An efficient synthesis of *N*-phosphinoylmethylamino acids and some of their derivatives

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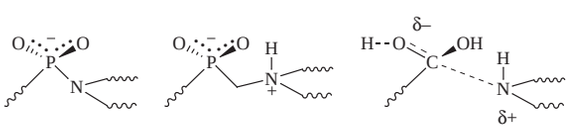
***N*-Phosphinoylmethylamino acid derivatives 11–18 are obtained in high yield on *N*-bromomethylation of hexafluoroacetone protected amino acids 1–5 and subsequent Michaelis–Arbusov reaction. The carboxy activated species 11–18 react with a wide range of nucleophiles to give the unprotected *N*-phosphinoylmethylamino acids 19–22, amides 23–25, peptides 26–28, azapeptide 29 and the hydroxamic acid 30, respectively. The reaction sequence is suitable for generating libraries of *N*-phosphinoylmethylamino acid derivatives, which represent phosphonoamidate isosteres.**

Introduction

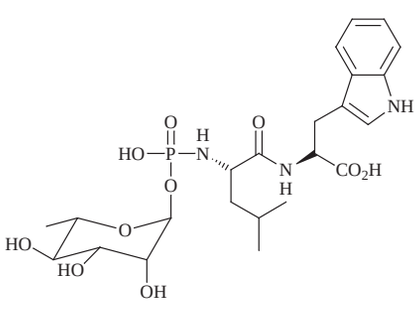
N-Phosphorylated peptides are naturally occurring species of current interest. 'Phosphoramidon' isolated from *Actinomycetes* and related structures are powerful inhibitors of the Zn metalloprotease thermolysin.[1] Nucleoside phosphonoamidates possess antitumor[2] and antiviral potential, including herpes and HIV activity.[3]

However, the phosphorus–nitrogen bond is relatively sensitive to hydrolysis. To overcome this drawback, *N*-phosphinoylmethylamino acid derivatives have been introduced. The insertion of a methylene spacer between phosphorus and nitrogen produces the non-hydrolyzable moiety N–CH_2–P, which is likely a zwitterion near physiological pH (Scheme 1).

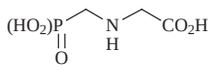


Scheme 1

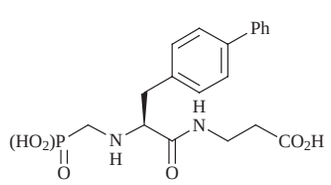
This construction could be representative of a late transition state/early product formation for amide bond cleavage reactions.[4] This class of amino acids has been used for the development of orally active antihypertensive drugs like CGS 24592.[5]



Phosphoramidon



Glyphosate



CGS 24592

N-Phosphonomethylglycine 'Glyphosate' inhibits the shikimic acid pathway in plants and has become one of the most widely used and trusted herbicides in the world today.[6]

Results and discussion

We now report on a preparatively simple stereoconservative route to *N*-phosphinoylmethylamino acids and some of their derivatives starting from hexafluoroacetone protected α-amino acids **1**–**5**.[7] In a three component condensation, compounds **1**–**5**, paraformaldehyde and phosphorus tribromide react to give *N*-bromomethyl-1,3-oxazolidinones **6**–**9**. The progress of the reaction can be monitored conveniently by ^{19}F NMR spectroscopy. Compounds **6**–**9** were purified by fractional distillation under reduced pressure and can be stored in a refrigerator without decomposition over weeks.

In the case of sterically hindered amino acids, like aminoisobutyric acid, *N*-bromomethylation is slow and decomposition was observed at elevated temperatures. Therefore, for α-alkylated amino acids it is advisable to use the *N*-chloromethyl compounds[8] for further derivatization reactions.

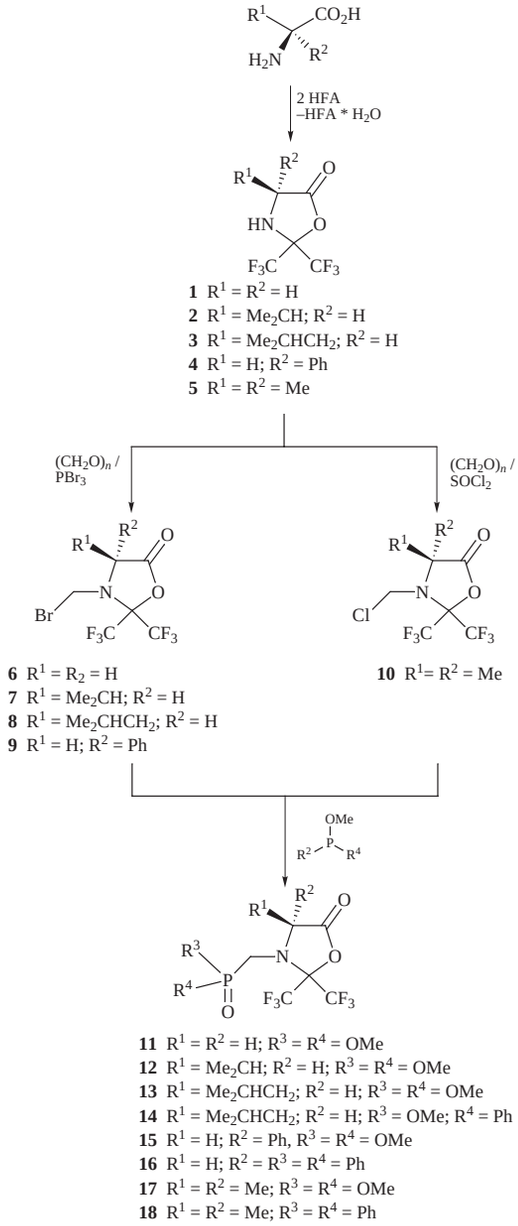
With phosphites, phosphinites and methoxyphosphines, compounds **6**–**10** undergo Michaelis–Arbusov reaction (Scheme 2).[9] While the *N*-bromomethyl compounds **6**–**9** react exothermally within minutes to give **11**–**16** respectively, the transformation of the *N*-chloromethyl compound **10** into derivatives **17** and **18** needs several days. On reaction of compound **8** with dimethoxyphenylphosphine, stereoisomers of **14** were formed in a 1:1 ratio. Compounds **11**–**18** were purified by flash chromatography or recrystallization.

