Intramolecular nucleophilic catalysis and the exceptional reactivity of *N*-benzyloxycarbonyl α-aminophosphonochloridates

Paul M. Cullis and Martin J. P. Harger

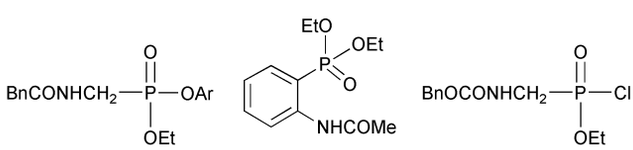
Department of Chemistry, University of Leicester, Leicester, UK LE1 7RH

Received (in Cambridge, UK) 22nd May 2002, Accepted 2nd July 2002
First published as an Advance Article on the web 29th July 2002

The chloridate $BnOCONHCH_2P(O)(OMe)Cl$ is 10^3–10^4 times more reactive than $ClCH_2P(O)(OMe)Cl$ in substitution with Pr^iOH; the α,α-dimethyl analogue is no less reactive and the *N*-methyl derivative is more reactive; nucleophilic participation (catalysis) by the carbamate group is implicated.

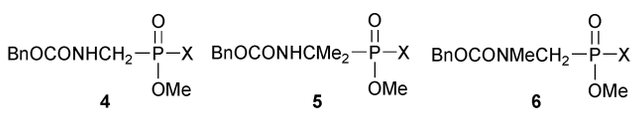
Aminophosphonic acids, especially the α-amino compounds, are important transition-state analogues for mechanistic studies of enzyme catalysis and they have been shown to inhibit a number of proteases, notably angiotensin-converting enzyme.[1] They have found use as haptens for obtaining catalytic antibodies (abzymes), especially those that catalyse dipeptide formation, and in some cases they display significant levels of antimicrobial, herbicidal and neurophysiological activity.[1] It is hardly surprising that aminophosphonic acids and their derivatives have become the focus of much synthetic work.[1b] In developing efficient synthetic strategies studies of reactivity have an important part to play.[2]

The α-amidophosphonate ester **1** undergoes hydrolysis (acid or base) much faster than analogous esters lacking the amide function.[3] Here, and also in related systems in which the CO–NH sequence (relative to the P=O group) is reversed,[4–6] the high reactivity seems to result from intramolecular *nucleophilic* catalysis by the carboxamide group, the carbonyl oxygen atom attacking at phosphorus to form a reactive five-membered cyclic intermediate (not detected).[3–5] A more modest rate enhancement is seen in the base-catalysed hydrolysis of the β-amidophosphonate **2** and in this case it has been attributed to intramolecular *electrophilic* catalysis, *i.e.* hydrogen bonding by the amide NH activating the phosphonyl centre towards normal intermolecular nucleophilic attack.[7] Most recently the reactivity of the protected α-aminophosphonochloridate **3**, in particular its apparent ability to form phosphonylammonium salts,[2] has also been attributed to intramolecular *electrophilic* catalysis by the acidic hydrogen of the NH group.[8] The reactivity of **3** could however be equally well explained in terms of intramolecular nucleophilic catalysis, especially if the supposed phosphonylammonium salts are actually cyclic oxazaphospholine oxides.[9]



1 **2** **3**

The distinction between electrophilic and nucleophilic catalysis is important, not only because of their contrasting geometrical requirements (disposition of amide NH or CO in relation to P=O) and steric implications (relative insensitivity of intramolecular nucleophilic attack to steric hindrance) but also because a fully substituted amide group (no H on N) can act as a nucleophile but not as an electrophile. We hoped to learn more about the relative importance of the two types of catalysis by comparing the reactivity of the chloridate **4** (X = Cl) and its analogues **5** and **6** (X = Cl) alkylated at C_α or on the N atom. †



4 **5** **6**

Results and discussion

Phosphonochloridates

The aminomethylphosphonate $H_2NCH_2P(O)(OMe)_2$ was obtained from commercially-available dimethyl phthalimidomethylphosphonate by deprotection with H_2NNH_2 in methanol,[10] and the 1,1-dimethyl-substituted analogue $H_2NCMe_2P(O)(OMe)_2$ was prepared from $HP(O)(OMe)_2$ by reaction with an acetone–ammonia mixture.[11] The amino phosphonates were then treated with benzyl chloroformate in a two-phase system ($CHCl_3$–aqueous $NaHCO_3$) to give the *N*-benzyloxycarbonyl derivatives **4** (X = OMe) and **5** (X = OMe). Partial hydrolysis of the former (aqueous NaOH at room temperature) and demethylation of the latter (NaI in acetone at 55 °C) gave the crystalline monoesters **4** (X = OH)[10] and **5** (X = OH). Alkylation of the diester **4** (X = OMe) with NaH and MeI in DMF prior to hydrolysis afforded the *N*-methyl monoester **6** (X = OH) (an oil). In the case of the *N*-methyl compound the two rotamers resulting from slow rotation about the carbamate C–N bond were seen to be present (in $CDCl_3$ solution) in a 55 : 45 ratio by NMR spectroscopy [^{31}P: δ_P 25.9 (major) and 25.5; ^1H: two distinct CH_2, NMe and OMe signals]. ‡ The corresponding NH compound **4** (X = OH) also displayed two rotamers in the ^{31}P NMR spectrum [δ_P 25.2 (major) and 24.4] but in a more unequal 90 : 10 ratio, while for the 1,1-dimethyl compound **5** (X = OH) one of the rotamers appeared to be totally dominant (δ_P 29.7 only).

The monoesters were converted into the chloridates using $SOCl_2$ in CH_2Cl_2 or $CDCl_3$. Even at low concentrations (0.1–0.2 mol dm^{-3} $SOCl_2$) and in the absence of DMF or any other catalyst, the reactions proceeded readily at room temperature. The ease of conversion (complete in ~0.5 h) must surely be a

† We chose OMe rather than OEt as the 'spectator' ligand on the phosphorus atom because then the sterically hindered dialkyl phosphonate precursors **5** and **10** (X = OMe) can the more easily be dealkylated by nucleophilic attack (at carbon) by iodide or *tert*-butylamine.

‡ Rotamer interconversion is sufficiently fast at room temperature to cause pronounced line broadening in the 400 MHz ^1H NMR spectra of the *N*-methyl compounds **6** (X = OH, Cl, OPr^i *etc.*) but at 0 °C the lines were sharp.

