under reduced pressure, to yield the product as a clear oil (0.302 g, 69%); $\delta_H(CDCl_3)$ 4.48 (d, 2 H, $POCH_2$, *J* 12 Hz), 4.20 (q, 2 H, OCH_2Me), 3.12 (d, 4 H, NCH_2CH_2, *J* 9.6 Hz), 2.62 (d, 3 H, NMe, *J* 9.6 Hz), and 1.26 (t, 3 H, OCH_2Me); $\delta_P(CDCl_3)$ 26.0; *m/z* (e.i.) 236.0950 (M^+, calc. for $C_8H_{17}N_2O_4P$: 236.0943, 27%), 221 (M^+ − Me, 0.5), 207 (M^+ − Et, 0.2), 191 (M^+ − OEt, 9), 180 (MH^+ − CH_2CH_2NMe, 16), 164 (MH^+ − CO_2Et, 3), 149 (M^+ − CH_2CO_2Et, 43), 133 (M^+ − OCH_2CO_2Et, base peak), 124 (73), 106 (15), 57 (15), and 43 (67); $\nu_{max.}$(liquid film) 2 979, 2 932, 1 755, 1 224 (P=O), 1 054, 940, 807, and 740 cm^{-1}.

1,3-*Dimethyl*-2-*oleyloxy*-1,3,2-*diazaphosphacyclopentane* 1-*Oxide* (**3e**).—A portion of standard dinitrogen tetraoxide solution (2.50 ml, 0.192 mmol) was added dropwise with vigorous stirring to a solution of 1,3-dimethyl-2-oleyloxy-1,3,2-diazaphosphacyclopentane (0.295 g, 0.77 mmol) in dichloromethane (25 ml) at −70 °C. The solution was allowed to warm to ambient temperature when the solvent was removed under reduced pressure, to yield the product as a clear oil (0.307 g, 100%); $\delta_H(CDCl_3)$ 5.30 (m, 2 H, CH=CH), 3.86 (m, 2 H, OCH_2), 3.08 (d, 4 H, NCH_2CH_2, *J* 9.6 Hz), 2.60 (d, 6 H, NMe, *J* 9.6 Hz), 2.00 (m, 4 H, 2 × CH_2C=), 1.64 (m, 2 H, OCH_2CH_2), 1.26 [m, 22 H, $(CH_2)_{11}$], and 0.86 (m, 3 H, CH_2Me); $\delta_P(CDCl_3)$ + 25.0; *m/z* (e.i.) 400.3210 (M^+, calc. for $C_{22}H_{45}N_2O_2P$: 400.3218, 6.5%), 372 (MH^+ − Et, 0.3), 315 (M^+ − Hex, <1), 247 (M^+ − undecenyl, <1), 219 (M^+ − tridecenyl, 0.4), 205 (M^+ − tetradecenyl, 0.2), 177 (M^+ − hexadecenyl, <1), 151 (MH_2^+ − oleoyl, McClafferty, base peak), 133 (M^+ − Ooleyl, 20), 56 (12), and 43 (51); $\nu_{max.}$(liquid film) 2 918, 2 845, 1 257 (P=O), and 1 027 cm^{-1}.

