Amino Acids and Peptides; XLIII[1]. Dehydroamino Acids; XVIII[2]. Synthesis of Dehydroamino Acids and Amino Acids from *N*-Acyl-2-(dialkyloxyphosphinyl)-glycin Esters; II[3]

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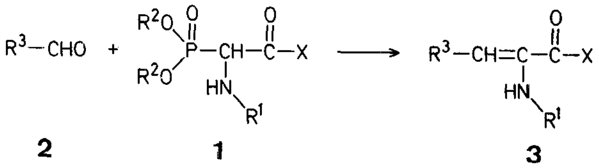
Recently, we reported[2] on a novel straightforward synthesis of dehydroamino acids (**3**) and amino acids, respectively, by condensation of aldehydes (**2**) with *N*-acyl-2-(dialkyloxyphosphinyl)-glycine ester (**1**) (in a Wittig-Horner-type $P=O$ olefination reaction) and subsequent hydrogenation. The dehydroamino compounds can be enantioselectively hydrogenated using a chiral rhodium-phosphine catalyst. (Scheme **A**).



Scheme **A**

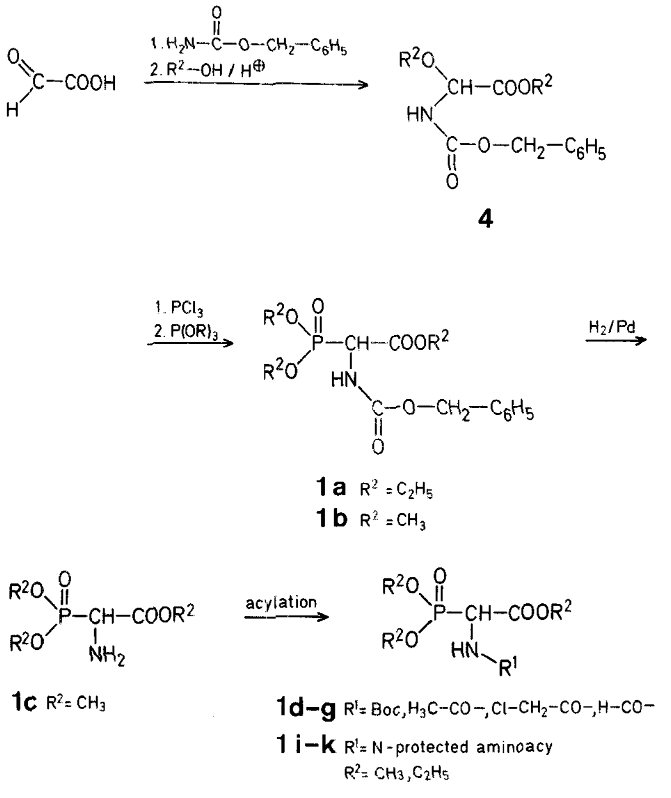
The method outlined in Scheme **A** has the following merits:

- even with complex or sterically hindered aldehydes **2** good yields (in general, 70–90%) of 2-amino-2-alkenoic esters **(3)** are obtained;
- the reaction leads directly to the *N*-protected 2-amino-2-alkenoic esters **(3)** which can be directly transformed into the corresponding saturated *N*-protected or free amino acids;
- the reaction is also applicable to the synthesis of non-conjugated 2-amino-2,n-alkadienoic esters which can be selectively hydrogenated, for example, to δ,ε- and ε,ζ-dehydroamino acid derivatives;
- performance of the condensation of aldehydes **(2)** with di- or tripeptides containing a phosphonoglycinate unit (**1**, $R^1 = \alpha$-acylaminoacyl) leads directly to the formation of di- or tripeptide esters containing a C=C double bond.
- the reaction is performed in either alkaline or neutral medium and is therefore applicable to the synthesis of amino acid derivatives containing acid-sensitive groups.

The utility of our method has been demonstrated in the total syntheses of mucronin B[4] and chlamydocin[1] in which rather complex and acid-sensitive amino acid derivatives were used as key intermediates which could not or only with difficulty be obtained by other methods. Our method has also found application in the synthesis of dehydroamino acids by others[5].

