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Diastereoselective Phosphonylation of Aldehydes using Chiral Diazaphospholidine Reagents

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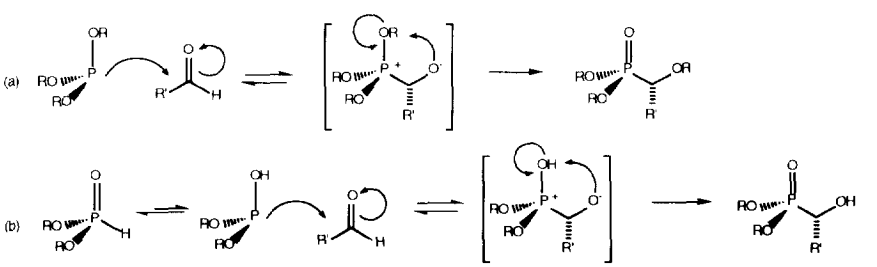
Abstract: *Stereocontrol in the asymmetric phosphonylation of aldehydes via organophosphorus esters is a function of the topology of the chiral reagents employed. We report here on the diastereoselective phosphonylation of selected unsaturated organic substrates using diazaphospholidine reagents based on the N,N'-bis[1-(S)-phenylethyl]-1,2-ethylenediamine auxiliary which affords a different profile of selectivities to those reported previously using diazaphospholidine reagents containing the N,N'-(dineopentyl)-trans-1,2-diaminocyclohexane auxiliary.*

Introduction

In recent years, there has been considerable interest in phosphorus-carbon [P—C] bond forming reactions in which stereochemical control is a fundamental consideration.[1] Our programme in this area has focused on the development of new protocols for phospho-transfer processes in which strategies from metallo-organic, organic and biological chemistries are combined and of these processes, the asymmetric phosphonylation of aldehydes has proved to be one of the most fruitful.[2]

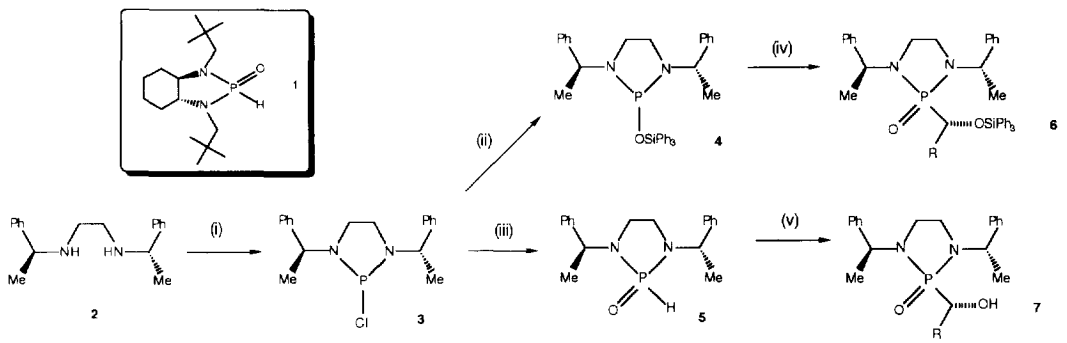
Two related asymmetric procedures have been used to achieve carbonyl phosphonylation; one based on the Abramov reaction and the other based on the Pudovik reaction (Scheme 1).[3] In the Abramov reaction, the phosphonylating agent is a chiral organophosphorus(III) ester whilst in the Pudovik reaction a *H*-phosphonate ester of phosphorus(V) is used as the source of phosphorus. The mechanisms of both reactions are closely related (Scheme 1) and in both cases stereocontrol at the newly generated α-carbon atom (C_α) has been acheived through the presence of a chiral auxiliary bound either to phosphorus or to the organic substrate. As an extension to our ongoing studies on the Abramov reaction[2] we report here our investigations on an asymmetric variant of the Pudovik reaction incorporating chiral diazaphospholidine reagents.

In practice, the auxiliaries of choice for both Abramov and Pudovik reactions are chelating systems based on the hard donor atoms nitrogen and oxygen which afford ease of introduction, established stereo-differentiating properties and ease of displacement after [P—C] bond formation *via* acid catalysed hydrolysis.



Scheme 1. The Abramov (a) and Pudovik (b) phosphonylation reactions

The presence of a chelating auxiliary bound to phosphorus has a profound effect upon phosphonylating ability. Thus, silylated organophosphorus(III) esters with chelating (+)-dimethyl-L-tartrate or *rac*-binaphthol auxiliaries do not phosphonylate benzaldehyde below 80°C and above this temperature multiple products are observed.[2b,c] This contrasts with analogous silylated phosphites containing unidentate alkoxo residues which react with aldehydes smoothly at 25°C.[4] Phosphonylating ability can be restored to the organophosphorus reagent if oxygen-bound auxiliaries are replaced by more electron-releasing nitrogen-bound ligands which encourage the phosphorus lone-pair of electrons to occupy a more polarisable orbital comprising a greater degree of phosphorus p-character and hence of a higher valence orbital energy. This in turn should facilitate reaction with a soft electrophile such as a carbonyl carbon atom.[2h]



Scheme 2. (i) PCl_3, 2 NEt_3, 4 h, r.t. toluene; (ii) Ph_3SiOH, 2 NEt_3, 3 h, r.t. toluene; (iii) H_2O, 2 NEt_3, 12 h, r.t., toluene; (iv) RCHO (R = Ph), 15 days, r.t., toluene; (v) $LiN(SiMe_3)_2$, -78°C, 30 mins. followed by RCHO (R = Ph; 2-BrC_6H_4; 3-BrC_6H_4; 4-BrC_6H_4; 1-$C_{10}H_7$; 2-$Ph_2PC_6H_4$).

This approach has been shown to be successful in both achiral[2h] and chiral environments.[1g] Spilling and co-workers[1c,d,i] have investigated the phosphonylating ability of phosphorodiamidite **1** in the Pudovik reaction in which chirality, imposed by formation of a rigid C_2 symmetric bicycle, is transferred to the newly generated stereocentre at C_α.[5] In this regard, neopentyl moeities on the nitrogen atoms were found to function best.[5] Our studies on the asymmetric Abramov reaction provide complementary results; in particular, we wished to investigate how (i) relaxing the rigidity of the chelating auxiliary and (ii) altering the topology of the chiral auxiliary would affect stereochemistry at the newly generated chiral C_α carbon atom.

Results and Discussion

Choice of Chiral Auxiliary

We envisaged that moving from a fused bicyclic system as in **1** to a monocyclic diazaphospholidine ring system would result in a more flexible phosphorus atom coordination sphere. Moreover, it was considered that flexibility could be increased further by switching from backbone-derived chirality as in **1** to N-substituent chirality whilst still maintaining the overall C_2 symmetric profile necessary to limit the number of stereochemical permutations in the product phosphonate esters. We wished to investigate how this presumed increase in flexibility would affect the stereoselectivity of the Pudovik reaction as shown in Scheme 2.