O-*Hexyl*-N-*methyl*-N-(2-*methylaminoethyl*)*phosphoramide* (**4a**).—Dilute aqueous hydrochloric acid (4.27 mM; 4 ml, 2 molar %) was added to a solution of 2-hexyloxy-1,3-dimethyl-1,3,2-diazaphosphacyclopentane 2-oxide (0.2 g, 0.85 mmol) in tetrahydrofuran (THF) (4 ml) and the mixture was stirred for 2 h. It was then neutralised by careful addition of dilute aqueous sodium hydroxide (4.27 mM; *ca.* 4 ml), to give a final pH of 6.95. The solvent was then removed under reduced pressure and the residue dissolved in chloroform (50 ml) and the solution dried ($MgSO_4$), and concentrated under reduced pressure. The residue was treated with light petroleum and the extract filtered and concentrated under reduced pressure to give the product as a white solid, which was pure by spectroscopic analysis (0.15 g, 77%). Analytical data were obtained on a small sample, crystallised from refluxing THF–light petroleum; $\delta_H(CDCl_3)$ 3.78 (m, 2 H, OCH_2), 3.26 (m, 2 H, $MeNHCH_2$), 3.00 (m, 2 H, $PNCH_2$), 2.76 (d, 3 H, NMe, *J* 8.6 Hz), 2.64 (s, 3 H, $MeNHCH_2$), 1.56 (m, 2 H, OCH_2CH_2), 1.30 (m, 6 H, 3 × CH_2), and 0.88 (m,

3 H, CH_2Me); $\delta_P(CDCl_3)$ + 8.76; *m/z* (f.a.b; thioglycerol/oxalic acid) 505 (M_2H^+, 1%), 271 ($M^+ + H_2O$, 6), 254 (MH^+, ^{13}C, 7), 253 (MH^+, 71), 235 ($MH^+ - H_2O$, 76), 206 ($M^+ - EtOH$, 3) 192 ($M^+ - PrOH$, 5), 179 ($MH^+ - BuOH$, 1), 166 ($MH^+ - PentO$, <1), 151 ($MH^+ - HexOH$, 8), 133 ($MH^+ - HexOH - H_2O$, 17), 89 ($CH_2CH_2NCH_2PO$, base peak), and 58 ($MeNHCH_2CH_2$, 75); $\nu_{max.}$(paraffin mull) 3 359 (NH), 1 207, and 1 033 cm^{-1} (Found: C, 44.8%; H, 9.9%; N, 10.55%. $C_{10}H_{25}N_2O_3P.H_2O$ requires C, 44.43%; H, 10.07%; N, 10.36%).

N-*Methyl*-N-(2-*methylaminoethyl*)-O-*octylphosphoramide* (**4b**).—Dilute aqueous hydrochloric acid (5.63 mM; 4 ml, 2 molar %) was added to a solution of 2-hexyloxy-1,3-dimethyl-1,3,2-diazaphosphacyclopentane 2-oxide (0.295 g, 1.13 mmol) in THF (4 ml), with stirring, at ambient temperature. After the mixture had been stirred for 2 h, the solution was neutralised by careful addition of dilute aqueous sodium hydroxide (5.63 mM; *ca.* 4 ml), to give a final pH of 6.94. The solvent was then removed under reduced pressure and the residue dissolved in chloroform (100 ml) and the solution, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was treated with light petroleum and the extract filtered and concentrated under reduced pressure to give the product as a white solid, which was pure by spectroscopic analysis, (0.251 g, 80%). Analytical data were obtained on a small sample, crystallised from refluxing light petroleum–THF; $\delta_H(CDCl_3)$ 3.76 (m, 2 H, OCH_2), 3.26 (m, 2 H, $MeNHCH_2$), 3.00 (m, 2 H, $PNCH_2$), 2.76 (d, 3 H, PNMe, *J* 8.6 Hz), 2.64 (s, 3 H, $MeNHCH_2$), 1.58 (m, 2 H, OCH_2CH_2), 1.26 (m, 10 H, 5 × CH_2), and 0.88 (m, 3 H, CH_2Me); $\delta_P(CDCl_3)$ +8.53; *m/z* (f.a.b.; thioglycerol/oxalic acid) 562 (M_2H^+, <1%), 282 (MH^+, ^{13}C, 10), 281 (MH^+, 81), 263 ($MH^+ - H_2O$, 51), 248 ($M^+ - MeOH$, <1), 206 ($M^+ - BuOH$, 2), 192 ($M^+ - PentOH$, 3), 151 ($MH^+ - octanol$, 61), 133 ($MH^+ - octanol - H_2O$, 8), 89 ($CH_2CH_2NCH_2PO$, base peak), and 58 ($MeNHCH_2CH_2$, 52); $\nu_{max.}$(paraffin mull) 3 359 (NH), 1 210, and 1 023 cm^{-1} [Found: C, 49.45; H, 10.3; N, 9.9. $C_{12}H_{29}N_2O_3P$·0.5(H_2O) requires C, 49.81; H, 10.45; N, 9.68%].