 DOI: 10.1039/b204935j

result of intramolecular catalysis by the carbamate group (*cf.* intermolecular catalysis by DMF); without it $ClCH_2P(O)(OH)OMe$, for example, is not only less reactive towards $SOCl_2$ but in the absence of DMF the first-formed anhydride is only very slowly converted into the chloride. The two NH chloridates, **4** (X = Cl), δ_P 37.3 (minor rotamer 36.8) and **5** (X = Cl), δ_P 47.6, were initially obtained as oils but could be obtained as crystalline solids by carrying out the $SOCl_2$ reaction at ~30 °C in a small volume of a solvent in which the product is only sparingly soluble (ether or ether-light petroleum) and then cooling the reaction mixture to 0 °C. They were however extremely sensitive to moisture, and any manipulation (in the absence of $SOCl_2$) generally introduced some of the anhydride (pyrophosphonate) [^{31}P NMR: 2 peaks (diastereoisomers) at *ca.* δ_P 17 or 23]. The NMe chloridate **6** (X = Cl), δ_P 36.5 and 36.3 (rotamers; ratio *ca.* 1 : 1) was not isolated but was used directly in the reaction mixture in which it was prepared (HCl, SO_2, excess $SOCl_2$ still present).

Reactivity of phosphonochloridates

The reactivity of the phosphonochloridates was examined using Pr^{i}OH as the nucleophile, a secondary alcohol being preferred to MeOH or EtOH as a more rigorous test of phosphonylating ability and of potential synthetic value.

The two NH chloridates **4** and **5** (X = Cl) reacted rapidly and cleanly with Pr^{i}OH in $CDCl_3$ at room temperature giving the expected isopropyl phosphonates **4** (X = OPr^i), δ_P 22.8 (minor rotamer 22.2) and **5** (X = OPr^i), δ_P 27.8, with characteristic ^{1}H NMR signals for the new alkoxy group [$\delta_H(CDCl_3)$ 4.7 (1H, d × septet, $J_{PH} \sim J_{HH} \sim 6$) and 1.3 (6H; two d, J_{HH} 6, diastereotopic CH_3 groups)]. Even at high dilution (0.08 mol dm^{-3} Pr^{i}OH) both reactions were ⩾ 90% complete in 6 minutes. To obtain a more precise measure of relative reactivity an equimolar mixture of the phosphonochloridates was allowed to react with 0.5 equiv. Pr^{i}OH. The ^{31}P NMR spectrum of the reaction mixture (Fig. 1) showed both substrates to be *ca.* 50% converted into product, implying that their reactivities are very similar. Thus the presence of two methyl groups on the α carbon atom of **5** (X = Cl) has no significant effect on its reactivity towards Pr^{i}OH in nucleophilic substitution.

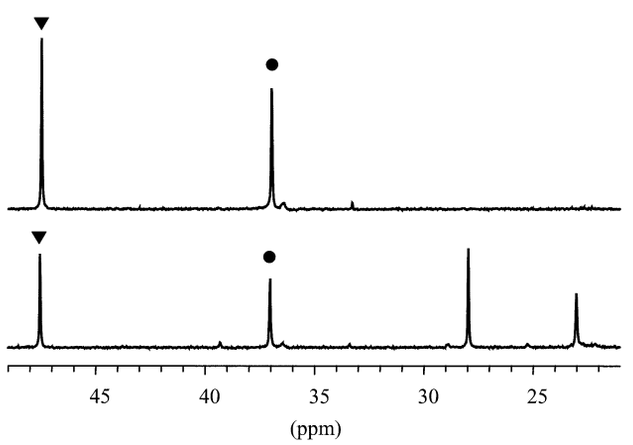
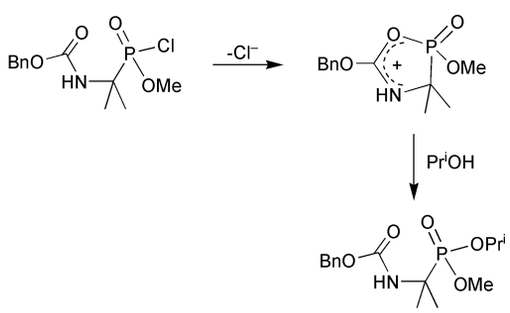


Fig. 1 ^{31}P NMR spectrum of the mixture (1 : 1) of **4** (X = Cl) (rotamers; ratio ~15 : 1) (●) and **5** (X = Cl) (▼) before (top) and after reaction (bottom) with Pr^{i}OH (0.5 equiv.).

To gain some measure of the importance of intramolecular catalysis by the carbamate group, a comparison was made with the corresponding α-chloro compounds $ClCH_2P(O)(OMe)Cl$§ and $ClCMe_2P(O)(OMe)Cl$,[12] reasoning that the inductive and steric effects of the carbamate group should be matched better by a Cl atom at C_α than by a H or alkyl group. Using Pr^{i}OH in $CDCl_3$ (~0.12 mol dm^{-3}; slight excess) the α-chloromethyl compound was only half-consumed in 5 days (T ~20 °C) while the more alkylated compound was practically unchanged (99%) after 5 months. Relative to a Cl substituent on C_α, therefore, the BnOCONH group accelerates the reaction with Pr^{i}OH by a factor of 10^3–10^4 in the case of **4** (X = Cl) and at least 10^6 in the case of **5** (X = Cl).

The fact that the two α-chloro phosphonochloridates differ greatly in reactivity is not surprising, given the general high sensitivity of nucleophilic substitution at a P=O centre to steric effects in the substrate.[13] In the particular case of $ClCMe_2P(O)(OMe)Cl$ we have previously seen that a nucleophile such as $PhNH_2$ or Bu^{t}NH$_2$ may actually dealkylate the *P*-methoxy group by nucleophilic attack at carbon more readily than it displaces the chloride leaving group from the phosphorus atom.[12,14] The fact that the carbamate-containing substrate **5** (X = Cl) is *not* less reactive than its unhindered counterpart **4** (X = Cl) is therefore diagnostically important. If the BnOCONH group were providing electrophilic catalysis of substitution (activation of the P=O group by hydrogen bonding) the rate-limiting step would still involve intermolecular nucleophilic attack at phosphorus; substitution would still be fully exposed to the effects of steric crowding, and the hindered compound **5** (X = Cl) could not possibly react so readily. If there is nucleophilic catalysis however, the leaving group will be displaced by intramolecular nucleophilic attack forming a reactive cyclic intermediate (Scheme 1). The same cyclic species



