Use of Bis[2-(trialkylsilyl)ethyl] *N,N*-Dialkylphosphoramidites for the Synthesis of Phosphate Monoesters[1]

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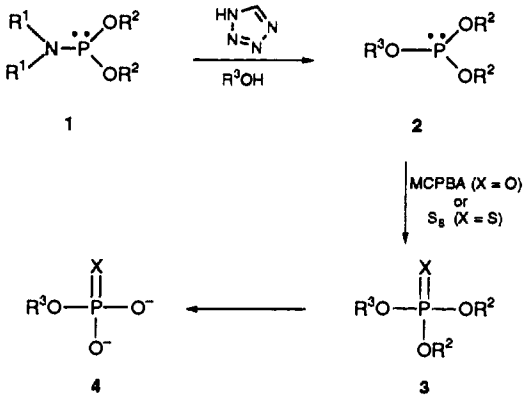
The bis[2-(trimethylsilyl)ethyl] *N,N*-dialkylphosphoramidites **7a** and **b** and bis[2-(methyldiphenylsilyl)ethyl] *N,N*-dialkylphosphoramidites **6a** and **b** have been prepared by reaction of the *N,N*-dialkylphosphorochloridites **5a** and **b** with the appropriate 2-(trialkylsilyl)ethanol. In the presence of 1*H*-tetrazole, the phosphoramidites **6a**, **b** and **7a**, **b** phosphorylated MeOH, $PhCH_2OH$, $PhCH_2CH_2OH$, $Me(PhCH_2CH_2)CHOH$, 2,3,4,5,6-penta-*o*-benzyl-*myo*-inositol and Bu^{t}OH, to give the phosphites **8a–h**. Without isolation, these were oxidised to the corresponding phosphate triesters **9a–h** with *m*-chloroperoxybenzoic acid. Treatment of the triesters **9a–h** with tetrabutylammonium fluoride removes only one 2-(trialkylsilyl)ethyl group to give the diesters **10a–h**, whereas treatment with a solution of hydrofluoric acid in acetonitrile–water gives the phosphate monoesters **11a–e**.

The P^{III} phosphoramidites **1** have recently joined the P^V phosphorylation strategies[2] as popular reagents for the synthesis of phosphate monoesters. The phosphoramidites **1** react with a range of alcohols in the presence of 1*H*-tetrazole to give the phosphites **2**, which are readily oxidised with, for example, *m*-chloroperoxybenzoic acid (MCPBA) or sulfur to give the triesters **3** (X = O, S). Removal of the protecting groups from **3** gives rise to the phosphate or thiophosphate monoesters **4** (Scheme 1). Several phosphoramidite reagents have been developed, each requiring a method of deprotection. Reese and Ward[3] have used bis(2-cyanoethyl) *N,N*-diethylphosphoramidite **1a** in their synthesis of *myo*-inositol phosphates and Uhlmann and Engels[4] have used bis(2-cyanoethyl) and bis[2-(*p*-nitrophenyl)ethyl] *N,N*-diisopropylphosphoramidites **1b** and **c** in their synthesis of nucleotides. The 2-cyanoethyl and 2-(nitrophenyl)ethyl groups are readily removed by a β-elimination catalysed by base. Two research groups[5,6] have evaluated the use of dibenzyl *N,N*-dialkylphosphoramidites **1d**, **e**, the benzyl substituents from the phosphate triester products being removed by hydrogenolysis. We have recently used the bis(*p*-acyloxybenzyl) *N,N*-diisopropylphosphoramidites **1f** to phosphorylate AZT, the *p*-acyloxybenzyl groups from the resulting triesters being removed either by chemical or esterase-catalysed hydrolyses.[7] Bannwarth and co-workers[8,9] have developed the bis(allyl) *N,N*-diisopropylphosphoramidites **1g**, the allyl groups from the phosphate triesters being removed with $[Pd^0(PPh_3)_4]$. Di-*tert*-butyl *N,N*-diethylphosphoramidite **1h** has also been utilised,[10,11] the *tert*-butyl groups being removed by treatment with acid. Watanabe and co-workers[12,13] have recently developed *o*-phenylenedimethylene *N,N*-diethylphosphoramidite **1i**, the protecting group being removed by hydrogenolysis on Pd–C or by reduction with sodium in liquid ammonia or sodium naphthalide in tetrahydrofuran.

Not all R^3 groups of the phosphate or thiophosphate triesters **3** or monoesters **4** will be stable to the deprotection conditions, therefore other R^2 groups which can be removed under mild conditions are of interest. Silicon-based protecting groups are used extensively because of the ease with which they are removed by fluoride ion.[14] Derivatisation of phosphates with, for example, 1,1,1,3,3,3-hexamethyldisilazane to give P–O–$SiMe_3$ esters is used for GLC and mass spectral analyses, however these esters are very unstable towards traces of moisture. In contrast, the P–O–CH_2–CH_2–SiR_3 group will be more stable, but should be readily cleaved by fluoride anion to give ethene and the corresponding trialkylsilyl fluoride. Very recently other groups have used 2-(methyldiphenylsilyl)ethyl bis(*N,N*-diisopropyl)phosphoramidite[15] and 2-(trialkylsilyl)-ethyl 2-cyanoethyl *N,N*-diisopropylphosphoramidite[16] for the phosphorylation of alcohols. Here, the phosphoramidites **6a**, **b** and **7a**, **b** bearing the 2-(methyldiphenylsilyl)ethyl and 2-(trimethylsilyl)ethyl groups, respectively, have been prepared and evaluated in the synthesis of phosphate monoesters. Since the completion of this study, Chao and co-workers[17] have communicated the use of bis[2-(trimethylsilyl)ethyl] *N,N*-diisopropylphosphoramidite **7a** to phosphorylate a tyrosine residue on a protected peptide.