N-*Methyl*-N-(2-*methylaminoethyl*)-O-*octadecylphosphoramide* (**4c**).—Dilute aqueous hydrochloric acid (3.27 mM; 4 ml, 2 molar %) was added to a solution of 1,3-dimethyl-2-octadecyloxy-1,3,2-diazaphosphacyclopentane 2-oxide (0.275 g, 0.65 mmol) in THF (8 ml), with stirring, at ambient temperature. After being stirred for 2 h, the solution was neutralised by careful addition of dilute aqueous sodium hydroxide (3.27 mM; *ca.* 4 ml), to give a final pH of 6.94. The solvent was then removed under reduced pressure and the residue dissolved in chloroform (100 ml) and the solution dried ($MgSO_4$), and concentrated under reduced pressure, to give the product as a white solid (0.203 g, 70%). Analytical data were obtained on a small sample, subjected to silica column chromatography, with methanol as eluant. $\delta_H(CDCl_3)$ 3.66 (m, 2 H, OCH_2), 3.26 (m, 3 H $MeNHCH_2$), 3.00 (m, 2 H, $PNCH_2$), 2.75 (d, 3 H, PNMe, *J* 8.6 Hz), 2.65 (s, 3 H, $MeNHCH_2$), 1.58 (m, 2 H, OCH_2CH_2), 1.26 (m, 30 H, 15 × CH_2), and 0.88 (m, 3 H, CH_2Me); $\delta_P(CDCl_3)$ +8.76; *m/z* (f.a.b.; thioglycerol/oxalic acid) 842 (M_2H^+, <1%), 422 (MH^+, ^{13}C, 13), 421 (MH^+, 54), 406 (MH^+ – Me, 1), 403 ($MH^+ - H_2O$, <1), 393 ($MH^+ - C_2H_4$, 6), 378 (MH^+ – Pr, <1), 364 (MH^+ – Bu, <1), 349 (M^+ – pentyl, <1), 337 (MH^+ – hexene, 4), 322 (MH^+ – heptyl, <1), 308 (MH^+ – octyl, <1), 294 (MH^+ – nonyl, <1), 280 (MH^+ – decyl, <1), 266 (MH^+ – undecyl, <1), 252 (MH^+ – dodecyl, <1), 238 (MH^+ – tridecyl, <1), 224 (MH^+ – tetradecyl, <1) 210 (MH^+ – pentadecyl, <1), 196 (MH^+ – hexadecyl, <1), 182 (MH^+ – heptadecyl, <1), 168 (MH^+ – octadecyl, <1), 151 (MH^+ – octadecanol, 15), 133 ($MH^+ - octadecanol - H_2O$, 7), 89 ($CH_2CH_2NCH_2PO$, base peak), and 58 ($MeNHCH_2CH_2$, 61); $\nu_{max.}$ (paraffin mull) 3 359 (NH), 1 197, and 1 023 cm^{-1} [Found: C, 61.7; H, 11.4; N, 6.6. $C_{22}H_{49}N_2O_3P$. 0.5 (H_2O) requires C, 61.5; H, 11.7; N, 6.5%].