Since compounds **11**–**18** have activated carboxylic groups they can be readily deprotected to give **19**–**22**, or transformed into amides (**23**–**25**), peptides (**26**–**28**), azapeptides (**29**) and hydroxamic acids (**30**), respectively (Scheme 3). The nucleophilic ring opening is coupled with the deblocking of the amino group. Demethylation was also observed when a methoxy group was present at the phosphorus atom of these compounds. No racemization was observed on reaction with chiral nucleophiles (^1H NMR analysis). The reaction sequence is suitable for generating libraries of *N*-phosphinoylmethylamino acid derivatives, which represent phosponoamidate isosteres.

Experimental

General

Solvents were purified and dried prior to use. Reagents were used as purchased. Thin layer chromatography (TLC) was performed on aluminium plates coated with Merck silica gel $60F_{254}$. Compounds were visualized by spraying with ceric ammonium nitrate in 9 M H_2SO_4 followed by heating up to 100 °C. Column



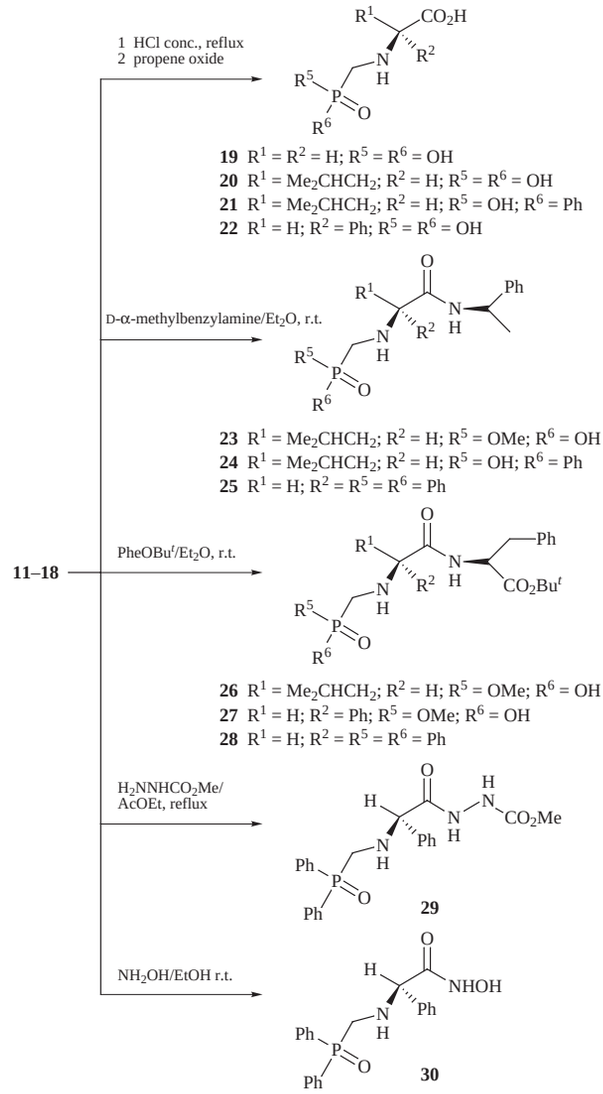
Scheme 2

chromatography was carried out on silica gel (32–63 μm, ICN Biomedicals).

Melting points (uncorrected) were determined with a Boetius heating table. Optical rotation indices $[\alpha]_D$ were measured with a Polartronic polarimeter (Schmidt & Haensch) in a 5 cm cell. For C, H, N analyses a CHNO-Rapid-Elemental-Analyser (Hereaus) was used. Mass spectra were recorded on a VG 12-250 (Masslab) electron ionization spectrometer (EI = 70 eV) or by VG ZAB-HSQ FAB spectrometer. IR spectra were obtained by using a FTIR spectrometer (Genesis ATI Mattson/Unicum). ^{1}H (200.041 or 300.075 MHz), ^{13}C (50.305 or 75.462 MHz), ^{31}P (80.978 or 121.470 MHz) and ^{19}F NMR (188.205 or 282.380 MHz) spectra were recorded with a Varian Gemini 200 or a Varian Gemini 300 spectrometer. TMS was used as reference standard for ^{1}H and ^{13}C NMR spectra (internal), H_3PO_4 (85%) for ^{31}P NMR, and TFA for ^{19}F NMR spectra (external). *J* Values are given in Hz.

Preparation of 2,2-bis(trifluoromethyl)-3-bromomethyl-1,3-oxazolidin-5-ones 6–9

A mixture of a 2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one[7] (20 mmol) and paraformaldehyde (1.2 g, 40 mmol) was stirred in phosphorus tribromide (4 cm^3) at room temperature until gas



Scheme 3

evolution ceased. Then the mixture was heated up to 60 °C with stirring to complete the reaction (1–5 h, ^{19}F NMR analysis). The reaction mixture was distilled *in vacuo*.

2,2-Bis(trifluoromethyl)-3-bromomethyl-1,3-oxazolidin-5-one 6. A strong exothermic reaction took place. The reaction mixture obtained consisted of two phases. The upper pulp-like phase was dissolved in dichloromethane (25 cm^3), filtered, evaporated and distilled *in vacuo*. (**1**, 4.46 g gave **6**, 2.69 g, 41%); bp 82–83 °C (11 mmHg); mp ~r.t.; ν_{max}(film)/cm^{-1} 1852s (CO); δ_H(200.04 MHz, $CDCl_3$) 3.95 (2H, s, CH_2N), 5.36 (2H, s, CH_2Br); δ_C(50.3 MHz, $CDCl_3$) 46.7 (CH_2N), 51.0 (CH_2Br), 88.6 [m, $C(CF_3)_2$], 120.6 (q, *J* 290, CF_3), 165.3 (CO); δ_F(188.2 MHz, $CDCl_3$) 1.89 (s, $2 \times CF_3$); *m*/*z* 236 [(M − Br)$^+$, 100] (Found: C, 22.92; H, 1.45; N, 4.81. Calc. for $C_6H_4BrF_6NO_2$: C, 22.81; H, 1.28; N, 4.43%).

