The Synthesis of Novel Phospholipids Related to Ethylenediamine

Michael S. Anson and Christopher McGuigan*

Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, U.K.

Novel phospholipids related to ethylenediamine have been prepared by a rapid three-step procedure using phosphoramidite methodology.

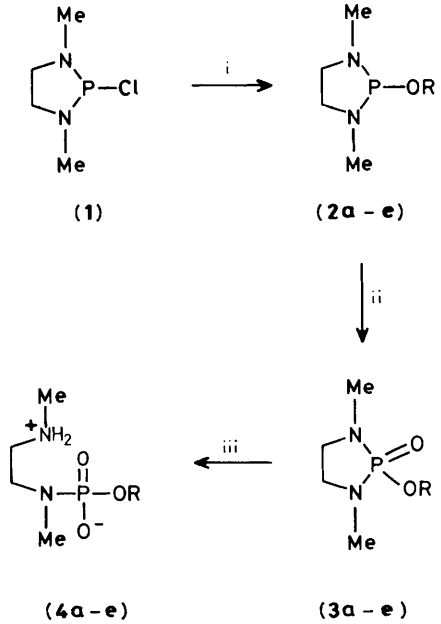
Phospholipids are major structural components of cell membranes,[1] and have been implicated in many physiological processes.[2] Modified phospholipids are of great interest in model membrane studies,[3] as enzyme inhibitors,[4] as drug carriers,[5] and as drugs in their own right.[6] The syntheses of many novel phospholipids have now been reported;[7] however, frequently these syntheses are slow and produce low yields. We[8] and others[9] have recently reported the application of phosphoramidite methodology to the preparation of novel phospholipids. Such reactions are rapid and often proceed in high yields. Here we report the application of phosphoramidite procedures to the preparation of novel phospholipids based on ethylenediamine.

1,3-Dimethyl-1,3,2-diazaphosphacyclopentane, (**1**)[10] was prepared in 72% yield by the low temperature condensation of phosphorus trichloride with *N,N'*-dimethylethylenediamine and triethylamine, in dry dichloromethane. Compound (**1**) reacts rapidly with long chain alcohols at low temperature, to give the phosphite triesters (**2a—d**) in *ca.* 80% yield. These phosphites were oxidised to the corresponding phosphates (**3a—d**) in 81—100% yield using dinitrogen tetroxide in dry dichloromethane at low temperature.[11] The use of low temperatures and non-oxygen containing solvents is reported to favour phosphite oxidation over reaction of the olefinic functionality[12] [as in (**2d**)] and, indeed, no reaction of the oleyl side-chain was observed. This is an important feature of the synthesis, since oleyl and other unsaturated moieties are frequently present in natural phospholipids.[13]

The phosphate triesters (**3a—d**) were hydrolysed to the novel acyclic phosphoryl *N*-methylethanolamine analogues (**4a—d**) by treatment with aqueous tetrahydrofuran (THF) containing a trace of acid. Although quantitative by ^{31}P n.m.r. spectroscopy, isolated yields for this step were only 65—80%. Alternative isolation procedures are currently being investigated.

Natural phospholipids often contain an ester functionality, in particular of a diacylglycerol form, and it was therefore 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[14] and condensed with (**1**) at low temperature to give the phosphite (**2e**) (70% yield), which was oxidised to the phosphate (**3e**) (75% yield) using dinitrogen tetroxide. Cleavage of this triester to the acyclic product (**4e**) proceeded as above (90% yield), with no discernible hydrolysis of the ester moiety.

Thus, in conclusion, novel phospholipids based on ethylenediamine can be prepared by a rapid three-step procedure



a; R = C_6H_{13}
b; R = C_8H_{17}
c; R = $C_{18}H_{37}$
d; R = Δ^9-$C_{18}H_{37}$
e; R = CH_2CO_2Et

Scheme 1. *Reagents:* i, ROH–Et_3N, CH_2Cl_2, −60°C; ii, N_2O_4, CH_2Cl_2, −60°C; iii, aq. HCl, THF.

which is fully compatible with the presence of olefinic and ester functionalities in the side chain.† The application of these methods to more complex phospholipids is currently underway.

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† Selected ^{31}P n.m.r. data (in $CDCl_3$, positive shifts downfield from external 85% H_3PO_4: (**1**) 165; (**2a**) 124; (**2b**) 125; (**2c**) 125; (**2d**) 126; (**2e**) 130; (**3a**) 25; (**3b**) 25; (**3c**) 25; (**3d**) 25; (**3e**) 26; (**4a**) 8.8; (**4b**) 8.5; (**4c**) 8.8; (**4d**) 8.9; (**4e**) 7.2 p.p.m.