O-(*Ethoxycarbonylmethyl*)-N-*methyl*-N-(2-*methylaminoethyl*)*phosphoramide* (**4d**).—Dilute aqueous hydrochloric acid (5.93 mM; 4 ml, 2 molar %) was added to a solution of ethyl 1,3-dimethyl-1,3,2-diazaphosphacyclopentan-2-yloxyacetate 2-oxide (0.28 g, 1.2 mmol) in THF (4 ml), with stirring, at ambient temperature. After being stirred for 15 min, the solution was neutralised by careful addition of dilute aqueous sodium hydroxide (5.93 mM; *ca.* 4 ml), to give a final pH of 6.94. This mixture was then lyophilised, and the residue dissolved in chloroform (100 ml) and the solution dried ($MgSO_4$) and concentrated under reduced pressure. The residue was treated with diethyl ether (50 ml) and the extract filtered and concentrated under reduced pressure to give the product as a white solid (0.267 g, 90%); $\delta_H(D_2O)$ 4.38 (d, 2 H, $POCH_2$, *J* 8.6 Hz), 4.42 (q, 2 H, OCH_2Me), 3.37 (m, 4 H, NCH_2CH_2), 2.90 (s, 3 H, $MeNHCH_2$), 2.81 (d, 3 H, MeNP, *J* 9.6 Hz), and 1.43 (t, 3 H, CH_2Me); $\delta_P(D_2O)$ + 10.26; *m/z* (f.a.b.; thioglycerol/oxalic acid) 509 (M_2H^+, 3%), 255 (MH^+, 69), 237 ($MH^+ - H_2O$, 4), 197 ($MH^+ - MeNHCH_2CH_2$, 4), 151 (9), 133 (7), 89 ($CH_2CH_2NCH_2PO$, base peak), and 58 ($MeNHCH_2CH_2$, 81) [Found: C, 36.0; H, 7.1; N, 10.2. $C_8H_{19}N_2O_5P$·0.5 (H_2O) requires C, 36.5; H, 7.7; N, 10.6%].

O-*Oleyl*-N-*methyl*-N-(2-*methylaminoethyl*)*phosphoramide* (**4e**).—Dilute aqueous hydrochloric acid (0.2 M; 210 µl, 5 molar %) was added to a solution of 1,3-dimethyl-2-oleyloxy-1,3,2-diazaphosphacyclopentane 2-oxide (0.307 g, 0.77 mmol) in THF (4 ml)/water (4 ml), with stirring, at ambient temperature. After being stirred for 2 h, the solution was neutralised by careful addition of dilute aqueous sodium hydroxide to give a final pH of 6.94. This mixture was lyophilised and the residue dissolved in chloroform (100 ml) and the solution dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by elution from a column of silica (50 g), with methanol. Appropriate fractions were pooled, concentrated under reduced pressure, and treated with dichloromethane, and the extract filtered and evaporated; lyophilisation of an aqueous solution of the residue, gave the product as a white powder (0.21 g, 65%); $\delta_H(CDCl_3)$ 5.24 (m, 2 H, CH=CH), 3.65 (m, 2 H, OCH_2), 3.14 (m, 2 H, NCH_2), 2.90 (m, 2 H, NCH_2), 2.66 (d, 3 H, PNMe), *J* 8.4 Hz), 2.54 (s, 3 H, $^+NH_2Me$), 1.92 (m, 4 H, CH_2CH=$CHCH_2$), 1.51 (m, 2 H, OCH_2CH_2), 1.24 [m, 22 H, $(CH_2)_{11}$], and 0.80 (m, 3 H, CH_2Me); δ_P +8.90; *m/z* (f.a.b.; thioglycerol/oxalic acid) 419 (MH^+, 11%), 151 (MH^+ – oleylOH, 6), 124 (MH^+ – Ooleylo – H_2O, 7), 89 (CH_2CH_2-NCH_2PO, base peak), and 58 ($MeNHCH_2CH_2$ 46); $\nu_{max.}$(KBr disc) 3 424 (NH), 2 999, 2 921, 2 849, 1 630, 1 182, and 1 065 cm^{-1} (Found: C, 60.3; H, 11.0; N, 6.8; $C_{22}H_{47}N_2O_3P·H_2O$ requires C, 60.5; H, 11.3; N, 6.4%.)

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