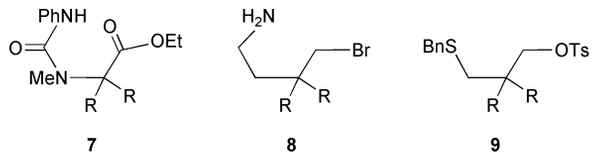
Scheme 1

is probably the immediate precursor of the oxazaphospholine oxides now thought to be formed when the NH chloridates are treated with Et_3N.[9]¶ Such intramolecular attack could benefit from the *gem*-dimethyl effect[15] resulting in an enhanced rate, as in hydantoin-forming cyclisation of the ester **7** (1100 times faster with R = Me than with R = H at pH ⩽ 2),[16] or at least a smaller than usual 'neopentyl' steric retardation, as in cyclisation of the aminoalkyl bromide **8** and in sulfur-assisted methanolysis of the tosylate **9** (<10 times slower with R = Me than with R = H).[17,18] For the α,α-dimethyl phosphonochloridate **5** (X = Cl) to be as reactive as its unmethylated counterpart **4** (X = Cl) but not more reactive, the beneficial *gem*-dimethyl effect would have to be balanced by the adverse effect of steric crowding at the P=O centre in the rate-limiting cyclisation (Scheme 1). Alternatively, if cyclisation is reversible a relatively fast intramolecular formation of the cyclic intermediate could be balanced by a relatively slow (steric hindrance) intermolecular reaction of the intermediate with the external nucleophile.

An obvious distinction between the two types of catalysis lies in their dependence on the acidic hydrogen of the carbamate group; without it electrophilic catalysis cannot occur whereas nucleophilic catalysis is possible and could even benefit from

§ Our $ClCH_2P(O)(OMe)Cl$ contained substantial amounts of $ClCH_2P(O)Cl_2$ and $ClCH_2P(O)(OMe)_2$ [reaction of $ClCH_2P(O)Cl_2$ with 1 equiv. MeOH shows rather poor selectivity]; its (slow) reaction with Pr^{i}OH was complicated by preferential reaction with traces of moisture and by degradation of the product (acid-catalysed dealkylation of *P*–OPr^i group).

¶ The oxazaphospholine oxides have not been isolated but the spectroscopic evidence of structure is good. They react very readily with nucleophiles but should be isolable if moisture can be completely excluded.



alkylation of the N atom. The behaviour of the *N*-methyl substrate **6** (X = Cl) is therefore of particular importance. Under similar conditions (0.08 mol dm^{-3} Pr^iOH in $CDCl_3$) it formed the corresponding isopropyl ester **6** (X = OPr^i), δ_P 22.7 and 22.15 (ratio 57 : 43, rotamers) at least as quickly as the NH substrates **4** and **5** (X = Cl), and when required to compete with **4** (X = Cl) for a limited amount of Pr^iOH (0.43 equiv.) it was seen to be substantially more reactive (Fig. 2). High reactivity of

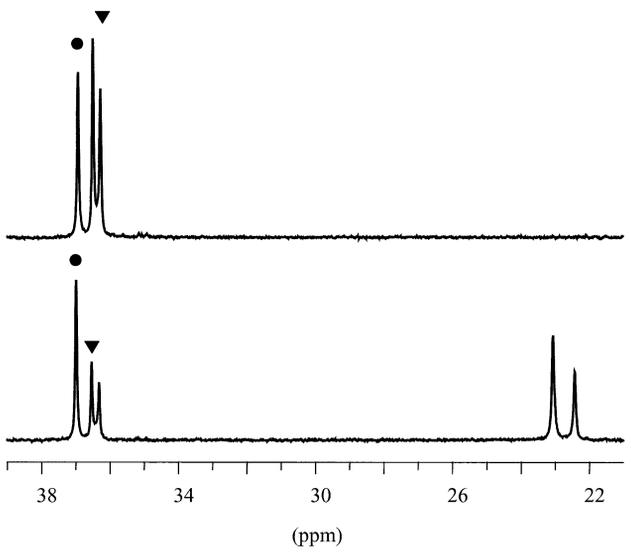
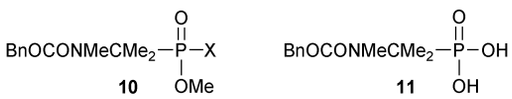


Fig. 2 ^{31}P NMR spectrum of the mixture (1 : 2) of **4** (X = Cl) (●) and **6** (X = Cl) (rotamers; ratio ~1 : 1) (▼) before (top) and after reaction (bottom) with Pr^iOH (0.43 equiv.) [minor (highfield) rotamer of **4** (X = Cl) hidden by lowfield rotamer of **6** (X = Cl); product **4** (X = OPr^i) (if present) hidden by lowfield rotamer of **6** (X = OPr^i); change in substrate ratio (1 : 2.0 to 1 : 0.8) implies product derived largely from **6** (X = Cl)].

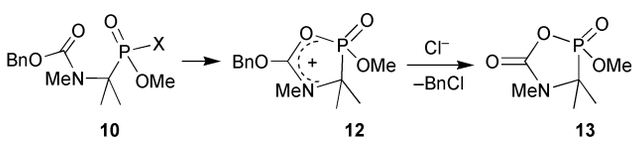
the chloridates under these non-basic conditions (no scavenging of liberated HCl) therefore does not depend on the presence of an NH group or by implication on intramolecular electrophilic catalysis.

It had been our intention to include the fully methylated chloridate **10** (X = Cl) in our study of reactivity but unfortunately we were unable to prepare it. The diester **5** (X = OMe) was successfully methylated on nitrogen (NaH then MeI in DMF) and demethylated at oxygen (NaI in acetone at 55 °C) giving an aqueous solution of the sodium salt of the monoester **10** (X = OH). However, acidification and extraction with $CHCl_3$ did not give the free monoester but rather the phosphonic acid **11** corresponding to loss of the remaining *O*-methyl group. Apparently the free monoester has only limited stability and is rapidly degraded by hydrolytic displacement of the OMe group from phosphorus (or less plausibly dealkylation of the OMe group by nucleophilic attack at carbon). When the acidification and extraction were carried out in an NMR tube and the spectrum of the $CDCl_3$ layer recorded as quickly as possible some degradation of the monoester was already apparent [δ_P 29.0 ⟶ 30.2; δ_H 3.79 (d, J_{PH} 12) ⟶ 3.50 (s) (MeOH)].