Consequently, we have synthesised compounds **4** and **5** containing the *N,N'*-bis[1-(*S*)-phenylethyl]-1,2-ethylenediamine (PEED) auxiliary[6] and have examined their phosphonylating abilities under a variety of reaction conditions as outlined in Scheme 1.

*{PEED}POSiPh$_3$ **4** and the Phosphonylation of Benzaldehyde under Abramov Conditions*

Triphenylsilanol reacts smoothly with phosphorochloridite **3** in the presence of triethylamine to afford triphenylsiloxyphosphorodiamidite **4** as a white crystalline solid in high (*ca.* 80%) yield. Compound **4** reacts slowly with benzaldehyde in toluene solvent (a 0.3 mmol. scale reaction requires more than 5 days to reach

completion at room temperature) to afford α-siloxophosphonate ester **6** as a mixture of two diastereoisomers with $^{31}P\{^{1}H\}$ NMR resonances at 32.1 ppm and 30.7 ppm (C_6D_6) in the ratio 1:1.3 respectively (diastereomeric excess, d.e. 13%). This result is comparable to the low degree of stereoselectivity observed by Spilling in related systems[1i] yet differs significantly from the high stereocontrol possible when (1*R*,2*S*)-ephedrine is used as the phosphorus-bound auxiliary (d.e. *ca.* 80-90%).[2f,i] We presume that the different levels of stereocontrol in these two systems reflects the detailed steric profile of the auxiliary but at this stage cannot provide a more definitive explanation and consequently, given the low levels of stereocontrol in this reaction we focused our attention on the Pudovik phosphonylation process.

{PEED}P(=O)H **5** *and the Phosphonylation of Benzaldehyde under Pudovik Conditions*

Following the observation of poor stereoselectivity in aldehyde phosphonylation using phosphorodiamidite **4** we have focused our attention on screening the *H*-phosphonate ester **5** as a substrate for the Pudovik reaction under both Lewis base mediated and Lewis acid mediated conditions.

Benzaldehyde is unaffected by **5** (1 equiv.) at room temperature in toluene solvent. Addition of either NEt_3 (1 equiv.) or $AlMe_3$ (1 equiv.) failed to initiate significant reaction after 24 h at room temperature in contrast to the reaction of $(MeO)_2P(=O)H$ with benzaldehyde which is catalysed by either reagent under ambient conditions.[7] Presumably, this lack of reactivity is associated with a lower acidity of the [P—H] bond as an oxygen-rich phosphorus coordination sphere is replaced by a more nitrogen-rich environment.[1i] However, treatment of **5** with a stronger base such as lithium bis(trimethylsilyl)amide (LSA) at -78°C prior to addition of aldehyde results in clean phosphonylation to afford, after suitable work up, α-hydroxophosphorodiamidate **7** (characterised *via* the usual techniques. See Experimental section). The diastereoselectivity (d.e.) for this reaction is 30%, which is still considerably lower than that observed using reagent **1** based on a bicyclic scaffold. Nevertheless, the observation of significant diastereoselectivity prompted us to investigate several functional benzaldehydes in which the nature and position of the functionality are varied. The results are illustrated in the Table.

Compound (R)	Yield[a]	δ_P(major)[b]	δ_P(minor)[b]	ΔP[c]	Ratio[d]	d.e.[e]
7 (C_6H_5)	80	34.0	34.5	-0.5	1.84:1	30[f]
8 (2-BrC_6H_4)	88	33.8	33.0	+0.8	3.39:1	54
9 (3-BrC_6H_4)	81	33.7	34.0	-0.3	1.91:1	31
10 (4-BrC_6H_4)	84	33.6	34.0	-0.4	1.71:1	26
11 (1-$C_{10}H_7$)	74	34.8	35.2	-0.4	1.89:1	31
12 (2-$Ph_2PC_6H_4$)	92	34.3	33.6	+0.7	2.50:1	43

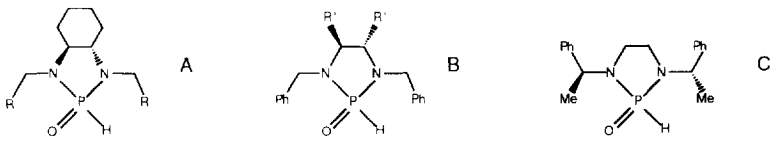
Table. [a] In %. [b] $CDCl_3$, 300 K, In ppm. [c] In ppm, (major - minor). [d] Major:minor. [e] In %. [f] 32% when performed compeletely at -70°C and 31% when performed at room temperature (*ca.* 20°C).

A number of points emerge from the data in the Table. (i) In each case, reaction is quite clean and product yields are high. (ii) In each case examined, the diastereoisomeric excess is quite modest, within the range 30-54%, with the highest values being obtained with *ortho*-substituted derivatives **8** and **12**. We presume that the closer proximity of the substituents to the reacting carbonyl centre in these two derivatives results in a greater degree of steric differentiation during approach of the phosphorus nucleophile. (iii) For these two derivatives **8** and **12**, the pattern of ^{31}P resonances is different from the remaining four products, the higher frequency ^{31}P resonance corresponding to the dominant epimer giving rise to a *positive ΔP value* for these systems. Consequently, given that α-hydroxyphosphonate esters of a similar nature to those in the Table have been reported to have ^{31}P NMR resonances that are sensitive to the configuration at the alpha carbon atom,[5] we envisage that the *dominant epimers of compounds* **8** *and* **12** *(ΔP positive) are opposite to those which dominate in derivatives* **7**, **9**, **10** *and* **11** *(ΔP negative).* Such a crossover in stereoselectivity has precedent from our earlier work on the asymmetric Abramov phosphonylation of aldehydes *via* {(1*R*,2*S*)-ephedrine}$PN(SiMe_3)_2$

where product stereochemistry at C_α changed from S_C for 2-$C_{10}H_7CHO$ to R_C for 2-$Ph_2PC_6H_4CHO$.[1e] Our working hypothesis is that the stereochemistry at C_α is influenced by the position of substitution on the aromatic ring of benzaldehyde primarily through steric effects. Unfortunately, we have been unable to obtain crystals of satisfactory quality for X-ray analysis to assign absolute configurations in these systems.