Synthesis of Alkyl N-*Acyl- and* N-*Alkoxycarbonyl-α-dialkoxyphosphinylglycinates* (**1**, Table 1)

N-Benzyloxycarbonyl-2-(diethoxyphosphinyl)-glycine ethyl ester **(1a)** is available in 95% yield[2] from N-benzyloxycarbonyl-2-ethoxyglycine ethyl ester[6] (**4**, R=C_2H_5). This procedure is useful for the synthesis[7] of **1a** on a kilogram scale from crude glyoxylic acid, obtained by evaporation of a technical-grade 50% aqueous solution. However, the corresponding trimethyl esters (**1b**, **d**) offer remarkable advantages in the synthesis of dehydroamino acids and amino acids since hydrolysis of the methyl esters is easier. The synthon **1b** was prepared from crude glyoxylic acid in 52% overall yield. Cleavage of the benzyloxycarbonyl group in **1a** and **1b** and reacylation provides the possibility of introducing other *N*-protecting groups. The synthesis of the *N*-*t*-butoxycarbonyl-, *N*-acetyl-, *N*-chloroacetyl-, and *N*-formyl compounds **(1d–g)** does not involve complications. The alkyl phosphonoglycinates were coupled with acylamino acids to give dipeptides **(1i–l)** which were condensed with aldehydes **(2)** to give dehydrodipeptide esters **(3r–u)** (Schemes **A** and **B**).



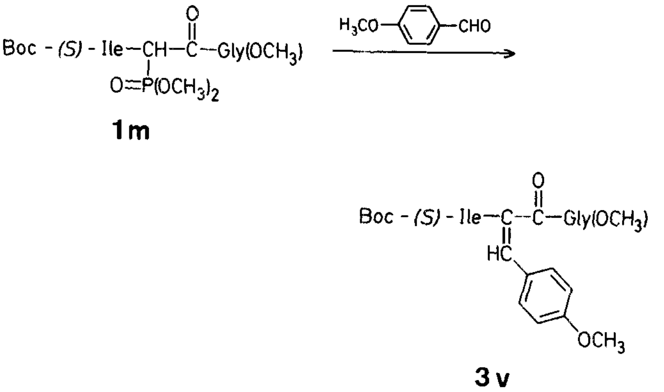
Scheme **B**

Table 1. *N*-Acyl-2-(dialkoxyphosphinyl)-glycine Derivatives **(1)** prepared

1	R^1	R^2	X	Yield [%]	m.p. [°C]	Molecular formula[a]
1b	C_6H_5—CH_2—O—CO—	CH_3	OCH_3	80	80°	$C_{13}H_{18}N_7P$ (331.3)
1d	Boc	CH_3	OCH_3	80	47–48°	$C_{10}H_{20}NO_7P$ (297.2)
1e	H_3C—CO—	CH_3	OCH_3	91	88–89°	$C_7H_{14}NO_6P$ (239.2)
1f	Cl—CH_2—CO—	CH_3	OCH_3	82	105°	$C_7H_{13}ClNO_6P$ (273.6)
1g	H—CO—	CH_3	OCH_3	81	—	$C_6H_{12}NO_6P$ (225.1)
1h	C_6H_5—CH_2—O—CO—	C_2H_5	O—C_4H_9-*t*	80	63°	$C_{18}H_{28}NO_7P$ (401.4)
1i	Boc-(*S*)-Leu	CH_3	OCH_3	85	—	$C_{16}H_{31}N_2O_8P$ (410.4)
1j	Ac-(*S*)-Leu	CH_3	OCH_3	78	—	$C_{13}H_{25}N_2O_7P$ (352.3)
1k	Boc-(*S*)-Isoleu	C_2H_5	OC_2H_5	85	—	$C_{19}H_{37}N_2O_8P$ (452.5)
1l	Boc-(*R*,*S*)-Tryp	C_2H_5	O—C_4H_9-*t*	80	65–72°	$C_{26}H_{40}N_3O_8P$ (553.6)
1m	Boc-(*S*)-Isoleu	CH_3	—NH—CH_2—$COOCH_3$	77	59–60°	$C_{18}H_{34}N_3O_9P$ (467.5)
1n	C_6H_5—CH_2—O—CO—	C_2H_5	OH	90	88–89°	$C_{14}H_{20}NO_7P$ (345.3)
1o	C_6H_5—CH_2—O—CO—	CH_3	OH	84	87–88°	$C_{12}H_{16}NO_7P$ (317.2)

[a] The microanalyses were in satisfactory agreement with the calculated values; C, ±0.24; H, ±0.14; N, ±0.35; P, ±0.21. Exceptions: **1g**, C, +0.58, P, −0.40; **1i**, C, −0.43; P, −0.58. The ^{1}H-N.M.R. spectra of all products **1** were in accord with the assigned structures.

Alkaline hydrolysis of esters **1a** and **1b** affords the stable carboxylic acids **1o** and **1n** in good yields. Acid **1n** has been converted into *t*-butyl *N*-benzyloxycarbonyl-*α*-diethoxyphosphinylglycinate (**1h**) by treatment with *t*-butanol/dicyclohexylcarbodiimide/4-dimethylaminopyridine[8]. The mentioned glycine derivatives are useful synthons for the preparation of *t*-butyl 2-benzyloxycarbonyl-2-alkenoates (*N*-benzyloxycarbonyldehydroamino acid *t*-butyl esters). The phosphonotripeptide ester **1m** was obtained in an analogous manner and was condensed with 4-methoxybenzaldehyde to afford the dehydrotripeptide ester **3v** (Scheme **C**).