1a R^1 = Et, R^2 = CH_2CH_2CN
b R^1 = Pr^i, R^2 = CH_2CH_2CN
c R^1 = Pr^i, R^2 = 4-$O_2NC_6H_4CH_2CH_2$
d R^1 = Et, R^2 = $PhCH_2$
e R^1 = Pr^i, R^2 = $PhCH_2$
f R^1 = Pr^i, R^2 = 4-$RCO_2C_6H_4CH_2$
g R^1 = Pr^i, R^2 = $CH_2CH{=}CH_2$
h R^1 = Et, R^2 = Bu^t
i R^1 = Et, R^2,R^2 = *o*-$Ph(CH_2)_2$

Scheme 1

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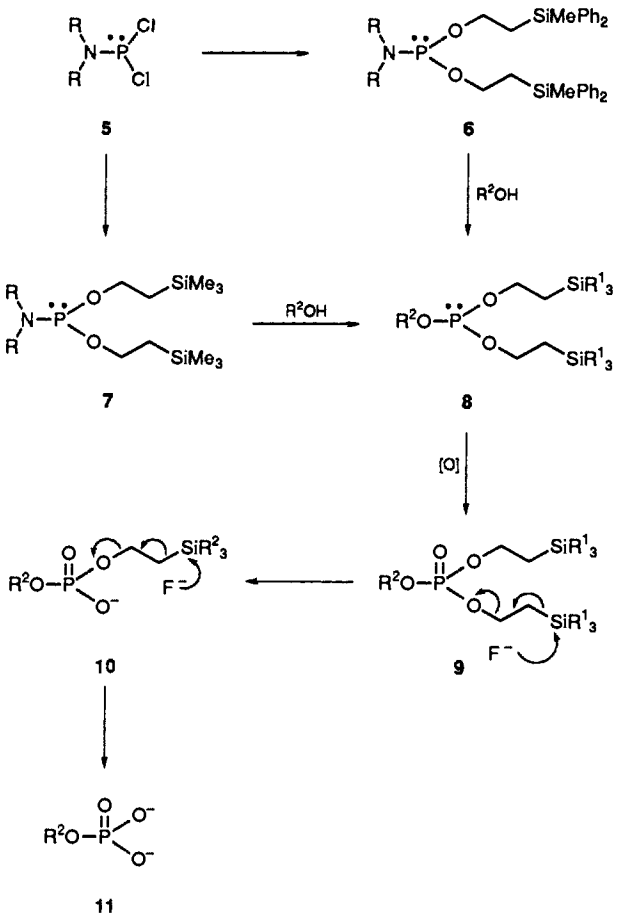

5–7
a R = Pr^i
b R = Et

8–10
a R^1 = Me, R^2 = $PhCH_2$
b $R^1{}_3$ = Ph_2Me, R^2 = $PhCH_2$
c R^1 = Me, R^2 = $Me(PhCH_2CH_2)CH$
d $R^1{}_3$ = Ph_2Me, R^2 = $Me(PhCH_2CH_2)CH$
e $R^1{}_3$ = Ph_2Me, R^2 = $PhCH_2CH_2$
f $R^1{}_3$ = Ph_2Me, R^2 = Me
g $R^1{}_3$ = Ph_2Me, R^2 = Bu^t
h $R^1{}_3$ = Ph_2Me, R^2 = 2,3,4,5,6-penta-*o*-benzyl-*myo*-inositol
i R^1 = Me, R^2 = calyculin A model

11
a R^2 = $PhCH_2CH_2$
b R^2 = $Me(PhCH_2CH_2)CH$
c R^2 = $PhCH_2$
d R^2 = Me
e R^2 = 2,3,4,5,6-penta-*o*-benzyl-*myo*-inositol
f R^2 = calyculin A model

Scheme 2

Results and Discussion

Bis[2-(trialkylsilyl)ethyl] *N,N*-dialkylphosphoramidites **6a**, **b** and **7a**, **b** were prepared by treatment of the *N,N*-dialkylphosphorochloridite **5a**, **b** with 2 equiv. of either 2-(trimethylsilyl)ethanol or 2-(methyldiphenylsilyl)ethanol in the presence of triethylamine (Scheme 2). The phosphoramidites were purified by flash column chromatography and were characterised by ^1H, ^{13}C and ^{31}P NMR spectroscopy. In the presence of 1*H*-tetrazole, the phosphoramidites **6a**, **b** and **7a**, **b** were then used to phosphorylate methanol, the primary alcohols benzyl alcohol and 2-phenylethanol, the secondary alcohols 4-phenylbutan-2-ol and 2,3,4,5,6-penta-*o*-benzyl-*myo*-inositol,[18] and *tert*-butyl alcohol to give the phosphites **8a–h**. Without isolation, the phosphites were treated with MCPBA to give the phosphate triesters **9a–h** which were isolated as oils by flash column chromatography in yields of *ca.* 50% and were fully characterised by ^1H, ^{13}C and ^{31}P NMR spectroscopy and IR spectrometry. In many cases, the mass spectra (EI, CI or FAB) of these compounds failed to give a molecular ion, which is attributable to the ease with which the $R^1{}_3Si$ group cleaves to give this fragment as the most abundant ion. In some cases the viscous oils also failed to give satisfactory elemental analysis data.

The deprotection of the $POCH_2CH_2SiR_3$ group has previously been achieved with tetrabutylammonium fluoride (TBAF). For example, this reagent has been used to remove a 2-(methyldiphenylsilyl)ethyl,[19,15] 2-(triphenylsilyl)ethyl[16] or 2-(trimethylsilyl)ethyl[20] group from nucleotide analogues. Here it was established that only one 2-(methyldiphenylsilyl)-ethyl group was removed from the triester **9b** with TBAF in either THF at room temperature or DMSO at 70 °C to give the diester **10b**. This result is an agreement with the recent findings of Sawabe and co-workers[21] who reported mono deprotection of the phosphate triester **9i** to the diester **10i** with this reagent.

A solution of lithium tetrafluoroborate in acetonitrile has been used by Lipshutz and co-workers to remove a 2-(trimethylsilyl)ethyl group from a variety of carbohydrates.[22] However, the deprotection of the phosphate triester **9c** using this reagent was unsuccessful, giving rise, as judged by ^{31}P NMR spectroscopy, to a mixture of unidentified products.