Stereocontrol in the Asymmetric Pudovik Reaction

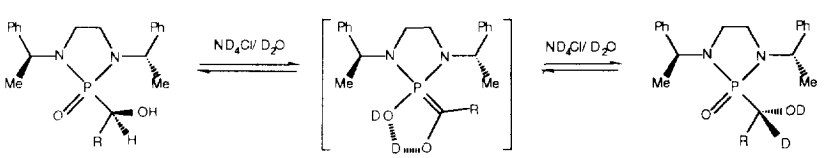
The asymmetric Pudovik reaction has now been probed *via* three diazaphospholidine systems (A-C, Scheme 3). Spilling and co-workers,[5] examining systems A and B (Scheme 3), found that (i) diastereoselectivity increased when neopentyl groups rather than benzyl groups were employed as nitrogen substituents and (ii) both fused bicyclic A and monocyclic B systems resulted in face-selectivity. Remarkably, the N,N'-dibenzyl analogue of bicycle A afforded a d.e. of *zero* in the phosphonylation of benzaldehyde (THF solvent, lithium bistrimethylsilylamide base) whilst the N,N'-dineopentyl derivative of **1** afforded a d.e. of 92% under identical conditions!



Scheme 3. R = CH_2Ph, $CH_2{}^tBu$; R' = Me, Ph

Although the precise mechanistic details of the Pudovik reaction have not yet been delineated to the same extent as the Abramov reaction,[2h,i] a reasonable picture has been developed[5,9] wherein a number of factors are likely to influence stereoselectivity including; (i) solvent, (ii) temperature, (iii) nature of the base used (iv) nature of the aldehyde substrate and (v) profile of the chiral auxiliary. Spilling has found however, that neither the nature of the solvent nor the nature of the cationic counter-ion has a significant effect upon stereoselectvity. It is difficult to speculate on the significance of this since the structure of the active phosphonylating agent, especially the state of aggregation,[10] is unknown yet it may indicate that coordination of both phosphoryl and carbonyl oxygen termini to the same lithium atom is not required to facilitate rapid [P—C] bond formation. Indeed, such a scenario is is agreement with a line of approach between phosphite and carbonyl in which the two oxygen termini are disposed in an *anti* arrangement as envisaged by Evans.[11] Spilling also observed that the stereoselectivity obtained in reactions with bicyclic H-phosphonates **A** decreased as the reaction temperature increased and that optimum selectivities were obtained at -60°C; reactions performed at room temperature with **A** (R = CH_2Ph) afforded d.e.'s of zero. When phosphonylation reactions employing H-phosphonate **C** and benzaldehyde are performed under conditions where the reaction vessel is maintained at -70°C for 3 h and then quenched at -70°C by the addition of $HBF_4.Et_2O$,[12a] d.e. of 32% is obtained, essentially unchanged from the our normal procedure and consequently, extrapolating the conclusions from Spillings work, setting the limit of d.e. for this reaction at this value of *ca.* 32%. Interestingly, a d.e. of 31% is recorded when the same reaction is performed at ambient temperature (*ca.* 20°C), although reaction is a little less clean.

Configurational Stability of α-Hydroxyphosphonodiamidate Esters



Scheme 4. Possible acid-catalysed mechanism for epimerisation in esters **7-12**

Since stereochemical integrity of the product α-hydroxyphosphonodiamidate esters is of prime concern

to this work,we were particularly interested to ascertain whether the mildly acidic work-up procedure resulted in epimerisation and the production of an equilibrium mixture of diastereoisomers for **7-12** since acid-mediated epimerisation has been noted in related systems.[2i] We envisaged that epimerisation in compounds **7-12** *via* an acid-catalysed processes may be unlikely based on the results of other workers,[5] yet we wished to provide some firm basis for our belief in this particular system. We reasoned that the most plausible mechanism for acid-catalysed epimerisation would be similar to that outlined in Scheme 3 in which protonation of the phosphonyl oxygen atom followed by rearrangement may afford an intramolecularly stabilised phospho-enol intermediate with an sp^2 C_α atom. This phospho-enol may then be reprotonated to afford either epimer. We have probed this mechanistic possibility by treatment of a diastereoisomeric mixture of compound **8**, with the composition shown in the Table, with a solution of ND_4Cl in D_2O following the work-up procedure of Scheme 2. Under these conditions, ^1H NMR spectroscopy revealed that there was *no* incorporation of deuterium at C_α after a period of 72 h, a result consistent with configurational stabilty at C_α under acidic conditions.[5]

Conclusions

It seems reasonably clear from a comparison of the three chiral diazaphospholidine envelopes **A-C** above that the rigidity of the bicyclic system **A** coupled with the ability of the nitrogen-bound substituents to orientate themselves in an appropriate conformation (cf; the differences in reactivity between N-benzyl and N-neopentyl derivatives[5]) delivers the highest selectivities. This orientating ability of the N-substituents may also play a significant role in influencing the stereoselectivity as a function of reaction temperature.[5] Conversely, with system **C**, the results indicate that any differences in conformational preferences of the N-substituent stereocentres at -70°C and +20°C have relatively little influence over the stereochemistry at the newly generated C_α atom.

Experimental

All reactions and manipulations were performed under an atmosphere of dry dinitrogen using Schlenk and dry-box techniques as described previously.[2i] Elemental analyses and solution molecular mass measurements were performed by the Microanalytical Laboratory of this department. Mass spectra were collected on a VG Autospec instrument operating in the electron impact mode. The isotopic mass error on high resolution mass peaks are within 10 ppm. IR spectra were recorded as either thin films (for liquids) or nujol mulls (for solids) between KBr windows using a Perkin-Elmer 257 grating spectrophotometer. NMR spectra were obtained on JEOL FX90Q, JEOL FX100, Bruker AM 400 and Bruker ARX 250 instruments operating at 100 MHz, 250 MHz or 400 MHz for ^1H, 63 MHz and 100 MHz for ^{13}C and 36 MHz, 101 MHz and 162 MHz for ^{31}P. Referencing of NMR spectra is as reported previously.[2i] Optical rotations were recorded on an Optical Activity AA 10 polarimeter operating at 589.44 nm. The compounds PCl_3, NEt_3, N-methyl morpholine, (*S*)-α-phenylethylamine ($[\alpha]^{20}$ -38.9° (neat); Lit: -39°), hexamethylphosphorus triamide and all carbonyl compounds were purchased from commercial sources and were either recrystallised solid carbonyls, chromatographed on a short column of Brockmann Grade I basic alumina [(*S*)-α-phenylethylamine, N-methyl morpholine, NEt_3, and liquid carbonyls], used as received [PCl_3, $LiN(SiMe_3)_2$ as a 1 M solution in THF and hexamethylphosphorus triamide]. 2-(diphenylphosphino)benzaldehyde was prepared using the previously reported method.[13] Diastereomeric excess (d.e.) refers to the percentage excess of the major component A to a mixture of epimers A and B, {[A] - [B]}/{[A] + [B]} x 100 and were determined by integration of appropriate resonances in both ^{31}P and ^1H NMR spectra.