(4*S*)-2,2-Bis(trifluoromethyl)-3-bromomethyl-4-(prop-2-yl)-1,3-oxazolidin-5-one 7. (**2**, 5.3 g gave **7**, 3.94 g, 55%); bp 96–98 °C (12 mmHg); $[\alpha]_D^{25}$ +7.6 (*c* 1.6, $CHCl_3$); ν_{max}(film)/cm^{-1} 1841s (CO); δ_H(200.04 MHz, $CDCl_3$) 0.99 (3H, d, *J* 7.0, CH_3), 1.25 (3H, d, *J* 7.0, CH_3), 2.26 (1H, m, CH), 3.97 (1H, d, *J* 3.2, CHN), 5.21 (1H, d, *J* 10.8, CH_2Br), 5.46 (1H, d, *J* 10.8, CH_2Br); δ_C(50.3 MHz, $CDCl_3$) 15.7 (CH_3), 17.2 (CH_3), 27.4 (CH), 50.1 (CH_2Br), 61.0 (CHN), 87.3 [m, $C(CF_3)_2$], 120.5 (q, *J* 287, CF_3), 121.0 (q, *J* 287, CF_3), 166.8 CO; δ_F(188.2 MHz, $CDCl_3$) 0.9 (3F, q, *J* 8.8, CF_3), 4.52 (3F, q, *J* 8.8, CF_3); *m*/*z* 278 [(M − Br)$^+$, 100] (Found: C, 30.07; H, 3.33; N, 4.16. Calc. for $C_9H_{10}BrF_6NO_2$: C, 30.19; H, 2.81; N, 3.91%).

(4*S*)-2,2-Bis(trifluoromethyl)-3-bromomethyl-4-(2-methylpropyl)-1,3-oxazolidin-5-one 8. (**3**, 5.58 g gave **8**, 5.98 g, 80%); bp 48 °C (0.16 mmHg); $[\alpha]_D^{25}$ +9.9 (*c* 1.45, $CHCl_3$); ν_{max}(film)/cm^{-1} 1846s (CO); δ_H(200.04 MHz, $CDCl_3$) 0.99 (3H, d, *J* 6.6, CH_3), 1.02 (3H, d, *J* 6.6, CH_3), 1.72 (2H, m, CH_2), 1.97 (1H, m, CH), 4.07 (1H, m, CHN), 5.25 (1H, d, *J* 10.8, CH_2Br), 5.46 (1H, d, *J* 10.8, CH_2Br); δ_C(50.3 MHz, $CDCl_3$) 22.3 (CH_3), 23.7 (CH_3), 24.3 (CH), 38.3 (CH_2), 50.3 (CH_2Br), 54.6 (CHN), 88.0 [m, $C(CF_3)_2$], 120.5 (q, *J* 288, CF_3), 121.0 (q, *J* 287, CF_3), 168.6 (CO); δ_F(188.2 MHz, $CDCl_3$) −0.15 (3F, m, CF_3), 4.60 (3F, m, CF_3); *m*/*z* 292 [$(M - Br)^+$, 36] (Found: C, 32.62; H, 3.57; N, 3.98. Calc. for $C_{10}H_{12}BrF_6NO_2$: C, 32.28; H, 3.25; N, 3.76%).

(4*R*)-2,2-Bis(trifluoromethyl)-3-bromomethyl-4-phenyl-1,3-oxazolidin-5-one 9. A strong exothermal reaction takes place. (**4**, 5.98 g gave **9**, 6.9 g, 88%); bp 60 °C (0.02 mmHg); $[\alpha]_D^{25}$ −10.0 (*c* 2.1, $CHCl_3$); ν_{max}(film)/cm^{-1} 1852s (CO); δ_H(200.04 MHz, $CDCl_3$) 4.91 (1H, d, *J* 10.6, CH_2Br), 5.04 (1H, s, CHN), 5.42 (1H, d, *J* 10.6, CH_2Br), 7.43 (5H, H_{Ph}); δ_C(50.3 MHz, $CDCl_3$) 50.0 (CH_2Br), 61.3 (CHN), 87.8 [m, $C(CF_3)_2$], 120.6 (q, *J* 288, CF_3), 120.9 (q, *J* 292, CF_3), 127.6–131.1 (C_{Ph}, CH_{Ph}), 166.8 (CO); δ_F(188.2 MHz, $CDCl_3$) 0.61 (3F, m, CF_3), 4.50 (3F, m, CF_3); *m*/*z* 312 [$(M - Br)^+$, 100] (Found: C, 36.87; H, 2.25; N, 3.77. Calc. for $C_{12}H_8BrF_6NO_2$: C, 36.76; H, 2.06; N, 3.57%).

Preparation of 2,2-bis(trifluoromethyl)-3-chloromethyl-4,4-dimethyl-1,3-oxazolidin-5-one 10

A mixture of 2,2-bis(trifluoromethyl)-4,4-dimethyl-1,3-oxazolidin-5-one **5** (5.02 g, 20 mmol) and paraformaldehyde (1.2 g, 40 mmol) was stirred in thionyl chloride (5 cm^3) until gas evolution ceased (5 h). The progress of the reaction was monitored by ^{19}F NMR spectroscopy. After removal of the excess of thionyl chloride, the residue was distilled *in vacuo.* (5.9 g, 19.7 mmol, 98%); bp 85–88 °C (17 mmHg); mp 30–32 °C; ν_{max}(KBr disk)/cm^{-1} 1840s (CO); δ_H(200.04 MHz, $CDCl_3$) 1.60 (6H, s, 2 × CH_3), 5.36 (2H, s, CH_2Br); δ_C(50.3 MHz, $CDCl_3$) 24.9 (2 × CH_3), 56.9 (CH_2Cl), 60.0 (CN), 88.6 [m, $C(CF_3)_2$], 120.7 (q, *J* 291, 2 × CF_3), 172.1 (CO); δ_F(188.2 MHz, $CDCl_3$) 1.10 (s, 2 × CF_3); *m*/*z* 263 [$(M - Cl)^+$, 100] (Found: C, 32.13; H, 2.80; N, 4.60. Calc. for $C_8H_8ClF_6NO_2$: C, 32.07; H, 2.69; N, 4.68%).

Preparation of 2,2-bis(trifluoromethyl)-3-phosphinoylmethyl-1,3-oxazolidin-5-ones 11–16

To a solution of a 1,3-oxazolidin-5-one **6**–**9** (5 mmol) in dichloromethane (2 cm^3) the methoxyphosphine (6 mmol) was added dropwise with stirring. An exothermic reaction started immediately. The mixture was stirred to completion (0.5 h). Then the volatile compounds were evaporated. The residue was purified by recrystallization or flash chromatography.