Zhang and Robins[23] used a solution of ammonium fluoride in methanol at 60 °C to remove various silyl groups from protected nucleosides. Under these conditions only one silyl protecting group was removed from the phosphate triesters **9c** and **e** to give the diesters **10c** and **e**.

A solution of trifluoroacetic acid in acetonitrile was used by Chao and co-workers to remove two 2-(trimethylsilyl)ethyl

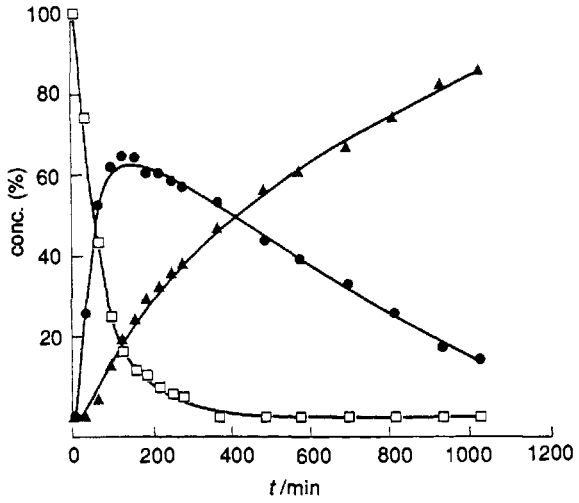

Fig. 1 Degradation profile of bis[2-(methyldiphenylsilyl)ethyl] benzyl phosphate **9b** with 15 equiv. of aqueous hydrofluoric acid in acetonitrile at 40 °C. The reaction was monitored by ^{1}H NMR spectroscopy and the percentages of the triester (**9b**, □), diester (**10b**, ●) and monoester (**11c**, ▲) were determined by the integration of PhCH_2OP peaks.

groups from a phosphate triester of a protected peptide.[17] With this method both 2-(methyldiphenylsilyl)ethyl protecting groups were removed from the phosphate triester **9e**, although, surprisingly the other phosphate triesters were stable to these deprotection conditions.

During the course of this work, Sawabe and co-workers[21] showed that the triester **9i** gave the monoester **11f** in the presence of a solution of aqueous hydrofluoric acid in MeCN. The reaction of the phosphate triesters **9b**, **c**, **f** and **h** with 15 equiv. of aqueous hydrofluoric acid in CD_3CN were monitored by ^{31}P and ^{1}H NMR spectroscopy. The 2-(trimethylsilyl)ethyl group was cleaved at room temperature whereas the 2-(methyldiphenylsilyl)ethyl group required heating to 40 °C.[17] In each case, some loss of one 2-trialkylsilyl protecting group was observed within 1 h, with the formation of ethene, δ_H(CD_3CN) 5.42 (s), and the trialkylsilyl fluoride, δ_H 0.23 (d, J_{FH} 7.3, Me_3SiF) and δ_H 0.77 (d, J_{FH} 7.3, $MePh_2SiF$) as by-products, consistent with the reaction proceeding by fluoride anion attack at silicon. Removal of the second 2-(trialkylsilyl)-ethyl group was typically complete within 24 h.

Fig. 1 shows the degradation profile for the phosphate triester **9b**, the percentage of each component being determined from the integration of the $PhCH_2OP$ groups in the ^{1}H NMR spectra. The chemical shifts for the relevant peaks are δ_H 4.88 (d, J_{PH} 8.3, triester **9b**), 4.95 (d, J_{PH} 7.9, diester **10b**) and 5.03 (d, J_{PH} 7.4, monoester **11c**). The data fitted the kinetic profile **9** $\xrightarrow{k_2}$ **10** $\xrightarrow{k_2}$ **11**, where k_1 and k_2 are first order rate constants, using the program developed by Irwin.[24] The rate constant k_1, for the conversion of the triester **9b** into the diester **10b** is 0.0119 min^{-1} ($t_{\frac{1}{2}}$ 58 min) (r = 0.991), and the rate constant k_2, for the conversion of the diester **10b** into the monoester **11c** is 0.002 24 min^{-1} ($t_{\frac{1}{2}}$ 309 min) (r = 0.980), which demonstrates that removal of the second 2-(methyldiphenylsilyl)ethyl group is five times slower than removal of the first.

An aqueous solution of hydrofluoric acid in MeCN was then used on a preparative scale to remove both 2-(trialkylsilyl)ethyl groups from the phosphate triesters **9b–f** and **9h** to give the monoesters **11a–e** in quantitative yields. The deprotection of the phosphate triester **9g** using HF in MeCN–H_2O was not successful owing to the anticipated loss of the *tert*-butyl group.

In summary, the bis[2-(trialkylsilyl)ethyl] *N,N*-dialkylphosphoramidites **6a**, **b** and **7a**, **b** have been used to phosphorylate a range of alcohols. Both of the 2-(trialkylsilyl)-ethyl groups on the triesters **9** could not be removed under very mild conditions, however in the presence of aqueous hydrofluoric acid in MeCN the monoesters **11** were formed in quantitative yields.

Experimental

Instrumentation, reagent suppliers and techniques were as previously described.[7] FAB mass spectra were recorded with a nitrobenzyl alcohol matrix, while CI mass spectra were recorded with NH_3 as carrier gas. NMR spectra were recorded on a Bruker AC-250 spectrometer with field strengths of 250.1 (^{1}H), 101.3 (^{31}P) and 62.9 MHz (^{13}C). *N,N*-Diisopropylphosphorochloridite **5a**[25] and *N,N*-diethylphosphorochloridite **5b**[10] were prepared from phosphorus trichloride and 2 equiv. of the appropriate amine using published procedures.