To obtain a salt that is soluble in aprotic solvents and avoid the need to isolate the free monoester the demethylation of the



diester **10** (X = OMe) was carried out by heating with Bu^tNH_2 (large excess; 40 h at 55 °C). Dilution of the reaction mixture with ether gave a precipitate of the pure anhydrous *tert*-butylammonium salt of the monoester (**10**; X = O^- $^+NH_3Bu^t$), and this reacted readily with $SOCl_2$ in $CDCl_3$. The product, however, was not the expected phosphonochloridate **10** (X = Cl). Instead, the benzyl group was removed as benzyl chloride [δ_H 4.59 (2H, s); δ_C 46.7; M^+ (GC–MS) 126 and 128] leaving what appears to be the oxooxazaphospholane oxide **13** (δ_P 31.1; ν_{max}/cm^{-1} 1775; M^+ 193). In accord with the proposed cyclic structure **13**, addition of MeOH to the reaction mixture produced the (known) aminophosphonate $MeNHCMe_2P(O)(OMe)_2$ corresponding to nucleophilic attack at phosphorus and ring opening followed by loss of CO_2. We have found no other examples of this ring system but it is not difficult to rationalise its formation. Nucleophilic participation by the carbamate group will convert the chloridate **10** (X = Cl) or more probably its precursor **10** (X = OSOCl) into the cyclic intermediate **12** (Scheme 2) but because of the methyl groups



Scheme 2

on C_α it is the benzylic carbon atom that is attacked by chloride ion rather than the sterically hindered P=O centre. A similar combination of intramolecular nucleophilic attack and debenzylation by chloride ion is well known for acyl chlorides derived from *N*-benzyloxycarbonyl-protected α-amino carboxylic acids.[19] The formation of **13** can therefore be seen as powerful support for nucleophilic participation by the carbamate group, although it is unfortunate that the very efficiency of participation has thwarted our attempts to prepare the phosphonochloridate we hoped to study.

Conclusion

N-Benzyloxycarbonyl derivatives of α-aminophosphonochloridates are highly reactive because of intramolecular catalysis by the carbamate group. The high reactivity is not diminished when the acidic hydrogen of the carbamate NH moiety is replaced by an alkyl group, as would be the case for intramolecular electrophilic catalysis (activation of the P=O group by hydrogen bonding), or when alkylation of the α carbon atom impedes intermolecular nucleophilic attack at the P=O centre (steric hindrance). It thus seems that intramolecular nucleophilic catalysis is responsible for the high reactivity, and that the external nucleophile reacts rapidly with the resulting cyclic species rather than with the phosphonochloridate itself. An understanding of the reactivity of these α-aminophosphonic acid derivatives will, we think, enhance their value in the synthesis of biologically significant phosphonates.

Experimental

Mps were determined using a Kofler hot-stage apparatus and are uncorrected. ^1H NMR spectra were recorded on Bruker ARX 250, DPX 300 or DRX 400 spectrometers (Me_4Si internal standard; coupling constants *J* given in Hz) at room temperature or (where indicated) 0 °C (to reduce rate of interconversion of rotamers); ^{31}P NMR spectra (^1H decoupled) were also recorded on these instruments at 101, 122 or 162 MHz (positive chemical shifts downfield from 85% H_3PO_4).

Mass spectra were obtained in EI (70 eV) or FAB (NBA matrix) mode using a Kratos Concept spectrometer or in ES mode using a Micromass Quattro spectrometer. DMF and isopropanol were repeatedly dried over 3 Å molecular sieves

(pellets and powder respectively). $SOCl_2$ was distilled. Ether refers to diethyl ether.

N-(Benzyloxycarbonyl)aminomethylphosphonates

Following the published procedure[10] dimethyl phthalimidomethylphosphonate (4.25 g, 15.9 mmol) was treated with hydrazine hydrate (0.88 g, 17.5 mmol) in MeOH (25 ml) at ~26 °C. After 49 h reaction was still incomplete (^{31}P NMR spectroscopy) but the yield of dimethyl aminomethylphosphonate (~70%) was not improved by extending the reaction time because of degradation of the product (δ_P 31.8 ⟶ 15.4 ppm; probably demethylation). After isolation the crude amino compound was immediately dissolved in $CHCl_3$ (45 ml), stirred vigorously with $NaHCO_3$ (1.8 g, 21.5 mmol) in water (18 ml) and cooled; benzyl chloroformate (3.5 g, 20.8 mmol) was added and stirring was continued for 25 min at room temperature. The organic layer was separated, washed with water (2 × 10 ml), dried (Na_2SO_4) and concentrated to give dimethyl *N*-(benzyloxycarbonyl)aminomethylphosphonate **4** (X = OMe) (an oil; >95% by ^{31}P NMR spectroscopy) (see below). Purification was not attempted at this point.

The crude dimethyl ester was hydrolysed by stirring with 2.0 mol dm^{-3} aqueous NaOH (20 ml) at 20–25 °C for 40 min. The resulting solution was washed with $CHCl_3$, acidified by careful addition of H_2SO_4, and extracted repeatedly with $CHCl_3$ (6 × 10–15 ml). The combined extracts were dried (Na_2SO_4) and concentrated. Crystallisation from toluene afforded *methyl hydrogen N-(benzyloxycarbonyl)aminomethylphosphonate* **4** (X = OH) (2.50 g, 61% overall); mp 103–104 °C (lit.,[10] 106–106.5 °C); δ_P ($CDCl_3$) 25.2 (rotamer 24.4); δ_H ($CDCl_3$, 250 MHz) 9.9 (br s, OH), 7.33 (5H), 5.35 (br, NH), 5.11 (2H, s), 3.71 (3H, d, J_{PH} 11, OMe) and 3.615 (2H, d, J_{PH} 12, CH_2P); ν_{max}(Nujol)/cm^{-1} 3340 (NH), 3000–2000 (OH) and 1720 (C=O).

Pure *dimethyl N-(benzyloxycarbonyl)aminomethylphosphonate* **4** (X = OMe) was obtained by treating **4** (X = OH) with diazomethane: (EI) *m*/*z* 273 (M$^+$, 15%), 166 (M$^+$ − $PhCH_2O$, 25) and 91 (100); δ_P ($CDCl_3$) 25.2; δ_H ($CDCl_3$, 250 MHz) 7.4–7.25 (5H), 5.90 (1H, br t, NH), 5.10 (2H, s), 3.72 (6H, d, J_{PH} 11, OMe) and 3.62 (2H, dd, J_{PH} 11, J_{HH} 6, CH_2P); ν_{max} (film)/cm^{-1} 1725 (C=O).