2,2-Bis(trifluoromethyl)-3-(dimethoxyphosphinoyl)methyl-1,3-oxazolidin-5-one 11. (Trimethoxyphosphine 0.74 g, and **6** 1.58 g gave **11**, 1.14 g, 66%); mp 61–62 °C (*n*-hexane); ν_{max}(KBr disc)/cm^{-1} 1852s (CO); δ_H(200.04 MHz, $CDCl_3$) 3.34 (2H, d, *J* 12.8, CH_2P), 3.81 (6H, d, *J* 11.0, 2 × OCH_3), 3.95 (2H, s, CH_2N); δ_C(50.3 MHz, $CDCl_3$) 43.8 (d, *J* 170, CH_2P), 50.2 (CH_2N), 53.8 (d, *J* 7, 2 × OCH_3), 90.1 [m, $C(CF_3)_2$], 121.4 (q, *J* 291, 2 × CF_3), 166.8 (CO); δ_F(188.2 MHz, $CDCl_3$) 1.65 (s, 2 × CF_3); δ_P(80.98 MHz, $CDCl_3$) 22.24 (s); *m*/*z* 345 [$(M)^+$, 11] (Found: C, 27.57; H, 2.70; N, 3.89. Calc. for $C_8H_{10}F_6NO_5P$: C, 27.85; H, 2.92; N, 4.06%).

(4*S*)-2,2-Bis(trifluoromethyl)-3-(dimethoxyphosphinoyl)methyl-4-(prop-2-yl)-1,3-oxazolidin-5-one 12. (Trimethoxyphosphine 0.74 g, and **7**, 1.79 g gave **12**, 1.83 g, 95%); R_f 0.33 (EtOAc–light petroleum, 1:1); mp 75–77 °C; $[\alpha]_D^{25}$ +18.0 (*c* 1.0, $CHCl_3$); ν_{max}(KBr disc)/cm^{-1} 1835s (CO); δ_H(200.04 MHz, $CDCl_3$) 0.93 (3H, d, *J* 7.0, CH_3), 1.18 (3H, d, *J* 7.0, CH_3), 2.65 (1H, m, CH), 3.29 (1H, m, CH_2P), 3.58 (1H, m, CH_2P), 3.76 (3H, d, *J* 4.2, OCH_3), 3.81 (4H, m, CHN and OCH_3); δ_C(50.3 MHz, $CDCl_3$) 15.1 (CH_3), 18.1 (CH_3), 28.5 (CH), 42.4 (d, *J* 169, CH_2P), 53.3 (d, *J* 7, OCH_3), 53.6 (d, *J* 7, OCH_3), 65.3 (CHN), 88.9 [m, $C(CF_3)_2$], 120.8 (q, *J* 289, CF_3), 122.3 (q, *J* 294, CF_3), 168.1 (CO); δ_F(188.2 MHz, $CDCl_3$) 0.67 (3F, m, CF_3), 3.79 (3F, m, CF_3); δ_P(80.98 MHz, $CDCl_3$) 23.31 (s); *m*/*z* 387 [M^+, 5] (Found: C, 34.08; H, 4.20; N, 3.74. Calc. for $C_{11}H_{15}F_6NO_5P$: C, 34.21; H, 3.91; N, 3.63%).

(4*S*)-2,2-Bis(trifluoromethyl)-3-(dimethoxyphosphinoyl)-methyl-4-(2-methylpropyl)-1,3-oxazolidin-5-one 13. (Trimethoxyphosphine 0.74 g, and **8**, 1.86 g gave **13**, 1.67 g, 83%); R_f 0.17 (light petroleum–EtOAc, 2:1); oil; $[\alpha]_D^{25}$ +42.9 (*c* 1.3, $CHCl_3$); ν_{max}(film)/cm^{-1} 1837s (CO); δ_H(200.04 MHz, $CDCl_3$) 0.96 (6H, d, *J* 6.6, CH_3), 1.58 (1H, m, CH_2), 1.88 (1H, m, CH_2), 2.09 (1H, m, CH), 3.42 (2H, m, CH_2P), 3.79 (6H, m, 2 × OCH_3), 4.16 (1H, d, *J* 10.8, NCH); δ_C(50.3 MHz, $CDCl_3$) 21.3 (CH_3), 23.8 (CH_3), 24.1 (CH), 37.7 (CH_2), 40.0 (d, *J* 170, CH_2P), 53.4 (m, 2 × OCH_3), 56.4 (NCH), 89.0 [m, $C(CF_3)_2$], 120.9 (q, *J* 292, CF_3), 121.5 (q, *J* 292, CF_3), 169.8 (CO); δ_F(188.2 MHz, $CDCl_3$) 0.99 (3F, q, *J* 7.7, CF_3), 1.77 (3F, q, *J* 7.7, CF_3); δ_P(80.98 MHz, $CDCl_3$) 23.02 (br m); *m*/*z* 401 [M^+, 6] (Found: C, 35.73; H, 4.57; N, 3.20. Calc. for $C_{12}H_{18}F_6NO_5P$: C, 35.92; H, 4.52; N, 3.49%).

2,2-Bis(trifluoromethyl)-3-(methoxyphenylphosphinoyl)-methyl-4-(2-methylpropyl)-1,3-oxazolidin-5-one 14. (Dimethoxyphenylphosphine 1.02 g and **8**, 1.86 g gave **14**, 2.1 g, 94%, mixture of diastereomers in 1:1 ratio); oil; R_f 0.47 diastereomer 1, 0.41 diastereomer 2 (light petroleum–$CHCl_3$–EtOAc, 2:1:1); ν_{max}(film)/cm^{-1} 1835s (CO); δ_H(200.04 MHz, $CDCl_3$) diastereomer 1: 0.98 (3H, d, *J* 6.0, CH_3), 1.02 (3H, d, *J* 6.0, CH_3), 1.57 (1H, m, CH_2), 2.10 (2H, m, CH, CH_2), 3.57 (2H, m, CH_2P), 3.68 (3H, d, *J* 11.0, OCH_3), 4.30 (1H, m, CHN), 7.51–7.80 (5H, H_{Ph}); diastereomer 2: 0.97 (3H, d, *J* 6.0, CH_3), 0.99 (3H, d, *J* 6.0, CH_3), 1.61 (1H, m, CH_2), 2.04 (2H, m, CH, CH_2), 3.54 (2H, m, CH_2P), 3.70 (3H, d, *J* 11.0, OCH_3), 4.28 (1H, m, CHN), 7.52–7.77 (5H, H_{Ph}); δ_C(50.3 MHz, $CDCl_3$) diastereomer 1: 21.2 (CH_3), 23.8 (CH_3), 24.2 (CH), 37.1 (CH_2), 43.6 (d, *J* 120, CH_2P), 51.9 (d, *J* 7, OCH_3), 56.2 (NCH), 89.9 [m, $C(CF_3)_2$], 121.0 (q, *J* 290, 2 × CF_3), 126.9–133.9 (C_{Ph}, CH_{Ph}), 169.9 (CO); diastereomer 2: 21.3 (CH_3), 23.8 (CH_3), 24.2 (CH), 37.8 (CH_2), 44.6 (d, *J* 117, CH_2P), 52.0 (d, *J* 6, OCH_3), 56.8 (NCH), 89.9 [m, $C(CF_3)_2$], 121.3 (q, *J* 290, 2 × CF_3), 126.8–133.9 (C_{Ph}, CH_{Ph}), 169.9 (CO); δ_F(188.2 MHz, $CDCl_3$) diastereomer 1: 0.07 (3F, q, *J* 8.0, CF_3), 2.59 (3F, q, *J* 8.0, CF_3); diastereomer 2: 0.99 (3F, q, *J* 8.1, CF_3), 2.07 (3F, q, *J* 8.1, CF_3); δ_P(80.98 MHz, $CDCl_3$) diastereomer 1: 36.89 (br m); diastereomer 2: 38.58 (br m); *m*/*z* 447 [M^+, 8] (Found: C, 45.53; H, 4.42; N, 3.26. Calc. for $C_{17}H_{20}F_6NO_4P$: C, 45.65; H, 4.51; N, 3.13%).