Bis[2-(*trimethylsilyl*)*ethyl*] N,N-*Diisopropylphosphoramidite* **7a**.—A solution of 2-(trimethylsilyl)ethanol (1.12 g, 9.45 mmol) and triethylamine (0.956 g, 1.32 cm^3, 9.45 mmol) in diethyl ether (20 cm^3) was added dropwise over 10 min to a stirred solution of *N,N*-diisopropylphosphorochloridite (0.955 g, 4.725 mmol) in diethyl ether (10 cm^3) at −78 °C under an atmosphere of argon. After 4 h at −78 °C, the insoluble material was filtered off and washed with diethyl ether. The filtrate was concentrated under reduced pressure and then subjected to purification by flash column chromatography eluting with hexane–triethylamine (9:1), R_f 0.50, which gave the title compound as a colourless oil (0.18 g, 16%); δ_H($CDCl_3$) 0.13 (18 H, s, $SiMe_3$), 0.9–1.1 (4 H, m, OCH_2CH_2Si), 1.24 (12 H, d, J_{HH} 6.8, Me_2CH), 3.4–3.6 (2 H, m, Me_2CH) and 3.6–3.9 (4 H, m, OCH_2CH_2Si); δ_C −1.5 (s, $SiMe_3$), 20.0 (d, J_{PC} 6.7, OCH_2CH_2Si), 24.5 (d, J_{PC} 7.2, Me_2CH), 42.6 (d, J_{PC} 12.2, Me_2CH) and 60.6 (d, J_{PC} 18.4, OCH_2CH_2Si); δ_P 142.9 (s).

The following compounds were prepared from the appropriate *N,N*-dialkylphosphorochloridite **5a**, **b** and the appropriate 2-(trialkylsilyl)ethanol using a method similar to that described above.

Bis[2-(*trimethylsilyl*)*ethyl*] N,N-*diethylphosphoramidite* **7b**. Purification by flash column chromatography not required, (88%), δ_H($CDCl_3$) 0.02 (18 H, s, $SiMe_3$), 0.9–1.1 (4 H, m, OCH_2CH_2Si), 1.03 (6 H, t, J_{HH} 7.1, CH_3CH_2N), 3.04 (4 H, dq, J_{PH} 9.1, J_{HH} 7.1, CH_3CH_2N) and 3.6–3.7 (4 H, m, OCH_2CH_2Si); δ_C −1.1 (s, $SiMe_3$), 15.4 (d, J_{PC} 6.2, CH_3CH_2N), 20.4 (d, J_{PC} 2.9, OCH_2CH_2Si), 37.6 (d, J_{PC} 20.4, CH_3CH_2N) and 60.9 (d, J_{PC} 16.8, OCH_2CH_2Si); δ_P 145.3 (s).

Bis[2-(*methyldiphenylsilyl*)*ethyl*] N,N-*diisopropylphosphoramidite* **6a**. R_f (hexane–ethyl acetate–triethylamine, 8:2:1) 0.56, (60%), δ_H($CDCl_3$) 0.55 (6 H, s, SiMe), 1.12 (12 H, d, J_{HH} 6.8, Me_2CH), 1.5–1.6 (4 H, m, OCH_2CH_2Si), 3.4–3.6 (2 H, m, Me_2CH), 3.6–3.8 (4 H, m, OCH_2CH_2Si) and 7.3–7.5 (20 H, m, Ph); δ_C −3.6 (s, SiMe), 18.3 (d, J_{PC} 6.4, OCH_2CH_2Si), 24.8 (d, J_{PC} 7.2, Me_2CH), 43.0 (d, J_{PC} 12.2, Me_2CH), 60.7 (d, J_{PC} 18.5, OCH_2CH_2Si), 128.2, 129.6, 134.7 and 136.9; δ_P 143.3 (s); *m/z* (FAB) 514 [$HP(OCH_2CH_2SiPh_2Me)_2$, 80%], 500 (5), 457 (11), 344 (16), 197 ($MePh_2Si^+$, 100) and 185 (7) (molecular ion not observed).

Bis[2-(*methyldiphenylsilyl*)*ethyl*] N,N-*diethylphosphoramidite* **6b**. R_f (hexane–ethyl acetate–triethylamine, 4:1:0.2) 0.42, (68%); δ_H($CDCl_3$) 0.55 (6 H, s, SiMe), 0.96 (6 H, t, J_{HH} 9.7, CH_3CH_2N), 1.5–1.6 (4 H, m, OCH_2CH_2Si), 2.93 (4 H, dq, J_{PH} 9.3, J_{HH} 7.1, CH_3CH_2N), 3.6–3.8 (4 H, m, OCH_2CH_2Si) and 7.3–7.5 (m, 20 H, Ph); δ_C −4.0 (s, SiMe), 14.9 (s, CH_3CH_2N), 17.9 (d, J_{PC} 5.7, OCH_2CH_2Si), 37.2 (d, J_{PC} 20.0, CH_3CH_2N), 60.2 (d, J_{PC} 16.7, OCH_2CH_2Si), 127.8, 129.3, 134.4 and 136.6; δ_P 145.4 (s, ^{1}H decoupled), (nonet, J_{PH} 8.6, ^{1}H coupled); *m/z* (CI) 586 (M + H^+, 15%), 530 (37), 457 (23), 316 (33), 214 (47) and 74 (100) (Found: M + H^+, 586.273. $C_{34}H_{45}NO_2PSi_2$ requires *M*, 586.273).