Scheme **C**

Scope and Conditions of the Condensation Reaction leading to Compounds 3 (Table 2)

The condensation of phosphonoglycine derivatives **1** with ketones fails, except for mesoxalic esters (to give the aminoethylenetricarboxylic esters **3w, x**). 2-Alkenals also fail to undergo condensation with **1** due to decomposition in the basic reaction medium. Other aldehydes including heterocyclic aldehydes undergo condensation with **1** to afford *N*-acyldehydroamino acid esters (**3**) in high yields. When the reaction is used for the synthesis of the tryptophane and histidine derivatives **3e, f, g** the ring N-atom has to be protected. When *N*-(trifluoroacetyl)-phosphonoglycinates are used in the sequence of Scheme **A** the condensation with aldehydes fails. This is probably caused by the rather high acidity of the NH-proton in these species.

Sodium hydride is used for the condensation of aromatic aldehydes (Method A, examples **3a, b, c, j**). In the reaction of aliphatic aldehydes, the use of lithium diisopropylamide at low temperature (Method B, examples **3k, m, p**) was found to be necessary. The condensation products are obtained as (*E*/*Z*)-mixtures. If desired they can be rearranged by means of alcoholic hydrogen chloride[9] to afford mainly the (*Z*)-isomers. However, the base of choice for the condensation of all types of aldehydes is potassium *t*-butoxide suspended in dichloromethane at −70 °C[10] (Method C, examples **3d, h, i, l, n, o, q**). Using this base, the (*Z*)-isomers are formed predominantly.

In order to estimate the degree of racemisation during the formation of di- and tripeptides, the isoleucine derivative **3r** was synthesized and then hydrolyzed. No trace of *allo*-isoleucine was found indicating that no racemisation had occurred.

Hydrogenation of Dehydroamino Acids and Esters

Catalytic hydrogenation of the *N*-*t*-butoxycarbonyl-, *N*-acetyl-, *N*-chloroacetyl-, and *N*-formyldehydroamino acid esters using palladium on charcoal affords the corresponding saturated *N*-protected amino acid esters in quantitative yield. Hydrogenation of the *N*-(benzyloxycarbonyl)-dehydroamino acid derivatives using palladium on charcoal affords the saturated amino acid esters with simultaneous hydrogenolysis of the protective group. By using rhodium on charcoal as catalyst in the presence of magnesium oxide in benzene as solvent it is possible to hydrogenate selectively the double bond without cleaving the protective group [conditions: (*Z*)-dehydroamino acid (4 mmol), 5% Rh/C (150 mg), MgO (100 mg), benzene (10 ml), 1 at hydrogen; 25 °C].

Non-conjugated 2-amino-2,n-dienoic acid esters (e.g., **3q**) are readily accessible by condensation of phosphonoglycinates **1** with 3- or 4-alkenals. The 2(3)-double bond of these dienoic amino acid derivatives can be selectively hydrogenated using a Wilkinson-type catalyst[11].

The enantioselective hydrogenation of *N*-acyldehydroamino acids using chiral Wilkinson catalysts is known[12]. By combining this method with our condensation method, acid-sensitive optically active amino acid esters can be prepared by condensing the *N*-chloroacetyl-, *N*-acetyl-, or *N*-formylphosphonoglycinates **1e, f, g** with aldehydes (**2**), hydrogenating the resultant dehydroamino acid derivatives **3** using a Wilkinson-type catalyst, and cleaving the *N*-protecting group (chloroacetyl with thioureas[13], formyl with hydrogen peroxide[14]). (*S*)-(5-Benzyloxycarbonyl-2-methoxyphenyl)-alanine, a key intermediate in the total synthesis of mucronin B was thus prepared in an enantiomeric excess (e.e.) of 80%[15].

The hydrogenation of dehydroamino acids having an urethane-type protective group may involve problems. In such cases, $[Rh(1,5\text{-}COD)diPAMP]^{\oplus} BF_4^{\ominus}$[16] often is a suitable catalyst which makes possible the enantioselective hydrogenation without loss of the protective group.

T.L.C. analyses were performed on silica (Merck silica 60 F_{254} sheets); for medium-pressure column chromatography, Merck Lichroprep Si 60 (12–25 μm) was used. Melting points (Kofler) are uncorrected. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. The ^{1}H-N.M.R. spectra were recorded on a Bruker Spectrospin at 80-MHz.