N,N'-bis(1-(S)-Phenylethyl)-1,2-ethylenediamine **2** *(PEED)*

This was prepared using the procedure of Feringa and co-workers.[6]
Isolated as a colourless oil in 60% yield by reduced pressure distillation (157°C at 0.9 mmHg). δ_H ($CDCl_3$) 7.4-7.2 (m, 10H, Ph-H), 3.63 (q, 2H, $^3J_{HH}$ 6.6, C*H*MePh), 2.50 (m, 4H, -CH_2CH_2-), 1.52 (br s, 2H, NH), 1.31 (d, 6H, $^3J_{HH}$ 6.6, CH*Me*Ph). δ_C ($CDCl_3$) 145.71 (s, Ph-C_{ipso}), 128.16 (s, Ph-$C_{o/m}$), 126.60 (s, (Ph-C_p), 126.36 (s, Ph-$C_{o/m}$), 58.02 (s, *C*HMePh), 47.21 (s, -CH_2CH_2-), 24.33 (s, CH*Me*Ph). $[\alpha]^{20}$ -62.2 (c 1.1; $CHCl_3$). Lit: -69.4.[6]

2-Chloro-1,3-diazaphospholidine, {PEED}PCl **3**[8]

A solution of N,N'-bis[1-(*S*)-phenylethyl]-1,2-ethylenediamine (0.70 g, 2.59 mmol) in toluene solvent

(15 cm^3) was added dropwise over the course of *ca.* 20 mins. to a stirred solution of PCl_3 (0.23 cm^3, 2.59 mmol) and NEt_3 (0.72 cm^3, 5.20 mmol) in toluene (15 cm^3) cooled to -78°C under an atmosphere of dinitrogen. After the addition the solution was allowed to warm to ambient temperature during which time a white flocculent material was observed to form and was stirred at this temperature for *ca.* 4 h. After this time the reaction mixture was filtered, the residue washed liberally with pentane (3 x 10 cm^3), the washings and filtrate combined and all the volatile materials removed under reduced pressure to afford a pale yellow solid. This solid was then recrystallised from pentane to afford the title compound as pale yellow crystals. (1.60 g, 76%). δ_H 7.47-7.12 (various resonances, 10H, Ph-*H*), 4.22 (s broad, 2H, C*H*), 3.04 (m, 4H, CH_2), 1.69 (dd, 6H, $^3J_{HH}$ 6.8, $^4J_{PH}$ 2.2, CH_3). δ_C 142.68 (s, Ar-C_{ipso}), 128.63-127.02 (various resonances, Ar-C), 57.87 (s broad, *C*H), 48.72 (m broad,CH_2), 22.72 (m broad,CH_3). δ_P 167.2 (s). (Found: C, 64.85; H, 7.05; N, 8.25. $C_{18}H_{22}N_2PCl$ requires C, 64.96; H, 6.66; N, 8.42). (Found: M^+, 332.122 236. Calc. for $C_{18}H_{22}N_2PCl^{35}$: M, 332.120 915).

*2-Triphenylsiloxy-1,3-diazaphospholidine, {PEED}POSiPh$_3$ **4***

A solution of Ph_3SiOH in toluene (0.50 g, 1.83 mmol in *ca.* 15 cm^3 solvent) was added dropwise over the course of 5 minutes to a stirred solution of {PEED}PCl **3** (0.61 g, 1.83 mmol) and triethylamine (0.51 cm^3, 3.65 mmol) in toluene solvent (10 cm^3) cooled to 0°C. The mixture was allowed to warm to room temperature and allowed to stir for 4 h. After this time the mixture is filtered and the residue washed with pentane (2 x 30 cm^3), the extracts combined and all volatiles removed under reduced pressure to afford the product as a white, crystalline solid. (0.84 g, 81%). This product was found to be suitably pure for further synthetic purposes. δ_H ($CDCl_3$) 7.7-7.2 (m, 25h, Ph-H), 4.24 (m, 1H, $^3J_{HH}$ = $^3J_{PH}$ 6.7, C*H*MePh), 3.84 (m, 1H, $^3J_{HH}$ = $^3J_{PH}$ 6.7, C*H*MePh), 2.85 (m, 4H, -CH_2-), 1.43 (d, 3H, $^3J_{HH}$ 6.6, CH*Me*Ph), 1.35 (d, 3H, $^3J_{HH}$ 6.9, CH*Me*Ph). δ_C ($CDCl_3$, assignments facilitated by DEPT and ^{1}H-^{13}C COSY experiments) 145.18 (d, $^3J_{PC}$ 7.7, Ph-C_{ipso} backbone), 144.53 (d, $^3J_{PC}$ 3.8, Ph-C_{ipso}-backbone), 135-126 (several resonances, Ph-C), 57.65 (d, $^2J_{PC}$ 12.9, *C*HMePh), 56.64 (d, $^2J_{PC}$ 23.8, *C*HMePh), 48.07 (d, $^2J_{PC}$ 9.1, -CH_2CH_2-), 46.74 (d, $^2J_{PC}$ 9.1, -CH_2CH_2-), 24.17 (d, $^3J_{PC}$ 16.2, CH*Me*Ph), 21.78 (d, $^3J_{PC}$ 14.1, CH*Me*Ph). δ_P ($CDCl_3$) 113.5 (s).

*Phosphorous acid diamide, {PEED}P(=O)H **5***

To a solution of {PEED}PCl in toluene (0.66 g, 1.97 mmol in 20 cm^3 solvent), containing triethylamine (0.55 cm^3, 3.9 mmol) maintained at -78°C was added water (35.5 µl, 1.97 mmol). The reaction mixture was then allowed to warm to ambient temperature with stirring and was left to stir thus for 16 h. After this time all volatiles were removed under reduced pressure and the crude product recrystallised from pentane to afford **5** as white crystals. (0.58 g, 94%). ν(P-H) 2340 cm^{-1} (w); ν(P=O) 1230 cm^{-1} (m). δ_P (C_6D_6) 10.2 (s). δ_H (C_6D_6) 7.00 (d, 1H, $^1J_{PH}$ 608, P-H), 7.4-7.0 (m, 10H, Ph-H), 4.32 (dq, 1H, $^3J_{HH}$ 6.9, $^3J_{PH}$ 6.9, C*H*MePh), 4.03 (dq, 1H, $^3J_{HH}$ 6.9, $^3J_{PH}$ 11.0, C*H*MePh), 2.6-2.2 (m, 4H, -CH_2CH_2-), 1.56 (d, 3H, $^3J_{HH}$ 7.0, CH*Me*Ph), 1.49 (d, 3H, $^3J_{HH}$ 6.9, CH*Me*Ph). δ_C (C_6D_6) 142.56 (d, $^3J_{PC}$ 3.3, Ph-C_{ipso}), 142.10 (d, $^3J_{PC}$ 5.5, Ph-C_{ipso}), 128.48-126.75 (several resonances, Ph-C), 55.24 (d, $^2J_{PC}$ 6.2, *C*HMePh), 54.38 (d, $^2J_{PC}$ 6.0, *C*HMePh), 42.91 (d, $^2J_{PC}$ 9.2, CH_2), 20.93 (d, $^3J_{PC}$ 4.5, CH*Me*Ph), 20.22 (d, $^3J_{PC}$ 3.1, CH*Me*Ph). {Found: M^+, 314.155 854. Calc. for $C_{18}H_{23}N_2OP$: *M*, 314.154 802; Mol. Wt: 315.4}.