Bis[2-(*trimethylsilyl*)*ethyl*] *Benzyl Phosphate* **9a**.—A solution of benzyl alcohol (0.153 g, 1.41 mmol) in tetrahydrofuran (2 cm^3) was added dropwise to a stirred solution of 1*H*-tetrazole (0.296 g, 4.23 mmol, 3 equiv.) and the phosphoramidite **7b** (0.475 g, 1.41 mmol) in tetrahydrofuran (5 cm^3) at room temp. under an argon atmosphere. After 30 min, the reaction mixture was cooled to −40 °C and a solution of MCPBA (0.243 g, 1.41 mmol) in dichloromethane (2 cm^3) was added. The reaction mixture was maintained at −40 °C for 30 min, after which time it was allowed to warm to room temp. and then stirred for a further 1 h. Diethyl ether (40 cm^3) was added and the solution was washed with aqueous sodium metabisulfite (5% w/v, 2 × 20 cm^3) and then with aqueous sodium hydrogen carbonate (5% w/v, 2 × 20 cm^3). After drying ($MgSO_4$), the ether layer was evaporated under reduced pressure to give a clear oil. The title compound (R_f 0.53) was separated from residual benzyl alcohol (R_f 0.30) by flash column chromatography eluting with hexane–ethyl acetate–triethylamine (8:2:1), 0.28 g (0.72 mmol, 51%); $\delta_H(CDCl_3)$ 0.00 (18 H, s, $SiMe_3$), 1.0–1.1 (4 H, m, OCH_2CH_2Si), 4.0–4.1 (4 H, m, OCH_2CH_2Si), 5.05 (2 H, d, J_{PH} 8.2, $PhCH_2$) and 7.3–7.4 (5 H, m, Ph); δ_C −1.6 (s, $SiMe_3$), 19.4 (d, J_{PC} 5.8, OCH_2CH_2Si), 66.1 (d, J_{PC} 6.3, OCH_2CH_2Si), 68.8 (d, J_{PC} 5.5, $PhCH_2$), 127.8, 128.3, 128.5 and 136.1; δ_P −0.83 (s).

Bis[2-(*methyldiphenylsilyl*)*ethyl*] *Benzyl Phosphate* **9b**.—A solution of benzyl alcohol (0.296 g, 2.74 mmol) in dichloromethane (2 cm^3) was added to a solution of the phosphoramidite **6b** (1.76 g, 3.02 mmol) in dichloromethane (20 cm^3). The reaction mixture was stirred at room temp. for 30 min, after which time a solution of 1*H*-tetrazole (0.211 g, 3.02 mmol) in acetonitrile (2 cm^3) was added. After 1 h, the reaction was cooled to 0 °C and a solution of MCPBA (0.196 g, 3.02 mmol) in dichloromethane (2 cm^3) was added. After 4 h at room temp., the reaction mixture was concentrated under reduced pressure. Flash column chromatography of the residue eluting with hexane–ethyl acetate–triethylamine (8:2:1) separated a trace of benzyl alcohol (R_f 0.18) from the title compound (R_f 0.36) (0.811 g, 1.27 mmol, 42%); ν_{max}(thin film)/cm^{-1} 1257 (P=O); $\delta_H(CDCl_3)$ 0.50 (6 H, s, SiMe), 1.5–1.6 (4 H, m, OCH_2CH_2Si), 4.0–4.1 (4 H, m, OCH_2CH_2Si), 4.95 (2 H, d, J_{PH} 8.2, $PhCH_2$) and 7.3–7.5 (25 H, m, Ph); δ_C −4.1 (s, SiMe), 17.4 (d, J_{PC} 5.7, OCH_2CH_2Si), 65.7 (d, J_{PC} 6.3, OCH_2CH_2Si), 68.9 (d, J_{PC} 5.6, $PhCH_2$), 127.8, 128.0, 128.4, 128.5, 129.5, 134.3 and 135.6 (one aromatic carbon overlapping); δ_P −1.10 (s, ^1H decoupled), (septet, J_{PH} 7.6, ^1H coupled); *m/z* (FAB) 425 (10%), 335 (54) and 197 ($MePh_2Si^+$, 100) (molecular ion not found).

The following compounds were prepared from the appropriate bis[2-(trialkylsilyl)ethyl] *N*,*N*-dialkylphosphoramidite and the appropriate alcohol using a method similar to that described above.

Bis[2-(*trimethylsilyl*)*ethyl*] 4-*phenylbutan*-2-*yl phosphate* **9c**. R_f (hexane–ethyl acetate–triethylamine, 8:2:1) 0.32, 60%; ν_{max}(thin film)/cm^{-1} 1252 (P=O); $\delta_H(CDCl_3)$ 0.01 (18 H, s, $SiMe_3$), 1.0–1.1 (4 H, m, OCH_2CH_2Si), 1.33 (3 H, d, J_{HH} 6.2, CH_3CH), 1.8–2.0 (2 H, m, $PhCH_2CH_2$), 2.6–2.8 (2 H, m, $PhCH_2CH_2$), 4.0–4.2 (4 H, m, OCH_2CH_2Si), 4.4–4.5 (1 H, septet, $J_{HH} = J_{PH} = 6.3$, CH_3CH) and 7.1–7.3 (5 H, m, Ph); δ_C −1.5 ($SiMe_3$), 19.51 (d, J_{PC} 6.0, OCH_2CH_2Si), 19.52 (d, J_{PC} 5.9, OCH_2CH_2Si), 21.6 (d, J_{PC} 2.8, CH_3CH), 31.5 ($PhCH_2CH_2$), 39.2 (d, J_{PC} 6.3, $PhCH_2CH_2$), 65.80 (d, J_{PC} 6.3, OCH_2CH_2Si), 65.85 (d, J_{PC} 6.3, OCH_2CH_2Si), 75.1 (d, J_{PC} 6.2, CH_3CH), 125.9, 128.3, 128.4 and 141.8; δ_P −1.50 (s, ^1H decoupled), (sextet, J_{PH} 6.5, ^1H coupled); *m/z* (FAB) 453 ($M + Na^+$, 15%), 375 (10), 315 (27), 243 (100), 227 (9) and 211 (16) (Found: $M + Na^+$, 453.200. $C_{20}H_{39}NaO_4PSi_2$ requires 453.202).