(4*R*)-2,2-Bis(trifluoromethyl)-3-(dimethoxyphosphinoyl)-methyl-4-phenyl-1,3-oxazolidin-5-one 15. (Trimethoxyphosphine 0.74 g, and **9**, 1.96 g gave **15**, 1.9 g, 90%); R_f 0.31 (EtOAc–$CHCl_3$–light petroleum, 2:1:1); mp 82–84 °C; $[\alpha]_D^{25}$ −106.0 (*c* 1.0, $CHCl_3$); ν_{max}(KBr disc)/cm^{-1} 1843s (CO); δ_H(200 MHz, $CDCl_3$) 3.41 (2H, m, CH_2P), 3.45 (3H, d, *J* 11.0, OCH_3), 3.53 (3H, d, *J* 11.0, OCH_3), 5.11 (1H, d, *J* 2.8, CHN), 7.41 (5H, H_{Ph}); δ_C(50.3 MHz, $CDCl_3$) 41.0 (d, *J* 165, CH_2P), 53.0 (m, 2 × OCH_3), 63.6 (CHN), 89.8 [m, $C(CF_3)_2$], 121.0 (q, *J* 288, CF_3), 121.9 (q, *J* 292, CF_3), 128.8–133.7 (C_{Ph}, CH_{Ph}), 168.2 (CO); δ_F(188.2 MHz, $CDCl_3$) 1.35 (3F, q, *J* 8.0, CF_3), 2.46 (3F, q, *J* 8.0, CF_3); δ_P(80.98 MHz, $CDCl_3$) 22.64 (m); *m*/*z* 421 [M^+, 18] (Found: C, 39.92; H, 3.37; N, 3.40. Calc. for $C_{14}H_{14}F_6NO_5P$: C, 39.92; H, 3.35; N, 3.32%).

(4*R*)-2,2-Bis(trifluoromethyl)-3-(diphenylphosphinoyl)-methyl-4-phenyl-1,3-oxazolidin-5-one 16. (Diphenylmethoxyphosphine, 1.3 g and **9**, 1.96 g gave **16**, 2.44 g, 95%); mp 168–170 °C (*n*-hexane); $[\alpha]_D^{25}$ −113.0 (*c* 1.0, $CHCl_3$); ν_{max}(KBr disc)/cm^{-1} 1840s (CO); δ_H(200.04 MHz, $CDCl_3$) 3.87 (1H, m, CH_2P), 4.02 (1H, m, CH_2P), 5.25 (1H, s, CHN), 7.06–7.66 (15H, H_{Ph}); δ_C(50.3 MHz, $CDCl_3$) 47.5 (d, *J* 77, CH_2P), 63.8 (CHN), 90.0 [m, $C(CF_3)_2$], 121.2 (q, *J* 288, CF_3), 121.7 (q, *J* 294, CF_3), 129.3–134.1 (C_{Ph}, CH_{Ph}), 168.5 (CO); δ_F(188.2 MHz, $CDCl_3$) 1.64 (3F, q, *J* 8.1, CF_3), 3.70 (3F, q, *J* 8.1, CF_3); δ_P(80.98 MHz, $CDCl_3$) 25.35 (br s); *m*/*z* 513 [M^+, 10] (Found: C, 56.01; H, 3.67; N, 2.72. Calc. for $C_{24}H_{18}F_6NO_3P$: C, 56.13; H, 3.53; N, 2.73%).

Preparation of 2,2-bis(trifluoromethyl)-4,4-dimethyl-3-phosphinoylmethyl-1,3-oxazolidin-5-ones 17, 18

To a solution of **10** (1.5 g, 5 mmol) in dichloromethane (2 cm^3) the methoxyphosphine (6 mmol) was added. The mixture was stirred to completion (3 h for **17**, 5 d for **18**). The progress of the reaction was monitored by ^{19}F NMR spectroscopy. Then the volatile compounds were evaporated. The residue was purified by recrystallization or flash chromatography.

2,2-Bis(trifluoromethyl)-4,4-dimethyl-3-(dimethoxyphosphinoyl)methyl-1,3-oxazolidin-5-one 17. (Trimethoxyphosphine, 0.74 g gave **17**, 1.55 g, 83%); oil; R_f 0.2 (EtOAc–light petroleum, 1:1); ν_{max}(film)/cm^{-1} 1836s (CO); δ_H(200.04 MHz, $CDCl_3$) 1.61 (6H, s, 2 × CH_3), 3.40 (2H, d, *J* 12.4, CH_2P), 3.81 (6H, d, *J* 11.0, 2 × OCH_3); δ_C(50.3 MHz, $CDCl_3$) 24.0 (2 × CH_3), 39.0 (d, *J* 171, CH_2P), 53.4 (d, *J* 7, 2 × OCH_3), 60.0 (CN), 89.6 [m, $C(CF_3)_2$], 121.0 (q, *J* 290, 2 × CF_3), 173.5 (CO); δ_F(188.2 MHz, $CDCl_3$) 1.38 (s, 2 × CF_3); δ_P(80.98 MHz, $CDCl_3$) 23.30 (br m); *m*/*z* 373 [M^+, 11] (Found: C, 32.07; H, 4.03; N, 3.55. Calc. for $C_{10}H_{14}F_6NO_5P$: C, 32.19; H, 3.78; N, 3.75%).