*Reaction of {PEED}POSiPh$_3$ **4** with PhCHO. Synthesis of {PEED}P(=O)CHPh(OSiPh$_3$) **6***

Benzaldehyde (29.9 ml, 0.29 mmol) was added to a toluene solution of {PEED}$POSiPh_3$ (0.169 g, 0.25 mmol in 2.0 cm^3 solvent) in a 10 mm NMR tube fitted with a 5 mm insert tube containing C_6D_6 as lock solvent. The $^{31}P\{^1H\}$ NMR spectrum of the mixture was analysed periodically over the ensuing 15 days. After this time, the solvent was removed under reduced pressure and the residue extracted in pentane, filtered and dried in vacuo to afford **6** as a white solid mixture of diastereoisomers. (0.19 g, 94 %). δ_P (C_6D_6) 31.9 (s, minor), 30.6 (s, major). δ_H (C_6D_6) 7.9-6.9 (m, 60H, Ph-H), 5.52 (d, 1H, $^2J_{PH}$ 10.2, PC*H*Ph major), 5.48 (d, 1H, $^2J_{PH}$ 11.0. PC*H*Ph minor), 5.05 (quin, 1H, $^3J_{HH}$ = $^3J_{PH}$ 6.9, C*H*MePh major), 4.23 (quin, 1H, $^3J_{HH}$ = $^3J_{PH}$ 6.9, C*H*MePh major), 4.01 (quin, 1H, $^3J_{PH}$ 6.8, C*H*MePh minor), 3.79 (dquart, 1H, $^3J_{PH}$ 9, $^3J_{HH}$ 7, C*H*MePh minor), 2.24-1.87 (m, 8H, -CH_2CH_2-), 1.69 (d, 3H, $^3J_{HH}$ 7, CH*Me*Ph minor), 1.47 (d, 3H, $^3J_{HH}$ 7, CH*Me*Ph minor), 1.42 (d, 3H, $^3J_{HH}$ 7, CH*Me*Ph major), 1.17 (d, 3H, $^3J_{HH}$ 7, CH*Me*Ph major). δ_C (C_6D_6) 144.71-126.05 (several resonances, Ph-C), 78.76 (d, $^1J_{PC}$ 144.3, P-C major), 77.74 (d, $^1J_{PC}$ 143.1, P-C minor), 57.63 (d, $^2J_{PC}$ 4.9, *C*HMePh minor), 57.08 (d, $^2J_{PC}$ 5.1, *C*HMePh minor), 52.88 (d, $^2J_{PC}$ 4.5,

*C*HMePh major), 52.60 (d, $^2J_{PC}$ 4.5, *C*HMePh major), 43.98 (d, $^2J_{PC}$ 9.1, -CH_2CH_2- minor), 43.42 (d, $^2J_{PC}$ 9.7, -CH_2CH_2- major), 40.30 (d, $^2J_{PC}$ 7.8, -CH_2CH_2- minor), 39.46 (d, $^2J_{PC}$ 8.5, -CH_2CH_2- major), 22.42 (br s, CH*Me*Ph minor), 22.06 (br s, CH*Me*Ph minor), 19.00 (d, $^3J_{PC}$ 5.1, CH*Me*Ph), 18.80 (d, $^3J_{PC}$ 5.3, CH*Me*Ph major).

Reaction of {PEED}P(=O)H 5 with PhCHO. Synthesis of {PEED}P(=O)CHPh(OH) 7

To a solution of {PEED}P(=O)H **5** in THF (0.68 g, 2.05 mmol in 20 cm^3 of solvent) at -78°C was added $LiN(SiMe_3)_2$ (2.05 cm^3 of a 1.0 M solution in THF) and stirred thus for 1 h. Benzaldehyde (208 µl, 2.05 mmol) was then added slowly at -78°C and the mixture stirred for 3 h, whilst warming to room temp. NH_4Cl(aq) (20 cm^3 of a saturated solution) was then added and the mixture was stirred for 30 mins. The product was then extracted into toluene (3 x 15 cm^3). The combined extracts were dried over Na_2SO_4 (anhydrous), filtered and the volatiles removed under reduced pressure to afford the title compound as white crystals. (0.69 g, 80%). $\delta_P(C_6D_6)$: 34.5 (s, minor, 35.2%), 34.0 (s, major, 64.8%). $\delta_H(C_6D_6)$: 7.47-6.76 (m, 15H, Ph-H), 5.38 (d, 1H, $^2J_{PH}$ 8.5, PC*H*Ph major), 5.35 (d, 1H, $^2J_{PH}$ 8.5, PC*H*Ph minor), 4.75 (dq, 1H, $^3J_{HH} = {}^3J_{PH}$ 7.1, C*H*MePh major), 4.50 (dq, 1H, $^3J_{HH} = {}^3J_{PH}$ 7.3, C*H*MePh minor), 4.44 (dq, 1H, $^3J_{HH} = {}^3J_{PH}$ 7.2, C*H*MePh major), 4.26 (dq, 1H, $^3J_{HH} = {}^3J_{PH}$ 6.6, C*H*MePh minor), 2.91-2.48 (m, 8H, -CH_2CH_2), 1.80 (d, 3H, $^3J_{HH}$ 6.9, CH*Me*Ph minor), 1.73 (d, 3H, $^3J_{HH}$ 7.0, CH*Me*Ph major), 1.56 (d, 3H, $^3J_{HH}$ 6.9, CH*Me*Ph minor), 1.46 (d, 3H, $^3J_{HH}$ 6.9, CH*Me*Ph major). $\delta_C(C_6D_6)$: 143.18-125.13 (several resonances, Ph-C), 73.21 (d, $^1J_{PC}$ 131.9, P*C*HPh major), 72.61 (d, $^1J_{PC}$ 130.2, P*C*HPh minor), 55.25 (d, $^2J_{PC}$ 4.9, *C*HMePh minor), 54.56 (d, $^2J_{PC}$ 4.9, *C*HMePh major), 51.91 (d, $^2J_{PC}$ 3.8, *C*HMePh minor), 51.85 (d, $^2J_{PC}$ 4.3, *C*HMePh major), 42.65 (d, $^2J_{PC}$ 8.7, -CH_2CH_2- minor), 41.33 (d, $^2J_{PC}$ 8.7, -CH_2CH_2-, major), 39.72 (d, $^2J_{PC}$ 8.2, -CH_2CH_2- minor), 39.54 (d, $^2J_{PC}$ 8.7, -CH_2CH_2- major), 20.85 (s, CH*Me*Ph minor), 19.99 (s, CH*Me*Ph major), 18.1 (d, $^3J_{PC}$ 4.4, CH*Me*Ph minor), 17.72 (d, $^3J_{PC}$ 4.4, CH*Me*Ph major).