Bis[2-(*methyldiphenylsilyl*)*ethyl*] 4-*phenylbutan*-2-*yl phosphate* **9d**. R_f (hexane–ethyl acetate–triethylamine, 8:2:1) 0.35, 64% (Found: C, 70.6; H, 6.9. $C_{40}H_{47}O_4PSi_2$ requires C, 70.78; H, 6.98%); ν_{max}(thin film)/cm^{-1} 1259 (P=O); $\delta_H(CDCl_3)$ 0.56 (6 H, s, SiMe), 1.26 (3 H, d, J_{HH} 6.2, CH_3CH), 1.6–1.7 (4 H, m, OCH_2CH_2Si), 1.8–2.0 (2 H, m, $PhCH_2CH_2$), 2.5–2.7 (4 H, m, $PhCH_2CH_2$), 4.1–4.2 (4 H, m, OCH_2CH_2Si), 4.42 (1 H, septet, $J_{PH} = J_{HH} = 5.9$, CH_3CH) and 7.1–7.5 (25 H, m, Ph); δ_C −4.0 (SiMe), 17.5 (d, J_{PC} 3.1, OCH_2CH_2Si), 21.5 (d, J_{PC} 2.8, CH_3CH), 31.4 ($PhCH_2CH_2$), 39.1 (d, J_{PC} 6.5, $PhCH_2CH_2$), 65.4 (d, J_{PC} 6.2, OCH_2CH_2Si), 75.2 (d, J_{PC} 6.2, CH_3CH), 126.8, 128.0, 128.2, 129.6, 134.3, 136.3 and 142.4 (one aromatic carbon overlapping); δ_P −1.71 (s, ^1H decoupled), (sextet, J_{PH} 7.1, ^1H coupled).

Bis[2-(*methyldiphenylsilyl*)*ethyl*] *phenethyl phosphate* **9e**. R_f (hexane–ethyl acetate–trimethylamine, 8:2:1) 0.60, 69%; ν_{max}(thin film)/cm^{-1} 1272 (P=O); $\delta_H(CDCl_3)$ 0.55 (6 H, s, SiMe), 1.5–1.6 (4 H, m, OCH_2CH_2Si), 2.88 (2 H, t, J_{HH} 7.0, $PhCH_2$), 4.0–4.1 (6 H, m, OCH_2CH_2Si, $PhCH_2CH_2$) and 7.1–7.4 (25 H, m, Ph); δ_C −4.1 (SiMe), 17.4 (d, J_{PC} 5.2, OCH_2CH_2Si), 36.7 (d, J_{PC} 7.2, $PhCH_2$), 65.6 (d, J_{PC} 6.2, OCH_2CH_2Si), 67.7 (d, J_{PC} 5.7, $PhCH_2CH_2$), 126.6, 128.0, 128.4, 128.9, 129.5, 134.3, 135.6 and 137.2; δ_P −1.23 (s, ^1H decoupled), (septet, J_{PH} 7.4, ^1H coupled); *m/z* (FAB) 335 (48%), 242 (10), 197 ($MePh_2Si^+$, 100) and 105 (52) (molecular ion not found).

Bis[2-(*methyldiphenylsilyl*)*ethyl*] *methyl phosphate* **9f**. R_f (hexane–ethyl acetate–triethylamine, 8:2:1) 0.41, 50% (elemental analysis not correct: Found: C, 62.7; H, 5.85. $C_{31}H_{37}O_4PSi_2$ requires C, 66.43; H, 6.65%); $\delta_H(CDCl_3)$ 0.58 (6 H, s, SiMe), 1.6–1.7 (4 H, m, OCH_2CH_2Si), 3.62 (3 H, d, J_{PH} 11.1, CH_3O), 4.1–4.2 (4 H, m, OCH_2CH_2) and 7.3–7.5 (20 H, m, Ph); δ_C −4.1 (SiMe), 17.4 (d, J_{PC} 5.7, CH_2Si), 53.9 (d, J_{PC} 6.0, CH_3O), 65.6 (d, J_{PC} 6.2, OCH_2CH_2Si), 127.9, 128.0, 129.5 and 134.3; δ_P −1.05 (s, ^1H decoupled).

Bis[2-(*methyldiphenylsilyl*)*ethyl*] tert-*butyl phosphate* **9g**. R_f (hexane–ethyl acetate–triethylamine, 8:2:1) 0.35, 83% (elemental analysis not correct: Found: C, 65.0; H, 7.3. $C_{34}H_{43}O_4PSi_2$ requires C, 67.76; H, 7.19%); ν_{max}(thin film)/cm^{-1} 1261 (P=O); $\delta_H(CDCl_3)$ 0.57 (6 H, s, SiMe), 1.40 (9 H, s, Bu^t), 1.6–1.7 (4 H, m, OCH_2CH_2Si), 4.0–4.1 (4 H, m, OCH_2CH_2Si) and 7.3–7.5 (20 H, m, Ph); δ_C −4.09 (SiMe), 17.4 (d, J_{PC} 4.8, OCH_2CH_2Si), 29.8 (d, J_{PC} 4.3, Me_3C), 65.0 (d, J_{PC} 6.2, OCH_2CH_2Si), 82.5 (d, J_{PC} 7.1, Me_3C), 128.0, 129.2, 134.3 and 135.7; δ_P −1.55 (s, ^1H decoupled) (pentet, J_{PH} 7.4, ^1H coupled).

2,3,4,5,6-*Penta*-O-*benzyl*-myo-*inositol* 1-{*bis*[2-(*methyldiphenylsilyl*)*ethyl*] *phosphate*} **9h**. R_f (hexane–ethyl acetate–triethylamine, 8:2:1) 0.20, 46% (elemental analysis not correct: Found: C, 67.8; H, 6.6. $C_{71}H_{75}O_9PSi_2$ requires C, 73.56; H, 6.52%); ν_{max}(thin film)/cm^{-1} 1257 (P=O); $\delta_H(CDCl_3)$ 0.49 (6 H, s, SiMe), 1.5–1.6 (4 H, m, CH_2Si), 3.45 (2 H, t, J_{HH} 8.6, 3-H and 5-H), 4.0–4.2 (7 H, m, 2 OCH_2CH_2Si, 1-H, 4-H and 6-H), 4.29 (1 H, s, 2-H), 4.7–4.9 (10 H, m, OCH_2Ph) and 7.2–7.5 (45 H, m, Ph); δ_C −4.16 (SiMe), 17.5 (d, J_{PC} 4.1, CH_2Si), 65.8–65.9 (2 overlapping d, OCH_2CH_2Si), 72.6, 75.0, 75.3, 75.8, 75.9 ($PhCH_2$), 78.3 (d, J_{PC} 6.1), 80.0 (d, J_{PC} 6.9), 80.3, 81.2, 83.0 (inositol CH, one CH overlapping or masked by $CDCl_3$), 127.4, 127.5, 127.6, 127.8, 127.9, 128.1, 128.3, 129.5, 134.2, 135.3, 135.4, 138.1, 138.4, 138.4, 138.5 and 138.7; δ_P −1.38 (s).