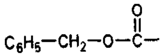
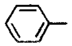
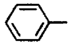
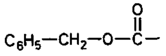
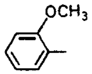
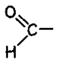
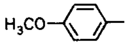
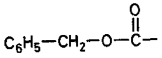
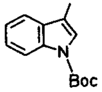
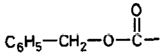
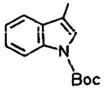
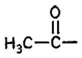
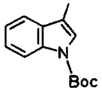
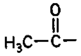
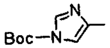
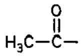
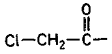
Methyl 2-Benzyloxycarbonylamino-2-(dimethoxyphosphinyl)-acetate (1b):

Methyl 2-benzyloxycarbonylamino-2-methoxyacetate[6] (76 g, 0.3 mol) is dissolved in toluene (300 ml) at 70 °C, phosphorus(III) chloride (32 ml, 0.3 mol) is added, and the mixture is kept at 70 °C for 18 h. Then, trimethyl phosphite (36 ml, 0.3 mol) is added dropwise to the stirred mixture at 70 °C and stirring is continued for a further 2 h at 70 °C. The solvent is distilled off under reduced pressure, the residual product redissolved in ethyl acetate, this solution washed with saturated sodium hydrogen carbonate solution (3 × 100 ml), and dried with sodium sulfate. The solution is concentrated to a volume of 150 ml and hexane is added with vigorous stirring to precipitate product **1b** as fine crystals; yield: 80 g (80%); m.p. 80 °C.

2-Benzyloxycarbonylamino-2-(diethoxyphosphinyl)-acetic Acid (1n) and 2-Benzyloxycarbonylamino-2-(dimethoxyphosphinyl)-acetic Acid (1o):

Compound **1a** or **1b** (0.1 mol) is dissolved in Dioxan (70 ml) and aqueous 2 normal sodium hydroxide (50 ml) is added with stirring. The mixture is stirred until hydrolysis is complete (checked by T.L.C.). The dioxan is removed under reduced pressure and the remaining aqueous solution washed with ethyl acetate (50 ml). The aqueous layer is acidified with 5 normal hydrochloric acid and extracted with ethyl acetate (2 × 100 ml). The combined extracts are dried with sodium sulfate and the solvent is evaporated to give a crystalline residue which is recrystallized from ethyl acetate.