Reaction of {PEED}P(=O)H 5 with 2-BrC_6H_4CHO. Synthesis of {PEED}P(=O)CH(C_6H_4Br-2)(OH) 8

To a solution of {PEED}P(=O)H **5** in THF (0.31 g, 0.98 mmol in 20 cm^3 of solvent) at -78°C was added a THF silution of $LiN(SiMe_3)_2$ (0.98 cm^3 of a 1.0 M solution in THF) and stirred thus for 1 h. 2-Bromoenzaldehyde (114 µl, 0.98 mmol) was then added slowly at -78°C and the mixture stirred for 3.5 h whilst warming to ambient temperature (*ca.* 23°C). NH_4Cl(aq) (20 cm^3 of a saturated solution) was then added and the mixture was stirred for 30 mins. The product was then extracted into toluene (3 x 15 cm^3). The combined extracts were dried over Na_2SO_4 (anhydrous), filtered and all volatile materials removed under reduced pressure to afford the product **8** as cream coloured crystals. (0.43 g, 88%). $\delta_P(C_6D_6)$: 33.8 (s, major, 77.2%), 33.0 (s, minor, 22.8%). $\delta_H(C_6D_6)$: 7.74-6.79 (m, 14H, Ph-H), 5.46 (d, 1H, $^2J_{PH}$ 11.6, PC*H*Ph minor), 5.41 (d, 1H, $^2J_{PH}$ 10.6, PC*H*Ph major), 4.82 (quin, 1H, $^3J_{HH} = {}^3J_{PH}$ 6.9, C*H*MePh minor), 4.64 (quin, 1H, $^3J_{HH} = {}^3J_{PH}$ 6.8, C*H*MePh major), 4.17 (quin, 1H, $^3J_{HH} = {}^3J_{PH}$ 7.1, C*H*MePh minor), 4.14 (quin, 1H, $^3J_{HH} = {}^3J_{PH}$ 7.0, C*H*MePh major), 3.00-2.55 (m, 8H, -CH_2CH_2-), 1.78 (d, 3H, $^3J_{HH}$ 6.9, CH*Me*Ph major), 1.75 (d, 3H, $^3J_{HH}$ 6.8, CH*Me*Ph minor), 1.52 (d, 3H, $^3J_{HH}$ 6.9, CH*Me*Ph minor), 0.86 (d, 3H, $^3J_{HH}$ 7.0, CH*Me*Ph major). $\delta_C(C_6D_6)$: 142.58-123.12 (several resonances, Ph-C), 72.39 (d, $^1J_{PC}$ 127.6, P*C*HPh minor), 72.08 (d, $^1J_{PC}$ 122.5, P*C*HPh major), 54.96 (d, $^2J_{PC}$ 5.7, *C*HMePh major), 54.25 (d, $^2J_{PC}$ 4.3, *C*HMePh minor), 51.99 (d, $^2J_{PC}$ 3.9, *C*HMePh major), 51.83 (d, $^2J_{PC}$ 4.9, *C*HMePh minor), 41.45 (d, $^2J_{PC}$ 11.3, -CH_2CH_2- major), 41.15 (d, $^2J_{PC}$ 8.7, -CH_2CH_2- minor), 39.35 (d, $^2J_{PC}$ 10.4, -CH_2CH_2- minor), 39.03 (d, $^2J_{PC}$ 9.4, -CH_2CH_2- major), 20.74 (s, CH*Me*Ph major), 19.80 (s, CH*Me*Ph minor), 17.98 (d, $^3J_{PC}$ 3.4, CH*Me*Ph minor), 16.62 (d, $^3J_{PC}$ 6.2, CH*Me*Ph major).

Reaction of {PEED}P(=O)H 5 with 3-BrC_6H_4CHO. Synthesis of {PEED}P(=O)CH(C_6H_4Br-3)(OH) 9

To a solution of {PEED}P(=O)H **5** in THF (1.33 g, 4.22 mmol in 20 cm^3 of solvent) at -78°C was added $LiN(SiMe_3)_2$ (4.22 cm^3 of a 1.0 M solution in THF) and the resulting mixture stirred thus for 1 h. 3-Bromobenzaldehyde (492 µl, 4.22 mmol) is then added slowly at -78°C and then the mixture was stirred for 3 hours, whilst warming to room temperature. NH_4Cl(aq) (20 cm^3 of a saturated solution) was then added and the mixture stirred for 30 mins. The product was then extracted into toluene (3 x 15 cm^3). The combined extracts were dried over Na_2SO_4 (anhydrous), filtered and the volatile components were removed under reduced pressure to afford the title compound **9** as pale yellow crystals. (1.71 g, 81%). $\delta_P(C_6D_6)$: 34.0 (s, minor, 34.4%), 33.7 (s, major, 65.6%). $\delta_H(C_6D_6)$: 7.93-7.15 (m, 14H, Ph-H), 5.36 (d, 1H, $^2J_{PH}$ 9.0, PC*H*Ph