Attempted Deprotection of Bis[2-(*methyldiphenylsilyl*)*ethyl*] *Benzyl Phosphate* **9b** *with Tetrabutylammonium Fluoride in THF*.—TBAF (0.128 g, 0.41 mmol) in THF (1 cm^3) was added over 5 min to a stirred solution of **9b** (0.129 g, 0.203 mmol) in THF (1 cm^3). After 24 h at room temp., the solvent was evaporated under reduced pressure and portions of ethanol (2 cm^3) were added and removed by evaporation several times. An aqueous solution of ammonia (1 cm^3) was added to give a precipitate of the diester **10b**, $\delta_H(CDCl_3)$ 0.41 (3 H, s, SiMe),

1.4–1.5 (2 H, m, OCH_2CH_2Si), 3.9–4.0 (2 H, m, OCH_2CH_2Si), 4.92 (2 H, d, J_{PH} 8.2, $PhCH_2O$) and 7.1–7.4 (15 H, m, Ph); δ_P 0.13 (pentet, J_{PH} 7.2, ^1H coupled).

Attempted Deprotection of Bis[2-(methyldiphenylsilyl)ethyl] Benzyl Phosphate **9b** *with Tetrabutylammonium Fluoride in DMSO.*—A solution of TBAF (0.049 g, 0.156 mmol) in DMSO (1 cm^3) was added to a solution of **9b** (0.050 g, 0.078 mmol) in DMSO (1 cm^3). The mixture was stirred at 70 °C for 2 h, under an argon atmosphere. The ^{31}P NMR spectrum of the crude reaction mixture was consistent with the diester **10b**, δ_P −0.85 (pentet, J_{PH} 6.3, ^1H coupled, 90%). The reaction was left at 70 °C for a further 16 h which gave monoester **11c**, δ_P −0.48 (t, J_{PH} 6.0, ^1H coupled), together with 30% inorganic phosphate, δ_P 0.03 (s, ^1H coupled).

Attempted Deprotection of Bis[2-(methyldiphenylsilyl)ethyl] Phenethyl Phosphate **9e** *with Ammonium Fluoride.*—A solution of ammonium fluoride (0.045 g, 1.21 mmol) in MeOH (1 cm^3) was added to a stirred solution of **9e** (0.057 g, 0.088 mmol) in MeOH (1 cm^3). The mixture was stirred under an argon atmosphere at 60 °C for 72 h, after which the solvent was removed under reduced pressure and the residue treated with aqueous ammonia (1 cm^3) to give a white precipitate, the ^{31}P NMR spectrum of which was consistent with the diester **10e**, $\delta_P(CD_3OD)$ 2.61 (pentet, J_{PH} 6.3, ^1H coupled).

Phenethyl Phosphate (Free Acid) **11a**.—Trifluoroacetic acid (0.035 g, 0.308 mmol) was added to a stirred solution of **9e** (0.050 g, 0.077 mmol) in THF (1 cm^3). The reaction mixture was stirred at room temp. under an argon atmosphere for 24 h. The solvent was evaporated under reduced pressure to give a white solid which was washed with chloroform. Deprotection was quantitative, shown by ^{31}P NMR spectroscopy, to give the title compound, $\delta_H(D_2O)$ 2.98 (2 H, t, J_{HH} 6.9, $PhCH_2$), 4.07 (2 H, dt, $J_{PH} = J_{HH} = 6.9$, CH_2CH_2O) and 7.3–7.5 (5 H, m, Ph); δ_C 33.7 (d, J_{PC} 6.9, $PhCH_2$), 63.1 (d, J_{PC} 5.2, CH_2O), 123.9, 126.0, 126.5 and 136.2; δ_P 1.68 (t, J_{PH} 6.4, ^1H coupled).

Deprotections were attempted on the following compounds using a method analogous to that described above.

Attempted deprotection of bis[2-(methyldiphenylsilyl)ethyl] 4-phenylbutan-2-yl phosphate **9d**. The ^{31}P NMR spectrum of the aqueous layer showed no phosphorus-containing material, whereas the chloroform layer gave δ_P −1.62 (sextet, J_{PH} 6.7, ^1H coupled) consistent with the triester **9d**.

Attempted deprotection of bis[2-(methyldiphenylsilyl)ethyl] benzyl phosphate **9b**. ^{31}P NMR spectroscopy of the aqueous layer showed a small amount of the monoester **11c**, δ_P 1.00 (t, J_{PH} 7.0, ^1H coupled). The chloroform layer contained the majority of the material, which proved to be starting material, δ_P −1.07 (sept, J_{PH} 7.7, ^1H coupled).

Phenethyl Phosphate (Ammonium Salt) **11a**.—Hydrofluoric acid (40% aqueous solution; 0.034 g, 1.702 mmol) was added to a stirred solution of the triester **9e** (0.074 g, 0.114 mmol) in MeCN (1 cm^3). The reaction mixture was stirred at 40 °C under an argon atmosphere for 24 h. A solution of aqueous ammonia (1 cm^3) was added and the resultant ammonium fluoride salt was filtered off. The solvent was evaporated under reduced pressure to give the title compound, quantitatively by ^{31}P NMR spectroscopy, as a white solid, $\delta_H(D_2O)$ 2.59 (2 H, t, J_{HH} 6.8, $PhCH_2$), 3.70 (2 H, dt, $J_{PH} = J_{HH} = 6.8$, CH_2CH_2O) and 7.0–7.1 (5 H, m, Ph); δ_C 33.6 (d, J_{PC} 7.1, $PhCH_2$), 63.3 (d, J_{PC} 4.3, CH_2O), 123.8, 125.9, 126.4 and 135.9; δ_P 1.13 (t, J_{PH} 7.0, ^1H coupled); *m/z* (FAB) peaks included 171 (37%), 203 (M + H, 15), 220 (M + NH_4, 17) and 226 (M + Na, 5).