N-(Benzyloxycarbonyl)-1-amino-1-methylethylphosphonates

Ammonia was passed through stirred and ice-cooled acetone (11.6 g, 0.20 mol) and dimethyl phosphite (16.5 g, 0.15 mol) was added dropwise over 45 min.[11] While continuing to pass ammonia the mixture was allowed to warm to room temperature; it was then heated at 50 °C (bath temp.) for 10 min. Volatile material was evaporated *in vacuo* and the residue was extracted with ether to give a mixture (18.65 g) of dimethyl 1-amino-1-methylethylphosphonate, δ_P ($CDCl_3$) 34.1, δ_H ($CDCl_3$, 250 MHz) 3.80 (d, J_{PH} 12, OMe) and 1.30 (d, J_{PH} 15, Me_2C) and the corresponding 1-hydroxy compound, δ_P 29.7, δ_H 3.81 (d, J_{PH} 12) and 1.43 (d, J_{PH} 14), in a ratio ~ 2 : 1. A portion of the mixture (10.3 g) was dissolved in $CHCl_3$ (80 ml) and was stirred vigorously with $NaHCO_3$ (5.05 g, 60 mmol) in water (45 ml); benzyl chloroformate (8.2 g, 48 mmol) was added and stirring was continued for 1.3 h. The organic layer was collected, washed with water (2 × 50 ml) and dried (Na_2SO_4). The solvent was evaporated and the resulting solid was washed with ether and crystallised from a small volume of $CHCl_3$ diluted with ether and light petroleum (bp 60–80 °C) to give *dimethyl N-(benzyloxycarbonyl)-1-amino-1-methylethylphosphonate* **5** (X = OMe) (9.7 g, 39% overall); mp 113.5–114 °C; (EI) *m*/*z* 301 (M$^+$, 2%), 192 [M$^+$ − P(O)(OMe)$_2$, 30], 148 (25) and 91 (100); δ_P ($CDCl_3$) 29.9; δ_H ($CDCl_3$, 300 MHz) 7.45–7.35 (5H), 5.06 (2H, s), 5.05 (1H, s, NH), 3.79 (6H, d, J_{PH} 10.5, OMe) and 1.605 (6H, d, J_{PH} 16.5, Me_2C); ν_{max} ($CDCl_3$)/cm^{-1} 3420 (NH), 1735 (C=O) and 1260 (P=O). Found: C, 51.8; H, 6.6; N, 4.7%; M$^+$, 301.1080. $C_{13}H_{20}NO_5P$ requires: C, 51.8; H, 6.7; N, 4.65%; M, 301.1079.

A solution of the diester **5** (X = OMe) (602 mg, 2.0 mmol) in acetone (4 ml) containing NaI (1.50 g, 10.0 mmol) was maintained at 55 °C for 18 h. Volatile material was evaporated *in vacuo* and the residue was dissolved in water (10 ml). The solution was washed with $CHCl_3$ (2 ml) and acidified with 12 mol dm^{-3} HCl (0.33 ml) and the product was extracted into $CHCl_3$ (30 ml; 4 × 10 ml). The extract was dried (Na_2SO_4) and concentrated; crystallisation from $CHCl_3$ diluted with ether and light petroleum (bp 60–80 °C) afforded *methyl hydrogen N-(benzyloxycarbonyl)-1-amino-1-methylethylphosphonate* **5** (X = OH) (528 mg, 91%); mp 112–113.5 °C; (EI) *m*/*z* 287 (M$^+$, 3%), 192 [M$^+$ − P(O)(OH)OMe, 30], 148 (25) and 91 (100); δ_P ($CDCl_3$) 29.7; δ_H ($CDCl_3$, 300 MHz) 12.01 (1H, s, OH), 7.33 (5H), 5.42 (1H, s, NH), 5.05 (2H, s), 3.73 (3H, d, J_{PH} 11, OMe) and 1.575 (6H, d, J_{PH} 15.5, Me_2C); ν_{max} (Nujol)/cm^{-1} 3335 (NH), 3000–2000 (OH) and 1730 (C=O). Found: C, 50.3; H, 6.4; N, 4.9%; M$^+$, 287.0923. $C_{12}H_{18}NO_5P$ requires: C, 50.2; H, 6.3; N, 4.9%; M, 287.0923.

N-(Benzyloxycarbonyl)-*N*-methylaminomethylphosphonates

A solution of dimethyl *N*-(benzyloxycarbonyl)aminomethylphosphonate **4** (X = OMe) (519 mg, 1.9 mmol) in DMF (4 ml) was stirred and cooled in ice while NaH (64 mg, 2.65 mmol) was added. The mixture was allowed to warm to room temperature and after 15 min was again cooled while MeI (480 mg, 3.4 mmol) was added. After a further 15 min at room temperature MeOH (100 µl) was added (to destroy any remaining NaH) and volatile material was removed *in vacuo* at ~ 40 °C giving a mixture (70 : 30 by ^{31}P NMR in MeOH) of the required dimethyl phosphonate **6** (X = OMe) and the corresponding monomethyl compound (Na salt) contaminated with much DMF. The dimethyl phosphonate was hydrolysed by stirring the mixture with 1.5 mol dm^{-3} NaOH (4 ml) for 2 h. More water (3 ml) was added and the solution was washed repeatedly with $CHCl_3$ to remove all DMF and give an aqueous solution of pure sodium methyl *N*-(benzyloxycarbonyl)-*N*-methylaminomethylphosphonate **6** (X = ONa), δ_P (H_2O) 19.85 and 19.5 (ratio ~1 : 1; rotamers). Acidification with 2 mol dm^{-3} HCl and repeated extraction with CH_2Cl_2 afforded *methyl hydrogen N-(benzyloxycarbonyl)-N-methylaminomethylphosphonate* **6** (X = OH) as an oil, (EI) *m*/*z* 273 (M$^+$, 10%), 256 (20) and 91 (100); δ_P ($CDCl_3$) 25.9 and 25.5 (ratio 55 : 45; rotamers); δ_H ($CDCl_3$, 400 MHz at 0 °C) 8.0 (br s, OH + H_2O), 7.4–7.25 (5H), 5.14 (2H, s), 3.77 (major rotamer) and 3.73 (total 2H; both d, J_{PH} 10.5, CH_2P), 3.75 (major) and 3.645 (total 3H; both d, J_{PH} 11, OMe) and 3.06 and 3.05 (major) (total 3H; both s, NMe); ν_{max} ($CDCl_3$)/cm^{-1} 1700 (C=O), 1220 (P=O) and 1065. Found: M$^+$, 273.0766; $C_{11}H_{16}NO_5P$ requires M, 273.0766. This compound is much more stable than **10** (X = OH) but was used with a minimum of delay.