2,2-Bis(trifluoromethyl)-4,4-dimethyl-3-(diphenylphosphinoyl)-methyl-1,3-oxazolidin-5-one 18. (Diphenylmethoxyphosphine, 1.3 g gave **18**, 1.44 g, 62%); R_f 0.3 (light petroleum–EtOAc, 3:2); mp 116–117 °C (*n*-hexane); ν_{max}(KBr disc)/cm^{-1} 1832s (CO); δ_H(200.04 MHz, $CDCl_3$) 1.67 (6H, s, 2 × CH_3), 3.87 (2H, d, *J* 8.2, CH_2P), 7.45–7.84 (10H, H_{Ph}); δ_C(50.3 MHz, $CDCl_3$) 24.3 (2 × CH_3), 45.9 (d, *J* 81, CH_2P), 60.7 (CN), 89.6 [m, $C(CF_3)_2$], 121.1 (q, *J* 291, 2 × CF_3), 129.4–133.1 (C_{Ph}, CH_{Ph}), 174.0 (CO); δ_F(188.2 MHz, $CDCl_3$) 2.18 (s, 2 × CF_3); δ_P(80.98 MHz, $CDCl_3$) 26.73 (br m); *m*/*z* 265 [M^+, 21] (Found: C, 51.56; H, 3.93; N, 2.96. Calc. for $C_{20}H_{18}F_6NO_3P$: C, 51.62; H, 3.90; N, 3.01%).

Ring opening reactions of compounds 11–18: preparation of *N*-phosphinoylmethylamino acids 19–22

Oxazolidinones **11**–**18** (2 mmol) were refluxed in conc. HCl (5 cm^3). After complete hydrolysis (^{19}F NMR analysis) the reaction mixture was evaporated to dryness *in vacuo*. The residue was dissolved in ethanol and propene oxide (1 cm^3) was added. After stirring of the precipitate with diethyl ether a crystalline product was obtained. Filtration and drying *in vacuo* gave pure compounds **19**–**22**.

***N*-Phosphonomethylglycine ('Glyphosate') 19.** (**11**, 0.69 g gave **19**, 0.32 g, 95%); mp 215–217 °C (lit.,[10] mp 220–225 °C). Spectral data were consistent with literature data.[10]

***N*-Phosphonomethyl-L-leucine 20.** (**13**, 0.8 g gave **20**, 0.34 g, 76%); mp 201 °C; $[\alpha]_D^{25}$ +13.5 (*c* 2.0, 3 M HCl); δ_H(200.04 MHz, D_2O) 0.72 (6H, d, *J* 5.6, CH_3), 1.56 (3H, m, CH, CH_2), 2.99 (2H, d, *J* 12.6, CH_2P), 3.93 (1H, m, NCH); δ_C(50.3 MHz, D_2O) 21.2 (CH_3), 22.2 (CH_3), 24.6 (CH), 38.3 (CH_2), 42.8 (d, *J* 139, CH_2P), 60.2 (d, *J* 7, NCH), 172.2 (CO_2H); δ_P(80.98 MHz, D_2O) 9.21 (t, *J* 13.4) (Found: C, 36.62; H, 7.15; N, 5.99. Calc. for $C_7H_{16}NO_5P{\cdot}\frac{1}{4}H_2O$: C, 36.61; H, 7.13; N, 6.10%).

***N*-Hydroxyphenylphosphinoylmethyl-L-leucine 21.** (**14**, 0.89 g gave **21**, 0.38 g, 67%); mp 237–238 °C; $[\alpha]_D^{25}$ +19.0 (*c* 2.0, DMSO + 5% TFA); δ_H(200.04 MHz, [$^2H_6$]DMSO + 5% TFA) 0.85 (6H, d, *J* 5.2, 2 × CH_3), 1.66 (3H, m, CH, CH_2), 3.44 (2H, m, CH_2P), 3.93 (1H, m, NCH), 7.52–7.84 (5H, H_{Ph}); δ_C(50.3 MHz, [$^2H_6$]DMSO + 5% TFA) 22.0 (CH_3), 23.5 (CH_3), 25.1 (CH), 38.4 (CH_2), 44.5 (d, *J* 98, CH_2P), 59.5 (d, *J* 7, NCH), 129.4–134.7 (C_{Ph}, CH_{Ph}), 171.3 (CO_2H); δ_P(80.98 MHz, [$^2H_6$]DMSO + 5% TFA) 9.21 (br m) (Found: C, 53.79; H, 6.98; N, 4.75. Calc. for $C_{13}H_{20}NO_4P{\cdot}\frac{1}{4}H_2O$: C, 53.88; H, 7.30; N, 4.83%).

***N*-Phosphonomethyl-D-phenylglycine 22.** (**15**, 0.84 g gave **22**, 0.37 g, 76%); mp 217–219 °C (decomp.); $[\alpha]_D^{25}$ −128.5 (*c* 2.0, 3 M HCl); δ_H(200.04 MHz, D_2O) 2.93 (2H, m, CH_2P), 4.96 (1H, s, NCH), 7.32–7.40 (5H, H_{Ph}); δ_C(50.3 MHz, D_2O) 42.5 (d, *J* 138, CH_2P), 65.0 (d, *J* 7, NCH), 129.3–148.2 (C_{Ph}, CH_{Ph}), 170.8 (CO_2H); δ_P(80.98 MHz, D_2O) 9.45 (t, *J* 13.4) (Found: C, 43.98; H, 5.19; N, 5.49. Calc. for $C_9H_{12}NO_5P$: C, 44.10; H, 4.93; N, 5.71%).

Preparation of N^{α}-(phosphinoyl)methylamino acid amides and peptides 23–28

Oxazolidinones **13**–**16**, **18** (2 mmol) and the corresponding amine or amino acid ester (4 mmol) were dissolved in diethyl ether (2 cm^3) and stirred at room temperature. After completion of the reaction (^{19}F NMR analysis) the precipitate was collected and washed with diethyl ether (15 cm^3) to give **23**–**28** analytically pure.