major), 5.30 (d, 1H, $^2J_{PH}$ 8.8, PC*H*Ph minor), 4.79 (quin, 1H, $^3J_{HH}$ = $^3J_{PH}$ 7.0, C*H*MePh major), 4.46 (quin, 1H, $^3J_{HH}$ = $^3J_{PH}$ 7.0, C*H*MeP minor), 4.44 (quin, 1H, $^3J_{HH}$ = $^3J_{PH}$ 7.1, C*H*MePh major), 4.36 (quin, 1H, $^3J_{HH}$ = $^3J_{PH}$ 6.7, C*H*MePh minor), 3.19-2.57 (m, 8H, -CH_2CH_2-), 1.80 (d, 3H, $^3J_{HH}$ 7.0, CH*Me*Ph minor), 1.74 (d, 3H, $^3J_{HH}$ 6.9, CH*Me*Ph major), 1.58 (d, 3H, $^3J_{HH}$ 7.0, CH*Me*Ph minor), 1.52 (d, 3H, $^3J_{HH}$ 6.9, CH*Me*Ph major). $\delta_C(C_6D_6)$: 146.04-122.07 (several resonances, Ph-C), 72.52 (d, $^1J_{PC}$ 132.2, PCHPh major), 72.20 (d, $^1J_{PC}$ 130.5, PCHPh minor), 55.36 (d, $^2J_{PC}$ 5.0, *C*HMePh minor), 54.55 (d, $^2J_{PC}$ 5.1, *C*HMePh major), 52.12 (d, $^2J_{PC}$ 4.1, *C*HMePh minor), 52.00 (d, $^2J_{PC}$ 4.9, *C*HMePh major), 42.45 (d, $^2J_{PC}$ 8.4, -CH_2CH_2- minor), 41.28 (d, $^2J_{PC}$ 9.1, -CH_2CH_2-, major), 39.98 (d, $^2J_{PC}$ 8.2, -CH_2CH_2- minor), 39.72 (d, $^2J_{PC}$ 8.7, -CH_2CH_2- major), 20.86 (s, CH*Me*Ph minor), 20.18 (s, CH*Me*Ph major), 18.29 (d, $^3J_{PC}$ 4.5, CH*Me*Ph minor), 17.90 (d, $^3J_{PC}$ 4.3, CH*Me*Ph major).

*Reaction of {PEED}P(=O)H **5** with 4-BrC_6H_4CHO. Synthesis of {PEED}P(=O)CH(C_6H_4Br-4)(OH) **10***

To a solution of {PEED}P(=O)H **5** in THF (0.66 g, 1.99 mmol in 20 cm^3 of solvent) at -78°C was added LiN($SiMe_3$)$_2$ (1.99 cm^3 of a 1.0 M solution in THF) and stirred thus for 1 h. 4-Bromobenzaldehyde (0.37 g, 0.66 mmol) is then added slowly at -78°C and then the mixture is stirred for 3 h, whilst warming to room temperature. A saturated aaueous solution of NH_4Cl(aq) (20 cm^3 of a saturated solution) was then added and the mixture was stirred for 30 mins. The product was then extracted into toluene (3 x 15 cm^3). The combined extracts were dried over Na_2SO_4 (anhydrous), filtered and the volatiles removed under reduced pressure to afford the product **10** as pale yellow crystals. (0.83 g, 84%). $\delta_P(C_6D_6)$: 34.0 (s, minor, 36.9%), 33.6 (s, major, 63.1%). $\delta_H(C_6D_6)$: 7.96-7.04 (m, 14H, Ph-H), 5.34 (d, 1H, $^2J_{PH}$ 9.2, PC*H*Ph major), 5.28 (d, 1H, $^2J_{PH}$ 9.0, PC*H*Ph minor), 4.78 (quin, 1H, $^3J_{HH}$ = $^3J_{PH}$ 6.9, C*H*MePh major), 4.45 (quin, 1H, $^3J_{HH}$ = $^3J_{PH}$ 7.0, C*H*MePh minor), 4.37 (quin, 1H, $^3J_{HH}$ = $^3J_{PH}$ 7.3, C*H*MePh major), 4.32 (quin, 1H, $^3J_{HH}$ = $^3J_{PH}$ 6.6, C*H*MePh minor), 3.12-2.43 (m, 8H, -CH_2CH_2-), 1.77 (d, 3H, $^3J_{HH}$ 6.9, CH*Me*Ph minor), 1.68 (d, 3H, $^3J_{HH}$ 7.0, CH*Me*Ph major), 1.52 (d, 3H, $^3J_{HH}$ 7.0, CH*Me*Ph major), 1.39 (d, 3H, $^3J_{HH}$ 6.7, CH*Me*Ph minor). $\delta_C(C_6D_6)$: 143.68-120.88 (several resonances, Ph-C), 72.52 (d, $^1J_{PC}$ 133.5, PCHPh major), 72.08 (d, $^1J_{PC}$ 131.3, PCHPh minor), 55.02 (d, $^2J_{PC}$ 4.9, *C*HMePh minor), 54.40 (d, $^2J_{PC}$ 4.9, *C*HMePh major), 51.86 (d, $^2J_{PC}$ 4.9, *C*HMePh major), 51.86 (d, $^2J_{PC}$ 4.9, *C*HMePh minor), 42.42 (d, $^2J_{PC}$ 8.7, -CH_2CH_2- minor), 41.23 (d, $^2J_{PC}$ 9.3, -CH_2CH_2-, major), 39.77 (d, $^2J_{PC}$ 9.3, -CH_2CH_2- minor), 39.62 (d, $^2J_{PC}$ 9.3, -CH_2CH_2- major), 20.89 (s, CH*Me*Ph minor), 20.14 (s, CH*Me*Ph major), 18.19 (d, $^3J_{PC}$ 4.4, CH*Me*Ph minor), 17.90 (d, $^3J_{PC}$ 3.8, CH*Me*Ph major).

*Reaction of {PEED}P(=O)H **5** with 1-$C_{10}H_7$CHO. Synthesis of {PEED}P(=O)CH($C_{10}H_7$-1)(OH) **11***