A pure sample of *dimethyl N-(benzyloxycarbonyl)-N-methylaminomethylphosphonate* **6** (X = OMe) was obtained by treating **6** (X = OH) with diazomethane: (EI) *m*/*z* 287 (M$^+$, 20%), 152 (M$^+$ − BnOCO, 30) and 91 (100); δ_P ($CDCl_3$) 25.1 and 24.5 (ratio ~3 : 2; rotamers); δ_H ($CDCl_3$, 300 MHz) 7.45–7.3 (5H), 5.15 (2H, s), 3.76 (6H, d, J_{PH} 10.5, OMe), 3.73 and 3.67 (major rotamer) (total 2H; both d, J_{PH} 11, CH_2P) and 3.05 (3H, s, NMe); ν_{max} ($CDCl_3$)/cm^{-1} 1705 (C=O), 1220 (P=O), 1065 and 1045. Found: M$^+$, 287.0923; $C_{12}H_{18}NO_5P$ requires M, 287.0923.

N-(Benzyloxycarbonyl)-*N*-methyl-1-amino-1-methylethylphosphonates

NaH (96 mg, 4 mmol) was added to a stirred solution of dimethyl *N*-(benzyloxycarbonyl)-1-amino-1-methylethylphosphonate **5** (X = OMe) (602 mg, 2.0 mmol) in DMF. Much solid precipitated. After 20 min the mixture was cooled in ice and MeI (850 mg, 6.0 mmol) was added; stirring was continued for

30 min at room temperature, then NH_4Cl (160 mg, 3 mmol) was added to destroy any remaining NaH. The mixture was diluted with CH_2Cl_2 (40 ml) and filtered through Celite, and volatile material was removed as completely as possible *in vacuo* (some DMF remained). Without further purification the dimethyl phosphonate was demethylated by heating with NaI (1.45 g, 9.8 mmol) in acetone (4 ml) at 55 °C for 15 h (^{31}P NMR: δ_P 30.7 ⟶ 25.0), giving a solution of sodium methyl *N*-(benzyloxycarbonyl)-*N*-methyl-1-amino-1-methylethylphosphonate **10** (X = ONa), (−ES) *m/z* 300.

In an unsuccessful attempt to obtain the hydrogen methyl phosphonate, acetone was evaporated off and the residue was dissolved in water. Acidification (HCl) and extraction with $CHCl_3$ gave an oil but this contained no P–OMe group (^{1}H NMR); crystallisation from ether afforded *N-(benzyloxycarbonyl)-N-methyl-1-amino-1-methylethylphosphonic acid* **11** (420 mg, 74%); δ_P ($CDCl_3$) 30.4; δ_H ($CDCl_3$, 250 MHz) 10.83 (2H, s), 7.4–7.3 (5H), 5.14 (2H, s), 3.06 (3H, s, NMe) and 1.66 (6H, d, J_{PH} 15). [A similar experiment was conducted in an NMR tube using a D_2O solution of **10** (X = ONa), CF_3CO_2H for acidification, and $CDCl_3$ for extraction; the NMR spectrum of the $CDCl_3$ extract showed demethylation (hydrolysis) to be appreciable within just a few minutes: δ_P 29.0 ⟶ 30.2; δ_H 3.79 (d, J_{PH} 12) ⟶ 3.50 (s) (MeOH)].

The phosphonic acid **11** was treated with diazomethane to give pure *dimethyl N-(benzyloxycarbonyl)-N-methyl-1-amino-1-methylethylphosphonate* **10** (X = OMe) (an oil), (EI) *m/z* 315 (M^+, 0.2%), 206 [$M^+ - P(O)(OMe)_2$, 40], 162 (35) and 91 (100); (FAB) *m/z* 316 (M + H^+, 95%), 206 (100) and 162 (55); δ_P ($CDCl_3$) 29.9; δ_H ($CDCl_3$, 300 MHz) 7.5–7.3 (5H), 5.12 (2H, s), 3.73 (6H, d, J_{PH} 10, OMe), 3.075 (3H, s, NMe) and 1.69 (6H, d, J_{PH} 15.5, Me_2C); ν_{max} (film)/cm^{-1} 1715 (C=O), 1255 (P=O), 1060 and 1040. Found: M^+, 315.1236. $C_{14}H_{22}NO_5P$ requires M, 315.1236.

A solution of **10** (X = OMe) (490 mg, 1.55 mmol) in *tert*-butylamine (3 ml) was heated in a sealed vessel at 55 °C for 40 h (δ_P 30.3 ⟶ 20.2). Most of the *tert*-butylamine was evaporated off and ether (10 ml) was added; on refrigeration *tert-butylammonium methyl N-(benzyloxycarbonyl)-N-methyl-1-amino-1-methylethylphosphonate* **10** (X = O^- $^+NH_3Bu^t$) (448 mg, 78%) precipitated: mp 110–112 °C (sealed tube; softens at variable lower *T*); (FAB) *m/z* 375 (M + H^+, 100%) and 302 (75); (−ES) *m/z* 300; δ_P ($CDCl_3$) 21.1; δ_H ($CDCl_3$, 300 MHz) 8.4 (3H, br s, $^+H_3NBu^t$), 7.45–7.25 (5H), 5.06 (2H, s), 3.55 (3H, d, J_{PH} 9.5, OMe), 3.14 (3H, s, NMe), 1.62 (6H, d, J_{PH} 13.5, Me_2C) and 1.33 (9H, s, Bu^t); ν_{max} (Nujol)/cm^{-1} 3500–2500 (NH), 1705 (C=O), 1465 and 1170. Found: C, 54.6; H, 8.4; N, 7.4%; M + H^+ (FAB), 375.2048. $C_{17}H_{31}N_2O_5P$ requires: C, 54.5; H, 8.35; N, 7.5%; M + H, 375.2049.