Table 2. 2-Acylamino- and 2-Alkoxycarbonylamino-2-alkenoic Esters (3) prepared

Product	R¹	R³	X	Method	(Z/E) Ratio[a] of Product 3	Yield [%]	m.p. [°C]	Molecular Formula[b] or Lit. m.p.	¹H-N.M.R. (CDCl₃/TMS$_{int}$) δ [ppm]
3a	 $C_6H_5-CH_2-O-\overset{O}{\overset{\|}{C}}-$		OC_2H_5	A	1.1	81	—	$C_{19}H_{19}NO_4$ (325.4)	(*E*): 0.94 (t, 3H); 4.02 (q, 2H); 5.13 (s, 2H); 7.13 (br.s, 1H); 7.20 (s, 5H); 7.31 (s, 5H); 7.56 (s, 1H) (*Z*): 1.26 (t, 3H); 4.24 (q, 2H); 5.06 (s, 2H); 6.53 (br.s, 1H); 7.14-7.61 (m, 11H)
3b	Boc		OC_2H_5	A C	0.8 2.5	74 88	— —	$C_{16}H_{21}NO_4$ (291.35)	(*E*): 0.97 (t, 3H); 1.45 (s, 9H); 4.05 (q, 2H); 6.90 (br.s, 1H); 7.17 (s, 5H); 7.39 (s, 1H) (*Z*): 1.30 (t, 3H); 1.33 (s, 9H); 4.25 (q, 2H); 6.41 (br. s, 1H); 7.13-7.59 (m, 6H)
3c	 $C_6H_5-CH_2-O-\overset{O}{\overset{\|}{C}}-$		OC_2H_5	A	1.8	83	— (*Z*): 85°	$C_{20}H_{21}NO_5$ (355.4)	(*E*): 0.96 (t, 3H); 3.73 (s, 3H); 4.02 (q, 2H); 5.13 (s, 2H); 6.69-7.39 (m, 10H); 7.55 (s, 1H) (*Z*): 1.26 (t, 3H); 3.76 (s, 2H); 4.21 (q, 2H); 5.03 (s, 2H); 6.60-6.95 (m, 3H); 7.05-7.54 (m, 8H)
3d	 $\overset{O}{\underset{H}{C}}-$		OCH_3	C	>20	(*Z*): 79	(*Z*): 136-137°	$C_{12}H_{13}NO_4$ (235.2)	(*Z*): 3.83 (s, 3H); 3.90 (s, 3H); 6.80-7.13 (m, 2H); 7.40-7.75 (m, 3H); 7.80-8.45 (m, 2H)
3e	 $C_6H_5-CH_2-O-\overset{O}{\overset{\|}{C}}-$		OC_2H_5	B	1.5	84	—	$C_{26}H_{28}N_2O_6$ (464.5)	(*E*): 1.13 (t, 3H); 1.63 (s, 9H); 4.18 (q, 2H); 5.13 (s, 2H); 7.05-7.60 (m, 9H); 7.74 (s, 1H); 7.95-8.25 (m, 2H) (*Z*): 1.31 (t, 3H); 1.61 (s, 9H); 4.25 (q, 2H); 5.09 (s, 2H); 6.41 (br. s, 1H); 7.14-7.36 (m, 7H); 7.54-7.71 (m, 2H); 7.88 (s, 1H); 7.96-8.15 (m, 1H)
3e	 $C_6H_5-CH_2-O-\overset{O}{\overset{\|}{C}}-$		OCH_3	C	>10	(*Z*): 74	—	$C_{25}H_{26}N_2O_6$ (450.9)	(*Z*): 1.62 (s, 9H); 3.81 (s, 3H); 5.16 (s, 2H); 6.53 (s (br. s, 1H)); 7.25-7.43 (m, 7H); 7.62-7.80 (m, 2H); 8.00 (s, 1H); 8.05-8.25 (m, 1H)
3f	 $H_3C-\overset{O}{\overset{\|}{C}}-$		OCH_3	C	>50	(*Z*): 86	(*Z*): 91°	$C_{19}H_{22}N_2O_5$ (358.4)	(*Z*): 1.67 (s, 9H); 2.15 (s, 3H); 3.85 (s, 3H); 7.20-7.43 (m, 3H); 7.58-8.23 (m, 4H)
3g	 $H_3C-\overset{O}{\overset{\|}{C}}-$		OCH_3	C	>20	(*Z*): 55	(*Z*): 130°	$C_{14}H_{19}N_3O_5$ (309.3)	(*Z*): 1.62 (s, 9H); 2.15 (s, 3H); 3.83 (s, 3H); 6.42 (s, 1H); 7.39 (s, 1H); 8.07 (s, 1H); 10.00 (br. s, 1H)
3h	 $H_3C-\overset{O}{\overset{\|}{C}}-$		OCH_3	C	>50	(*Z*): 82	97°	$C_{10}H_{11}NO_4$ (209.2)	(*Z*): 2.12 (s, 3H); 3.82 (s, 3H); 6.47-6.73 (m, 2H); 7.12 (s, 1H); 7.52-7.62 (m, 1H); 7.81 (br s, 1H)
3i	 $Cl-CH_2-\overset{O}{\overset{\|}{C}}-$		OCH_3	C	>50	(*Z*): 93	109°	$C_{10}H_{10}ClNO_4$ (243.65)	(*Z*): 3.87 (s, 3H); 4.24 (s, 2H); 6.55-6.65 (m, 1H); 6.70-6.79 (m, 1H); 7.22 (s, 1H); 7.60-7.68 (m, 1H); 8.54 (s, 1H)