The following compounds were prepared by treatment of the appropriate triester with 15 equiv. of hydrofluoric acid using a method similar to that described above.

4-Phenylbutan-2-yl Phosphate (Ammonium Salt) **11b** was prepared quantitatively from triester **9c**, $\delta_H(D_2O)$ 1.33 (3 H, d, J_{HH} 6.2, CH_3CH), 1.9–2.0 (2 H, m, CH_2CH_2CH), 2.7–2.8 (2 H, m, $PhCH_2$), 4.3–4.4 (1 H, m, OCH) and 7.3–7.5 (5 H, m, Ph); δ_C 23.4 (CH_3CH), 33.5 (s, $PhCH_2$), 41.5 (d, J_{PC} 5.9, $CHCH_2CH$), 75.4 (d, J_{PC} 5.7, OCH), 128.4, 130.9, 131.1 and 145.1; δ_P 2.43 (d, J_{PH} 7.2, ^1H coupled); *m/z* (FAB) peaks included 171 (100%), 231 (M + H, 50), 248 (M + NH_4, 30), 324 (30), 461 (2M + H, 45) and 478 (2M + NH_4, 10).

4-Phenylbutan-2-yl Phosphate (Ammonium salt) **11b** was prepared from **9d**, reaction temperature 40 °C. The data obtained were as described for the above experiment.

Benzyl Phosphate (Ammonium Salt) **11c** was prepared from **9b**, reaction temperature 40 °C, $\delta_H(D_2O)$ 4.82 (2 H, d, J_{PH} 8.3, $PhCH_2$) and 7.3–7.4 (5 H, m, Ph); δ_C 65.0 (d, J_{PC} 5.2), 125.2, 125.7, 126.1 and 135.0 (d, J_{PC} 7.1); δ_P −0.48 (t, J_{PH} 6.0, ^1H coupled); *m/z* (FAB) peaks included 171 (100%), 189 (M + H, 23), 211 (M + Na, 40), 324 (30), 377 (2M + H, 10) and 399 (2M + Na, 13).

Methyl Phosphate (Free Acid) **11d** was prepared from **9f**, reaction temperature 40 °C. After 24 h, the solvent was evaporated under reduced pressure and the residue was redissolved in CD_3CN, $\delta_H(CD_3CN)$ 3.59 (3 H, d, J_{PH} 9.5, Me); δ_C 54.8 (d, J_{PC} 5.7, Me); δ_P 5.47 (q, J_{PH} 9.9, ^1H coupled).

2,3,4,5,6-*Penta*-O-*benzyl*-myo-*inositol* 1-(*dihydrogen phosphate*) **11e** was prepared from **9h**, reaction temperature 40 °C. After 24 h, the solvent was evaporated under reduced pressure and the residue was redissolved in CD_3CN, $\delta_H(CD_3CN)$ 3.39 (2 H, t, J_{HH} 9.0, 3-H and 5-H), 4.0–4.2 (14 H, m, OCH_2Ph, 2-H, 1-H, 4-H and 6-H) and 7.2–7.6 (25 H, m, Ph); δ_C 73.1, 73.6 (d, J_{PC} 3.4), 76.2, 76.4 (d, J_{PC} 6.1), 76.7, 78.3 (inositol CH), 82.0, 82.2, 83.2, 84.0, 84.6 ($PhCH_2$), 128.7, 128.8, 129.2, 129.3, 129.4, 129.6, 129.7, 129.75, 129.8, 129.9, 129.95, 130.0, 130.5 and 135.3 (aromatics); δ_P 4.69 (d, J_{PH} 7.9, ^1H coupled).

Attempted deprotection of bis[2-(methyldiphenylsilyl)ethyl] tert-butyl phosphate **9g**. After 24 h the solvent was evaporated under reduced pressure and the residue was redissolved in CD_3CN. The ^1H NMR spectrum showed loss of the Bu^t group as 2-methylpropene [δ_H 1.73 (6 H, s, Me) and 4.67 (2 H, s, $=CH_2$)] and Bu^tOH [δ_H 1.20 (s, Bu^t)].

Deprotection Studies on Phosphates **9b**, **c**, **f**, **h** *by* ^1H *and* ^{31}P *NMR Spectroscopy.*—The phosphates **9b**, **c**, **f**, **h** (20 μmol) were dissolved in CD_3CN (0.5 cm^3) and 15 equiv. of 40% aqueous HF in acetonitrile (0.5 cm^3) was added. For **9c** the sample in the NMR tube was incubated at 25 °C, whereas for **9b**, **f**, **h** the reaction temperature was 40 °C. The reactions were followed by recording either a ^1H or ^{31}P NMR spectrum every 30 min. Reaction kinetics were analysed by integration of the $PhCH_2OP$ peaks for the triester, diester and monoester of the phosphate **9b** and by integration of the ethene and trialkylsilyl fluoride by-product peaks. The triester **9f** [δ_H included 3.57 (d, J_{PH} 11.1, OMe)] decomposed to give the diester **10f** [δ_H included 3.62 (d, J_{PH} 11.2, OMe)] which, in turn, was degraded to the monoester **11d** [δ_H included 3.69 (d, J_{PH} 11.3, OMe)]. The triester **9h** (δ_P −1.89) decomposed to give the diester **10h** (δ_P −1.73) and ultimately the monoester **11e** (δ_P −1.05). The triester **9c** (δ_P −1.63) decomposed to give the diester **10c** (δ_P −1.17), which degraded to the monoester **11b** (δ_P −0.50).

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