Phosphonochloridates

Thionyl chloride (45 mg, 0.38 mmol) was added to a suspension of methyl hydrogen *N*-(benzyloxycarbonyl)aminomethylphosphonate **4** (X = OH) (69 mg, 0.27 mmol) in ether (0.5 ml). The mixture was maintained at 25–30 °C with frequent agitation for 40 min during which time the initial solid passed into solution and a new solid began to precipitate. After cooling at 0–5 °C for 30 min the supernatant was removed using a fine-tipped pipette (minimum exposure to moisture) and the solid was pumped at 0.2 mmHg to give *methyl N-(benzyloxycarbonyl)aminomethylphosphonochloridate* **4** (X = Cl) (69 mg, 93%); δ_P ($CDCl_3$) 37.3 (rotamer 36.8); δ_H ($CDCl_3$, 300 MHz) 7.34 (5H), 5.72 (1H, br t, J_{HH} ~ 6, NH), 5.13 (2H, s) (rotamer 5.08), 3.96 (2H, dd, J_{PH} ~ J_{HH} ~ 6, NHCH_2P) and 3.86 (3H, d, J_{PH} 13, OMe); ν_{max} ($CDCl_3$)/cm^{-1} 3430 and 3280 br (NH), 1735 (C=O), 1245 (P=O) and 1055. This material is hydrolysed very readily; the mp (73–75 °C) is probably unreliable and a MS could not be obtained; the ^{31}P NMR spectrum contained evidence of some hydrolysis (δ_P 17.3 and 17.2; pyrophosphonate diastereoisomers).

The same method, but with a mixture of ether and light petroleum (bp 40–60 °C) as solvent, was used to convert **5** (X = OH) into *methyl N-(benzyloxycarbonyl)-1-amino-1-methylethylphosphonochloridate* **5** (X = Cl) (88%); mp 71–72 °C; δ_P ($CDCl_3$) 47.6 (trace 23.2 and 22.8, pyrophosphonate diastereoisomers); δ_H ($CDCl_3$, 300 MHz) 7.4–7.25 (5H), 5.39 (1H, s, NH), 5.06 (2H, s), 3.85 (3H, d, J_{PH} 12.5, OMe) and 1.69 (6H, d, J_{PH} 19, Me_2C); ν_{max} ($CDCl_3$)/cm^{-1} 3420 (NH), 1735 (C=O), 1260 (P=O) and 1050.

The *N*-methyl compound **6** (X = OH) was treated with $SOCl_2$ (1.5 equiv.) in $CDCl_3$ to give *methyl N-(benzyloxycarbonyl)-N-methylaminomethylphosphonochloridate* **6** (X = Cl) which was used without isolation: δ_P ($CDCl_3$) 36.5 and 36.3 (ratio ~1 : 1, rotamers); δ_H ($CDCl_3$, 400 MHz at 0 °C) 7.45–7.3 (5H), 5.18 and 5.165 (total 2H; both s), 4.13 (ABP; δ_A 4.25, δ_B 4.01, J_{AB} 16, J_{PH} 6.5) and 4.08 (ABP; δ_A 4.19, δ_B 3.97, J_{AB} 16, J_{PH} 6.5) (total 2H; CH_2P), 3.93 and 3.85 (total 3H; both d, J_{PH} 13, OMe) and 3.13 and 3.11 (total 3H; both s, NMe); ν_{max} ($CDCl_3$)/cm^{-1} 1710 (C=O), 1235 (P=O) and 1050.

Reaction of salt 10 (X = O^- $^+NH_3Bu^t$) with thionyl chloride

Thionyl chloride (excess) was added to a solution of the salt **10** (X = O^- $^+NH_3Bu^t$) in $CDCl_3$ giving a product δ_P 31.1; ν_{max}/cm^{-1} 1775 (C=O), 1280, 1235 and 1055; (EI) *m/z* 193 (M^+, 45%), 178 (M^+ − Me, 100) and 136 (20) (Found: M^+, 193.0504. $C_6H_{12}NO_4P$ requires M, 193.0504); the ^{1}H and ^{13}C NMR spectra of the reaction mixture were consistent with the oxooxazaphospholane oxide **13**, δ_H (300 MHz) 3.96 (3H, d, J_{PH} 11, OMe), 2.85 (3H, s, NMe), 1.51 (3H, d, J_{PH} 16.5, CMe) and 1.45 (3H, d, J_{PH} 15.5, CMe), δ_C (75 MHz) 149.1 (d, J_{PC} 11, CO), 56.1 (d, J_{PC} 130, C_a), 55.1 (d, J_{PC} 7, OMe), 26.5 (d, J_{PC} 11, NMe), 21.8 (s) and 21.55 (d, J_{PC} 3.5), accompanied by $PhCH_2Cl$, δ_H 7.45–7.3 (5H) and 4.59 (2H, s); δ_C 137.9 (s), 129.1 (s), 129.0 (s), 128.8 (s) and 46.7 (s) and $Bu^tNH_3^+Cl^-$ (partially insoluble), δ_H 8.3 (br s) and 1.47 (s), δ_C 53.4 (s) and 28.1 (s). The presence of $PhCH_2Cl$ was confirmed by GC–MS, (EI) *m/z* 128 and 126 (M^+, 80%) and 91 (100).

Addition of MeOH to the reaction mixture converted the product into $MeNHCMe_2P(O)(OMe)_2$ (initially as the hydrochloride) which was isolated and characterised by NMR spectroscopy, δ_P ($CDCl_3$) 33.3; δ_H ($CDCl_3$, 300 MHz) 3.80 (6H, d, J_{PH} 10), 2.46 (3H, s), 1.88 br (s, NH) and 1.32 (6H, d, J_{PH} 15.5), and by conversion into the picrate, mp 146–148 °C (lit.,[14] 147–148 °C).

Phosphonochloridate reactions with isopropanol

Isopropanol (30 mg, 0.5 mmol) was added to a solution of the phosphonochloridate **4** (X = Cl) (69 mg, 0.25 mmol) in $CDCl_3$ (0.6 ml). Reaction was complete (δ_P 37.4 ⟶ 23.5) inside 10 min. Volatile material was removed *in vacuo* to give *isopropyl methyl N-(benzyloxycarbonyl)aminomethylphosphonate* **4** (X = OPr^i); (EI) *m/z* 301 (M^+, 15%), 259 ($M^+ - C_3H_6$, 30), 152 (50), 108 (35) and 91 (100); (FAB) *m/z* 302 (M + H^+, 100%) and 260 (M + $H^+ - C_3H_6$, 30); δ_P ($CDCl_3$) 22.8 (rotamer 22.2); δ_H ($CDCl_3$, 300 MHz) 7.4–7.25 (5H), 5.64 br (1H, NH), 5.11 (2H, s), 4.715 (1H, d × septet, J_{PH} ~ J_{HH} ~ 6, OC*H*Me_2), 3.71 (3H, d, J_{PH} 11, OMe), 3.61 (2H, dd, J_{PH} 11.5, J_{HH} 6, NHCH_2P) and 1.31 and 1.275 (both 3H, d, J_{HH} 6; OCH*Me*$_2$); ν_{max} (film)/cm^{-1} 3235 (NH), 1725 (C=O), 1275, 1235 (P=O) and 1010. Found: M + H^+ (FAB) 302.1157. $C_{13}H_{20}NO_5P$ requires: M + H, 302.1157.