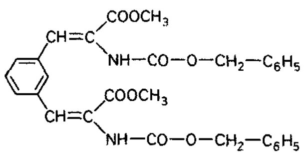
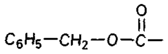
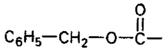
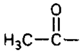
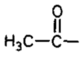
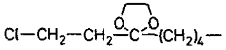
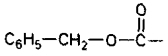
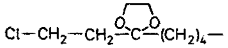
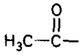
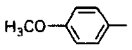
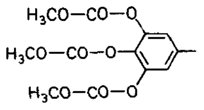
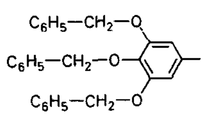
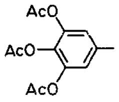
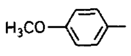
3j				A	[c]	57	(*Z,Z*): 146–147°	$C_{30}H_{28}N_2O_8$ (544.55)	(*Z,Z*): 3.78 (s, 6H); 5.06 (s, 4H); 6.36 (br. s, 2H); 7.20–7.40 (m, 15H); 7.58–7.66 (m, 1H) (*E,E*): 3.53 (s, 6H); 5.10 (s, 4H); 7.00–7.40 (m, 18H) (*Z,E*): 3.49 (s, 3H); 3.68 (s, 3H); 5.03 (s, 2H); 5.08 (s, 2H); 6.80 (br. s, 1H); 7.05–7.45 (m, 17H)
3k  $C_6H_5-CH_2-O-\overset{O}{\overset{\|}{C}}-$	n-C_3H_7	OC_2H_5		B	2.0	81	—	$C_{16}H_{21}NO_4$ (291.4)	(*E*): 0.94 (t, 3H); 1.29 (t, 3H); 1.22–1.70 (m, 2H); 2.37–2.68 (m, 2H); 4.23 (q, 2H); 5.10 (s, 2H); 6.72 (t, 1H); 6.82 (br. s, 1H); 7.29 (s, 5H) (*Z*): 0.91 (t, 3H); 1.24 (t, 3H); 1.20–1.71 (m, 2H); 2.02–2.34 (m, 2H); 4.17 (q, 2H); 5.09 (s, 2H); 6.34 (s, 1H); 6.58 (t, 1H); 7.27 (s, 5H)
3l  $C_6H_5-CH_2-O-\overset{O}{\overset{\|}{C}}-$	C_2H_5	OCH_3		C	20	86	37–38°	$C_{14}H_{17}NO_4$ (263.3)	(*E*): 1.07 (t, 3H); 2.37–2.75 (m, 2H); 3.78 (s, 3H); 5.12 (s, 2H); 6.73 (t, 1H); 6.70–6.88 (br. s, 1H) (*Z*): 1.00 (t, 3H); 1.95–2.38 (m, 2H); 3.66 (s, 3H); 5.08 (s, 2H); 6.55 (t, 1H); 6.55–6.73 (br. s, 1H)
3m Boc	n-C_3H_7	OC_2H_5		B	1.3	77	—	$C_{13}H_{23}NO_4$ (257.3)	(*E*): 0.94 (t, 3H); 1.34 (t, 3H); 1.46 (s, 9H); 1.16–1.75 (m, 2H); 2.36–2.71 (m, 2H); 4.28 (q, 2H); 6.50–6.75 (br. s, 1H); 6.64 (t, 1H) (*Z*): 0.94 (t, 3H); 1.30 (t, 3H); 1.46 (s, 9H); 1.25–1.75 (m, 2H); 1.95–2.13 (m, 2H); 4.21 (q, 2H); 6.07 (br. s, 1H); 6.53 (t, 1H)
3n  $H_3C-\overset{O}{\overset{\|}{C}}-$	n-C_3H_7	OCH_3		C	>10	84	—	$C_9H_{15}NO_3$ (185.2)	(*E*) (isolated with Method B): 0.83–1.08 (m, 3H); 1.25–1.68 (m, 2H); 2.07 (s, 3H); 2.38–2.70 (m, 2H); 3.82 (s, 3H); 6.99 (t, 1H); 7.42 (br. s, 1H) (*Z*): 0.81–1.06 (m, 3H); 1.26–1.73 (m, 2H); 2.09 (s, 3H); 1.97–2.31 (m, 2H); 3.74 (s, 3H); 6.68 (t, 1H); 7.28 (s, 1H)
3o  $H_3C-\overset{O}{\overset{\|}{C}}-$		OCH_3		C	>50	(*Z*): 78	—[1]		
3p  $C_6H_5-CH_2-O-\overset{O}{\overset{\|}{C}}-$		OCH_3		B	1.3	84	—[1]		
3q  $H_3C-\overset{O}{\overset{\|}{C}}-$	$H_2C=CH-CH_2-CH_2-$	OCH_3		C	>20	(*Z*): 84	44°	$C_{10}H_{15}NO_3$ (197.2)	(*Z*): 2.13 (s, 3H); 2.02–2.39 (m, 4H); 3.81 (s, 3H); 4.94–5.27 (m, 2H); 5.62–6.09 (m, 1H); 6.64–6.89 (m, 1H); 7.34 (br. s, 1H)