***N*$^{\alpha}$-(Hydroxymethoxyphosphinoyl)methyl-L-leucyl-D-α-methylbenzylamide 23.** (D-α-Methylbenzylamine, 0.49 g and **13**, 0.8 g gave **23**, 0.32 g, 46%); mp 225–227 °C; $[\alpha]_D^{25}$ +10.0 (*c* 1.0, $CHCl_3$); δ_H(200.04 MHz, $CDCl_3$) 0.84 (3H, d, *J* 6.5, CH_3), 0.91 (3H, d, *J* 6.5, CH_3), 1.48 (3H, d, *J* 7.0, CH_3), 1.73 (1H, m, CH_2), 1.95 (2H, m, CH, CH_2), 2.77 (2H, m, CH_2P), 3.42 (3H, d, *J* 10.8, OCH_3), 3.53 (1H, m, NCH), 5.11 (1H, m, NCH), 7.26 (5H, H_{Ph}), 9.17 (1H, d, *J* 8.2, NH), 10.34 (1H, br s, NH_2^+), 10.85 (1H, br s, NH_2^+); δ_C(50.3 MHz, $CDCl_3$) 21.9 (CH_3), 22.2 (CH_3), 24.0 (CH_3), 25.5 (CH), 38.1 (CH_2), 42.6 (d, *J* 145, CH_2P), 49.3 (NCH), 52.3 (d, *J* 6, OCH_3), 64.4 (d, *J* 12, NCH), 126.6–144.1 (C_{Ph}, CH_{Ph}), 167.1 (CONH); δ_P(80.98 MHz, $CDCl_3$) 7.0 (br m); *m*/*z* (FAB) 343 [(M + H)$^+$, 100], 365 [(M + Na)$^+$, 100] (Found: C, 56.09; H, 7.92; N, 8.25. Calc. for $C_{16}H_{27}N_2O_5P$: C, 56.13; H, 7.95; N, 8.18%).

***N*$^{\alpha}$-(Hydroxyphenylphosphinoyl)methyl-L-leucyl-D-α-methylbenzylamide 24.** (D-α-Methylbenzylamine, 0.49 g and **14**, 0.89 g gave **24**, 0.50 g, 64%); mp 261–263 °C (decomp.); $[\alpha]_D^{25}$ +66.0 (*c* 2.0, DMSO + 5% TFA); δ_H(200.04 MHz, [$^2H_6$]DMSO + 5% TFA) 0.85 (6H, m, 2 × CH_3), 1.33 (3H, d, *J* 7.0, CH_3), 1.60 (3H, m, CH, CH_2), 3.08 (2H, m, CH_2P), 3.89 (1H, m, NCH), 4.91 (1H, m, CHN), 7.20–7.30 (5H, H_{Ph}), 7.44–7.70 (5H, H_{Ph}), 9.05 (1H, d, *J* 7.6, NH); δ_C(50.3 MHz, [$^2H_6$]DMSO + 5% TFA) 22.3 (2 × CH_3), 23.6 (CH_3), 24.9 (CH), 44.5 (d, *J* 100, CH_2P), 49.5 (CHN), 60.8 (m, CHN), 107.3–144.5 (C_{Ph}, CH_{Ph}), 167.4 (CONH); δ_P(80.98 MHz, [$^2H_6$]DMSO + 5% TFA) 24.71 (br m); *m*/*z* (FAB) 411.2 [(M + Na)$^+$, 25], 799.4 [(2M + Na)$^+$, 12] (Found: C, 64.58; H, 7.39; N, 7.01. Calc. for $C_{21}H_{29}N_2O_3P$: C, 64.93; H, 7.53; N, 7.21%).

***N*$^{\alpha}$-(Diphenylphosphinoyl)methyl-D-phenylglycyl-D-α-methylbenzylamide 25.** (D-α-Methylbenzylamine, 0.49 g and **16**, 1.03 g gave **25**, 0.69 g, 74%); mp 210–212 °C; $[\alpha]_D^{25}$ +11.3 (*c* 2.0, $CHCl_3$); δ_H(200.04 MHz, $CDCl_3$) 1.37 (3H, d, *J* 7.0, CH_3), 2.24 (1H, br s, NH), 3.40 (2H, m, CH_2P), 4.24 (1H, s, NCH), 5.07 (1H, m, NCH), 7.23–7.72 (20H, H_{Ph}); δ_C(50.3 MHz, $CDCl_3$) 21.8 (CH_3), 48.2 (d, *J* 81, CH_2P), 48.6 (CHN), 69.4 (d, *J* 14, NCH), 126.8–147.9 (C_{Ph}, CH_{Ph}), 170.8 (CONH); δ_P(80.98 MHz, $CDCl_3$) 29.37 (br s); *m*/*z* (FAB) 469 [(M + H)$^+$, 48], 937 [(2M)$^+$, 1] (Found: C, 73.82; H, 6.17; N, 5.82. Calc. for $C_{29}H_{29}N_2O_2P{\cdot}\frac{1}{4}H_2O$: C, 73.64; H, 6.23; N, 5.92%).

***tert*-Butyl *N*$^{\alpha}$-(hydroxymethoxyphosphinoyl)methyl-L-leucyl-L-phenylalaninate 26.** (PheOBu^t, 0.89 g and **13**, 0.8 g gave **26**, 0.55 g, 62%); mp 182–184 °C; $[\alpha]_D^{25}$ −19.7 (*c* 2.0, $CHCl_3$); δ_H(300.075 MHz, $CDCl_3$) 0.82 (3H, d, *J* 6.6, CH_3), 0.91 (3H, d, *J* 6.6, CH_3), 1.38 [9H, s, $C(CH_3)_3$], 1.91 (3H, m, CH, CH_2), 2.71 (1H, m, CH_2P), 3.03 (1H, m, CH_2), 3.15 (1H, m, CH_2), 3.27 (1H, m, CH_2P), 3.53 (3H, d, *J* 10.7, OCH_3), 3.66 (1H, m, NCH), 4.60 (1H, m, NCH), 7.22 (5H, H_{Ph}), 9.13 (1H, d, *J* 6.3, NH), 10.30 (1H, br s, NH_2^+), 10.65 (1H, br s, NH_2^+); δ_C(50.3 MHz, $CDCl_3$) 21.7 (CH_3), 24.0 (CH_3), 25.5 (CH), 28.3 [$C(CH_3)_3$], 37.6 (CH_2), 41.4 (d, *J* 144, CH_2P), 52.6 (d, *J* 6, OCH_3), 55.0 (NCH), 64.4 (d, *J* 11, NCH), 82.1 [$C(CH_3)_3$], 127.1–137.8 (C_{Ph}, CH_{Ph}), 168.1 (CO), 171.2 (CO); δ_P(80.98 MHz, $CDCl_3$) 8.67 (br m); *m*/*z* (FAB) 443 [(M + H)$^+$, 20], 465 [(M + Na)$^+$, 100] (Found: C, 56.50; H, 7.72; N, 6.23. Calc. for $C_{21}H_{35}N_2O_6P$: C, 57.00; H, 7.97; N, 6.33%).