To a solution of CDA.P(=O)H **5** in THF solvent (0.89 g, 2.83 mmol in 20 cm^3 of solvent) at -78°C was added dropwise LiN($SiMe_3$)$_2$ (2.83 cm^3 of a 1.0 M solution in THF) and the resulting mixture stirred thus for 1 h. 1-Napthaldehyde (385 µl, 0.66 mmol) was then added slowly at -78°C and the mixture stirred for a further 3 h, whilst warming to room temperature. NH_4Cl(aq) (20 cm^3 of a saturated solution) was then added and the mixture stirred for 30 mins. The product was then extracted into toluene (3 x 15 cm^3), the combined extracts dried over Na_2SO_4 (anhydrous), filtered and the volatile components removed under reduced pressure to afford the product **11** as pale yellow crystals. (0.99 g, 74%). $\delta_P(C_6D_6)$: 35.2 (s, minor, 34.6%), 34.8 (s, major, 65.4%) $\delta_H(C_6D_6)$: 8.03-7.16 (m, 17H, Ph-H), 6.03 (d, 1H, $^2J_{PH}$ 8.8, PC*H*Ph minor), 6.01 (d, 1H, $^2J_{PH}$ 9.7, PC*H*Ph major), 4.69 (quin, 1H, $^3J_{HH}$ = $^3J_{PH}$ 7.3, C*H*MePh major), 4.53 (quin, 1H, $^3J_{HH}$ = $^3J_{PH}$ 7.0, C*H*MePh minor), 4.31 (quin, 1H, $^3J_{HH}$ = $^3J_{PH}$ 7.0, C*H*MePh major), 4.21 (quin, 1H, $^3J_{HH}$ = $^3J_{PH}$ 6.7, C*H*MePh minor), 3.10-2.48 (m, 8H, -CH_2CH_2-), 1.78 (d, 3H, $^3J_{HH}$ 6.9, CH*Me*Ph major), 1.73 (d, 3H, $^3J_{HH}$ 6.9, CH*Me*Ph minor), 1.63 (d, 3H, $^3J_{HH}$ 6.9, CH*Me*Ph minor), 0.68 (d, 3H, $^3J_{HH}$ 6.9, CH*Me*Ph major). $\delta_C(C_6D_6)$: 142.34-123.49 (several resonances, Ph-C), 69.76 (d, $^1J_{PC}$ 129.1, PCHPh minor), 69.63 (d, $^1J_{PC}$ 125.2, PCHPh major), 54.92 (d, $^2J_{PC}$ 4.6, *C*HMePh minor), 54.36 (d, $^2J_{PC}$ 5.3, *C*HMePh major), 52.22 (d, $^2J_{PC}$ 4.5, *C*HMePh minor), 51.93 (d, $^2J_{PC}$ 4.5, *C*HMePh major), 42.06 (d, $^2J_{PC}$ 8.7, -CH_2CH_2- minor), 40.75 (d, $^2J_{PC}$ 9.8, -CH_2CH_2- major), 39.93 (d, $^2J_{PC}$ 8.7, -CH_2CH_2- minor), 39.58 (d, $^2J_{PC}$ 9.2, -CH_2CH_2- major), 20.45 (s, CH*Me*Ph minor), 19.99 (s, CH*Me*Ph major), 18.08 (d, $^3J_{PC}$ 4.7, CH*Me*Ph minor), 16.65 (d, $^3J_{PC}$ 5.1, CH*Me*Ph major).

Reaction of {PEED}P(=O)H **5** *with 2-$Ph_2PC_6H_4CHO$. Synthesis of {PEED}P(=O)CH($C_6H_4PPh_2$-2)(OH))* ***12***

To a THF solution of CDA.P(=O)H **5** (0.31 g, 0.98 mmol in 20 cm^3 of solvent) at -78°C was added $LiN(SiMe_3)_2$ (0.98 cm^3 of a 1.0 M solution in THF) and the mixture stirred for 1 h. 2-Diphenylphosphinebenzaldehyde (0.28 g, 0.98 mmol) was then added slowly at -78°C and then the mixture stirred for a further 2.5 hours, whilst warming to room temperature. Acidic work up as above with NH_4Cl(aq) (20 cm^3 of a saturated solution) followed by extraction into toluene (3 x 15 cm^3), drying over Na_2SO_4 (anhydrous), filtration and removal of the volatile materials under reduced pressure affords **12** as pale yellow crystals. (0.54 g, 92%). $\delta_P(C_6D_6)$: 34.3 (s, major, 71.4%), 33.7 (s, minor, 28.6%). $\delta_H(C_6D_6)$: 8.04-6.82 (m, 30H, Ph-H), 5.92 (dd, 1H, $^2J_{PH}$ 10.1, $^4J_{PH}$ 7.0, PC*H*Ph major), 5.89 (dd, 1H, $^2J_{PH}$ 8.5, $^4J_{PH}$ 7.1, PC*H*Ph minor), 4.85 (quin, 1H, $^3J_{HH}$ = $^3J_{PH}$ 6.7, C*H*MePh minor), 4.62 (quin, 1H, $^3J_{HH}$ = $^3J_{PH}$ 6.9, C*H*MePh major), 4.39 (quin, 1H, $^3J_{HH}$ = $^3J_{PH}$ 7.0, C*H*MePh major), 4.29 (quin, 1H, $^3J_{HH}$ = $^3J_{PH}$ 7.1, C*H*MePh minor), 3.06-2.61 (m, 8H, $-CH_2CH_2-$), 1.76 (d, 3H, $^3J_{HH}$ 6.9, CH*Me*Ph major), 1.70 (d, 3H, $^3J_{HH}$ 6.9, CH*Me*Ph minor), 1.60 (d, 3H, $^3J_{HH}$ 6.9, CH*Me*Ph minor), 0.84 (d, 3H, $^3J_{HH}$ 7.0, CH*Me*Ph major). $\delta_C(C_6D_6)$: 143.02-126.84 (several resonances, Ph-C), 71.27 (d, $^1J_{PC}$ 133.4, $^3J_{PC}$ 4.6, PCHPh minor), 71.00 (d, $^1J_{PC}$ 133.0, $^3J_{PC}$ 5.5, PCHPh major), 53.63 (d, $^2J_{PC}$ 5.5, CHMePh major), 53.17 (d, $^2J_{PC}$ 3.8, CHMePh minor), 51.18 (d, $^2J_{PC}$ 5.6, CHMePh minor), 51.09 (d, $^2J_{PC}$ 5.0, CHMePh major), 40.52 (d, $^2J_{PC}$ 10.8, $-CH_2CH_2-$ major), 40.04 (d, $^2J_{PC}$ 8.2, $-CH_2CH_2-$ minor), 38.67 (d, $^2J_{PC}$ 9.8, $-CH_2CH_2-$ major), 38.56 (d, $^2J_{PC}$ 11.4, $-CH_2CH_2-$ minor), 20.04 (s, CH*Me*Ph major), 18.98 (s, CH*Me*Ph minor), 17.13 (d, $^3J_{PC}$ 2.2, CH*Me*Ph minor), 16.70 (d, $^3J_{PC}$ 4.8, CH*Me*Ph major).

Investigation of Configurational Stability in Phosphonodiamidates ***7-12***

ND_4Cl was prepared by stirring NH_4Cl in D_2O for 16 h followed by removal of all volatile materials under reduced pressure. The resulting white solid was shown to be effectively per-deuterated since ^1H NMR spectroscopy revealed that the hydrogen resonances had disappeared. A sample of ester **8** (0.1 g) with the same epimeric composition as that shown in the Table was then dissolved in $CDCl_3$:D_2O (30 cm^3; *ca.* 1:4 v/v) and stirred with ND_4Cl for *ca.* 72 h before all volatiles were removed *in vacuo* and the residue analysed by ^1H NMR spectroscopy in $CDCl_3$ solution. Careful integration of appropriate hydrogen resonances revealed that there had been no alteration of the epimeric ratio or incorporation of deuterium at the alpha carbon position.

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