Table 2, continued

Product	R_1	R^3	X	Method	(Z/E) Ratio[a] of Product 3	Yield [%]	m.p. [°C]	Molecular Formula[b] or Lit. m.p. [°C]	$_1$H-N.M.R. (CDCl$_3$/TMS$_{int}$) δ [ppm]
3r	Boc-(*S*)-Ileu		OC_2H_5	B	0.35	60[d]	(*E*): 82° (*Z*): 135–136°	$C_{23}H_{34}N_2O_6$ (434.5)	(*E*): 0.80–1.12 (m, 6H); 1.11 (t, 3H); 1.44 (s, 9H); 1.25–2.12 (m, 3H); 3.77 (s, 3H); 4.14 (q, 2H); 4.00–4.25 (m, 1H); 5.22 (d, *J*=9 Hz, 1H); 6.67–6.87 (m, 2H); 7.10–7.27 (m, 2H); 7.42 (s, 1H); 8.35 (br. s, 1H) (*Z*): 0.80–1.11 (m, 6H); 1.31 (t, 3H); 1.44 (s, 9H); 1.43–2.13 (m, 3H); 3.76 (s, 3H); 4.22 (q, 2H); 4.03–4.26 (m, 1H); 5.13 (d, *J*=9 Hz, 1H); 6.67–6.88 (m, 2H); 7.28–7.53 (m, 2H); 7.32 (s, 1H); 7.66 (br. s, 1H)
3s	Boc-(*R*, *S*)-Try		OC_4H_9-*t*	B	—	74	(*E*,*Z*): 105°	$C_{35}H_{41}N_3O_{14}$ (727.7)	(*E/Z*-mixture): 1.20, 1.50 (2s, 9H); 1.41 (s, 9 H); 3.15–3.38 (m, 2H); 3.76 (s, 3H); 3.88 (s, 3H); 3.93 (s, 3H); 4.40–4.75 (m, 1H); 5.05–5.40 (m, 1H); 6.75–8.50 (m, 9H); 9.04 (br. s, 1H)
3t	Boc-(*S*)-Leu		OCH_3	B C	0.66 2.6	89[e] 46	(*E*): 67–69° (*Z*): 132–135°	$C_{42}H_{48}N_2O_8$ (708.85)	(*E*): 0.97 (d, 6H); 1.45 (s, 9H); 1.40–1.94 (m, 3H); 3.56 (s, 3H); 4.15–4.62 (m, 1H); 4.80–5.10 (m, 6H); 5.49 (d, *J*=8 Hz, 1H); 6.60 (s, 2H); 7.12–7.52 (m, 16H); 9.30 (br. s, 1H) (*Z*): 0.93 (d, 6H); 1.39 (s, 9H); 1.29–1.94 (m, 3H); 3.79 (s, 3H); 4.16–4.54 (m, 1H); 5.00–5.24 (m, 7H); 6.92 (s, 2H); 7.21–7.61 (m, 16H); 7.96 (br. s, 1H)
3u	Ac-(*S*)-Leu		OCH_3	B	2.0[f]	83	(*E*,*Z*): 88–93°	$C_{24}H_{30}N_2O_{10}$ (506.5)	(*E/Z*-mixture): 0.85–1.03 (m, 6H); 1.50–1.78 (m, 3H); 1.95, 1.98 (2s, 3H); 2.25–2.33 (m, 9H); 3.71, 3.82 (2s, 3H); 4.45–4.75 (m, 1H); 6.76 (br. d, 1H); 7.0–7.06 (m, 1H); 7.3–7.38 (m, 2H); 8.34, 8.93 (2br. s, 1H)
3v	Boc-(*S*)-Ileu		NH—CH_2—$COOCH_3$	C	0.35	53[g]	(*E*): 180° (*Z*): 134–136°	$C_{24}H_{35}N_3O_7$ (477.6)	(*E*): 0.85–1.08 (m, 6H); 1.10–2.13 (m, 3H); 1.44 (s, 9H); 3.67 (s, 3H); 3.80 (s, 3H); 3.93 (d, 2H); 4.00–4.23 (m, 1H); 5.12 (br. d, 1H); 6.36 (br. t, 1H); 6.80–6.98 (m, 2H); 7.20–7.38 (m, 2H); 7.85 (s, 1H); 8.44 (s, 1H) (*Z*): 0.90–1.06 (m, 6H); 1.20–2.15 (m, 3H); 1.43 (s, 9H); 3.73 (s, 3H); 3.80 (s, 3H); 3.93–4.12 (m, 3H); 5.14 (br. d, 1H); 6.78–6.90 (m, 2H); 7.22–7.45 (m, 4H); 7.75 (br. s, 1H)

3w		B	—	50	—	$C_{18}H_{21}NO_8$ (379.4)	1.26 (t, 6H); 3.83 (s, 3H); 4.05–4.40 (m, 4H); 5.14 (s, 2H); 7.30 (s, 5H); 10.50 (br. s, 1H)
3x		C	—	75	75–78°	$C_{10}H_{13}NO_7$ (259.2)	2.20 (s, 3H); 3.78 (s, 3H); 3.85 (s, 3H); 3.88 (s, 3H); 10.93 (br. s., 1H)

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[a] Determined by medium-pressure chromatography on silica gel.

[b] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.33; H, ±0.16; N, ±0.23; Cl (**3i**), −0.7.

[c] (*Z,Z/E,E/Z,E*)=0.6/1/1.5.

[d] (*E*)-**3r**, $[\alpha]_D^{20}$: −2.01° (*c* 2.9, CH_2Cl_2); (*Z*)-**3r**, $[\alpha]_D^{20}$: +21.01° (*c* 4.8, CH_2Cl_2).

[e] (*E*)-**3t**, $[\alpha]_D^{20}$: −13.70° (*c* 1.4 CH_2Cl_2); (*Z*)-**3t**, $[\alpha]_D^{20}$: +11.69° (*c* 2.0, CH_2Cl_2).