***tert*-Butyl *N*$^{\alpha}$-(hydroxymethoxyphosphinoyl)methyl-D-phenylglycyl-L-phenylalaninate 27.** (PheOBu^t, 0.89 g and **15**, 0.84 g gave **27**, 0.4 g, 43%); mp 178–181 °C; $[\alpha]_D^{25}$ −49.0 (*c* 2.0,

CH_3OH); δ_H(300.075 MHz, CD_3OD) 1.43 [9H, s, $C(CH_3)_3$], 2.91 (4H, m, CH_2, CH_2P), 3.58 (3H, d, *J* 10.7, OCH_3), 4.64 (1H, m, NCH), 5.29 (1H, s, NCH), 6.87 (2H, m, H_{Ph}), 7.04 (3H, m, H_{Ph}), 7.41 (5H, s, H_{Ph}); δ_C(50.3 MHz, CD_3OD) 28.2 [$C(CH_3)_3$], 38.2 (CH_2), 52.9 (m, OCH_3), 55.8 (NCH), 64.9 (m, NCH), 83.4 [$C(CH_3)_3$], 127.8–137.7 (C_{Ph}, CH_{Ph}), 168.1 (CO), 171.2 (CO); δ_P(80.98 MHz, CD_3OD) 11.28 (m, br); *m*/*z* (FAB) 485 [$(M + Na)^+$, 100], 926 [$(2M + H)^+$, 63] (Found: C, 59.69; H, 6.65; N, 5.85. Calc. for $C_{23}H_{31}N_2O_6P$: C, 59.73; H, 6.76; N, 6.06%).

Preparation of *tert*-butyl N^{α}-(diphenylphosphinoyl)methyl-D-phenylglycyl-L-phenylalaninate 28

A solution of oxazolidinone **16** (1.30 g, 2 mmol) and PheOBu^t (0.89 g, 4 mmol) in diethyl ether (2 cm^3) was stirred at room temperature. After completion of the reaction (^{19}F NMR analysis) the volatile compounds were evaporated. The residue was dissolved in diethyl ether (0.5 cm^3). *n*-Hexane was added until the solution became opaque and the product started to crystallize. Drying *in vacuo* gave analytically pure **28**. (0.92 g, 81%); mp 147–149 °C; $[\alpha]_D^{25}$ +1.0 (*c* 4.0, $CHCl_3$); δ_H(200.04 MHz, $CDCl_3$) 1.39 [9H, s, $C(CH_3)_3$], 2.38 (1H, br s, NH), 2.92 (1H, m, CH_2), 3.11 (1H, m, CH_2), 3.27 (2H, d, *J* 8.0, CH_2P), 4.19 (1H, s, NCH), 4.65 (1H, m, NCH), 6.96–7.72 (20H, H_{Ph}); δ_C(50.3 MHz, $CDCl_3$) 28.35 [$C(CH_3)_3$], 37.9 (CH_2), 47.9 (d, *J* 79, CH_2P), 53.7 (CHN), 69.2 (d, *J* 13, NCH), 82.7 [$C(CH_3)_3$], 127.3–138.5 (C_{Ph}, CH_{Ph}), 170.7 (CO), 171.2 (CO); δ_P(80.98 MHz, $CDCl_3$) 29.75 (br s); *m*/*z* (FAB) 569 [M^+, 79], 591 [$(M + Na)^+$, 25] (Found: C, 70.74; H, 6.42; N, 4.83. Calc. for $C_{34}H_{37}N_2O_4P\cdot\frac{1}{2}H_2O$: C, 70.69; H, 6.63; N, 4.85%).

Preparation of methyl N^{α}-(diphenylphosphinoyl)methyl-D-phenylglycylazaglycinate 29

A solution of **16** (0.26 g, 0.5 mmol) and methyl azaglycinate (0.09 g, 1 mmol) in ethyl acetate (3 cm^3) was refluxed for 3 h. The precipitate was collected and recrystallized (ethanol–water). After drying *in vacuo* **29** was obtained analytically pure. (0.09 g, 40%); mp 173–174 °C; $[\alpha]_D^{25}$ −39.0 (*c* 2.0, CH_3OH); δ_H(300.075 MHz, CD_3OD) 3.60 (2H, m, CH_2P), 3.69 (3H, s, OCH_3), 4.46 (1H, s, NCH), 7.28–7.81 (15H, H_{Ph}); δ_C(75.46 MHz, CD_3OD) 47.2 (d, *J* 83, CH_2P), 53.2 (OCH_3), 67.4 (d, *J* 11, NCH), 128.9–138.7 (C_{Ph}, CH_{Ph}), 159.0 (CO_2Me), 173.7 (CONH); δ_P(121.47 MHz, CD_3OD) 34.12 (br s); *m*/*z* (FAB) 438 [$(M + H)^+$, 53], 460 [$(M + Na)^+$, 20] (Found: C, 61.32; H, 5.48; N, 9.04. Calc. for $C_{23}H_{24}N_3O_4P\cdot\frac{2}{3}H_2O$: C, 61.46; H, 5.67; N, 9.35%).

Preparation of *N*-[N^{α}-(diphenylphosphinoyl)methyl-D-phenylglycyl]hydroxylamine 30

A solution of **16** (0.26 g, 0.5 mmol) in ethanol (3 cm^3) was treated with an aqueous solution of hydroxylamine (0.5 cm^3, 50%). After 10 min the volatile compounds were evaporated. Stirring of the residue with diethyl ether (15 cm^3) gave a crystalline product. Filtration and drying *in vacuo* gave the analytically pure compound **30**. (0.18 g, 95%); mp 173–174 °C; $[\alpha]_D^{25}$ −43.0 (*c* 2.0, CH_3OH); δ_H(200.04 MHz, CD_3OD) 3.50 (2H, m, CH_2P), 4.26 (1H, s, NCH), 7.28–7.80 (15H, H_{Ph}); δ_C(50.3 MHz, CD_3OD) 65.3 (d, *J* 13, NCH), 127.7–138.5 (C_{Ph}, CH_{Ph}), 170.1 (CONH); δ_P(80.98 MHz, CD_3OD) 34.58 (br s); *m*/*z* (FAB) 381 [$(M + H)^+$, 40], 403 [$(M + Na)^+$, 17] (Found: C, 65.56; H, 5.42; N, 7.19. Calc. for $C_{21}H_{21}N_2O_3P\cdot\frac{1}{4}H_2O$: C, 65.53; H, 5.63; N, 7.28%).

Acknowledgements

We gratefully acknowledge financial support by the 'Deutsche Forschungsgemeinschaft', 'Hermann Schlosser Stiftung', 'Fonds der Chemischen Industrie' and Bayer AG/Leverkusen. We thank Hoechst AG, Frankfurt/Main for providing chemicals.

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Paper 8/01052H
Received 5*th February* 1998
Accepted 28*th April* 1998