The corresponding reaction of **5** (X = Cl) with isopropanol (δ_P 47.5 ⟶ 27.8; complete inside 10 min) gave *isopropyl methyl N-(benzyloxycarbonyl)-1-amino-1-methylethylphosphonate* **5** (X = OPr^i); (FAB) *m/z* 330 (M + H^+, 100%) and 288 (M + $H^+ - C_3H_6$, 20); δ_P ($CDCl_3$) 27.8; δ_H ($CDCl_3$, 300 MHz) 7.4–7.25 (5H), 5.21 (1H, d, J_{PH} 5.5, NH), 5.06 (2H, s), 4.73 (1H, d × septet, J_{PH} ~ J_{HH} ~ 6, OC*H*Me_2), 3.75 (3H, d, J_{PH} 10.5, OMe), 1.60 and 1.59 (both 3H, d, J_{PH} 16; Me_2C) and 1.33 and

1.315 (both 3H, d, J_{HH} 6; OCHMe_2); ν_{max} (film)/cm^{-1} 3240 (NH), 1735 (C=O), 1260, 1240 (P=O) and 1005. Found: M + H$^+$ (FAB) 330.1471. $C_{15}H_{24}NO_5P$ requires: M + H, 330.1470.

The corresponding reaction of **6** (X = Cl) with isopropanol [δ_P 36.45 and 36.25 (rotamers) ⟶ 23.05 and 22.45; complete inside 10 min] gave *isopropyl methyl N-(benzyloxycarbonyl)-N-methylaminomethylphosphonate* **6** (X = OPr^i); (FAB) *m/z* 316 (M + H$^+$, 100%); δ_P ($CDCl_3$) 22.7 and 22.15 (ratio 57 : 43, rotamers); δ_H ($CDCl_3$, 400 MHz at 0 °C) 7.45–7.3 (5H), 5.15 (2H, s), 4.82–4.68 [1H, m; with ^{31}P decoupling, 4.765 (major rotamer) and 4.73 (both septet, J_{HH} 7, OC*H*Me$_2$)], 3.85–3.61 (2H, m, CH_2P), 3.75 (major) and 3.63 (total 3H; both d, J_{PH} 10.5, OMe), 3.07 (major) and 3.065 (total 3H, both s; NMe) and 1.34 and 1.305 (major), 1.315 and 1.27 (total 6H; all d, J_{HH} 6.5; OCHMe_2); ν_{max} (film)/cm^{-1} 1710 (C=O), 1250, 1220 (P=O) and 1005. Found: M + H$^+$ (FAB) 316.1314. $C_{14}H_{22}NO_5P$ requires: M + H, 316.1314.

References

1 (*a*) P. Kafarski and B. Lejczak, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1991, **63**, 193; J. Huang and R. Chen, *Heteroat. Chem.*, 2000, **11**, 480; (*b*) V. P. Kukhar and H. R. Hudson, *Aminophosphonic and Aminophosphinic Acids*, Wiley, Chichester, 2000; . See also ref. 2 for a summary and leading references.

2 R. Hirschmann, K. M. Yager, C. M. Taylor, J. Witherington, P. A. Sprengeler, B. W. Phillips, W. Moore and A. B. Smith, III, *J. Am. Chem. Soc.*, 1997, **119**, 8177.

3 J. Rahil and R. F. Pratt, *J. Chem. Soc., Perkin Trans. 2*, 1991, 947.

4 R. Kluger and J. L. W. Chan, *J. Am. Chem. Soc.*, 1976, **98**, 4913.

5 R. Kluger, J. F. Chow and J. J. Croke, *J. Am. Chem. Soc.*, 1984, **106**, 4017.

6 L. A. Reiter and B. P. Jones, *J. Org. Chem.*, 1997, **62**, 2808.

7 R. A. Naylor and A. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1908.

8 A. B. Smith, III, L. Ducry, R. M. Corbett and R. Hirschmann, *Org. Lett.*, 2000, **2**, 3887.

9 P. M. Cullis and M. J. P. Harger, *Chem. Commun.*, 2002, 458.

10 N. A. Jacobsen and P. A. Bartlett, *J. Am. Chem. Soc.*, 1981, **103**, 654.

11 K. A. Petrov, V. A. Chauzov, I. V. Pastukhova and N. N. Bogdanov, *J. Gen. Chem. USSR (Engl. Transl.)*, 1976, **46**, 1226.

12 M. J. P. Harger and A. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1681.

13 R. S. Edmundson, in *Chemistry of Organophosphorus Compounds*, ed. F. R. Hartley, Wiley, Chichester, 1996, vol. 4, ch. 6. For some particularly relevant examples (P–Cl bond cleavage) see: A. A. Neimysheva and I. L. Knunyants, *J. Gen. Chem. USSR (Engl. Transl.)*, 1968, 38, 575; I. L. Knunyants and A. A. Neimysheva, *J. Gen. Chem. USSR (Engl. Transl.)*, 1972, **42**, 2415.

14 M. J. P. Harger and A. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1989, 563.

15 B. Capon and S. P. McManus, *Neighbouring Group Participation*, Plenum, New York, 1976, vol. 1, ch. 2; E. L. Eliel and S. H. Wilen, *Stereochemistry of Carbon Compounds*, Wiley, New York, 1994, pp. 682–684.

16 I. V. Blagoeva, D. T. Tashev and A. J. Kirby, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1157.

17 R. F. Brown and N. M. van Gulick, *J. Org. Chem.*, 1956, **21**, 1046.

18 E. L. Eliel and D. E. Knox, *J. Am. Chem. Soc.*, 1985, **107**, 2946.

19 M. Bodanszky, *Principles of Peptide Synthesis*, Springer-Verlag, Berlin, 1984, pp. 10–11.