[f] (*E/Z*)-Ratio determined by ^{1}H-N.M.R. spectrometry; no separation of isomers by medium-pressure chromatography.

[g] (*E*)-**3v**, $[\alpha]_D^{20}$: −22.28° (*c* 1.5, CH_2Cl_2); (*Z*)-**3v**, $[\alpha]_D^{20}$: −5.47° (*c* 0.5, CH_2Cl_2).

Hydrogenolytic Cleavage of Alkyl 2-(Benzyloxycarbonylamino)-2-dialkoxyphosphinyl)-acetates and Reacylation; Typical Procedures:

Methyl 2-Amino-2-(dimethoxyphosphinyl)-acetate (**1c**): A solution of compound **1b** (19.9 g, 60 mmol) in methanol (170 ml) is hydrogenated at 3 at in the presence of palladium on charcoal (5%; 1.5 g). After 1.5 h, the reaction is finished (checked by T.L.C.). The catalyst is removed by filtration and the filtrate is concentrated. The unstable methyl 2-amino-2-(dimethoxyphosphinyl)-acetate **1c** is immediately *N*-protected according to one of the following procedures (for **1d, f, g, i, j**). For the characterization of **1c**, the hydrogenolysis is carried out in the presence of oxalic acid (5.4 g, 60 mmol). Filtration and evaporation affords the oxalate of **1c** which is recrystallized from methanol; yield: 15 g (87%); m.p. 142–143 °C.

$C_7H_{14}NO_9P$	calc.	C 29.28	H 4.91	N 4.88
(287.2)	found	29.29	4.99	4.93

^{1}N-N.M.R. (DMSO-d_6/TMS$_{int}$): δ=3.70–3.86 (m, 6H); 3.78 (s, 3H); 4.53 (d, 1H, J=22 Hz); 8.69 ppm (s, 4H).

Ethyl 2-amino-2-(diethoxyphosphinyl)-acetate and t-*butyl 2-amino-(diethoxyphosphinyl)-acetate* are stable and can be stored at −10 °C.

*Methyl 2-(*t*-Butoxycarbonylamino)-2-(dimethoxyphosphinyl)-acetate* (**1d**): A solution of the free amine **1c** (11.8 g, 60 mmol) and di-*t*-butyl dicarbonate (14.4 g, 66 mmol) in dichloromethane (60 ml) ist stirred overnight at room temperature. The mixture is then washed with 1 normal potassium hydrogen sulfate solution (30 ml) and with saturated sodium hydrogen carbonate solution (30 ml), dried with sodium sulfate, and evaporated. The residue is dissolved in ether/pentane (1/1) and this solution cooled to 0 °C. After several hours, the precipitated crystalline product **1d** is isolated by suction; yield: 14.3 g (80%); m.p. 47–48 °C.

Methyl 2-Acetylamino-2-(dimethoxyphosphinyl)-acetate (**1e**): To a solution of compound **1b** (19.9 g, 60 mmol) in methanol (170 ml) is added palladium on charcoal (5%; 1.5 g) followed by the addition of acetic anhydride (15 ml). The mixture is immediately hydrogenated at 3 atm for 3 h. The catalyst is filtered off and the solvent and excess acetic anhydride are removed in vacuo. The residue is recrystallized from ethyl acetate containing a few ml of pentane; yield: 13 g (91%); m.p. 88–89 °C.

Methyl-2-Chloroacetylamino-2-(dimethoxyphosphinyl)-acetate (**1f**): To a stirred solution of the free amine **1c** (11.8 g, 60 mmol) in dichloromethane (40 ml), a solution of chloroacetic acid (5.76 g, 60 mmol) in dichloromethane (60 ml) is added at −10 °C. Then dicyclohexylcarbodiimide (13.6 g, 66 mmol) is added and the solution is stirred at room temperature for 5 h. The precipitated urea is filtered off and the filtrate is washed with 1 normal potassium hydrogen sulfate (30 ml) and with saturated sodium hydrogen carbonate solution (30 ml), dried with sodium sulfate, and evaporated. To remove traces of urea, the residue is dissolved in dichloromethane (50 ml) and this solution is kept at −10 °C overnight. The precipitated urea is filtered off and the filtrate concentrated in vacuo to afford the crude product **1f** which is recrystallized from ethyl acetate; yield: 13.5 g (82%); m.p. 105 °C.

Compounds **1g, i-l** are prepared in the same manner, but the condensation affording **1j** is carried out in 1:1 acetonitrile/dimethylformamide (100 ml). The products **1g, i-l** are purified by filtration through silica gel (eluent): **1g** (ethyl acetate); **1i** (pentane/ethyl acetate 3/7); **1j** (dichloromethane/methanol 95:5); **1k** (pentane/ethyl acetate 1/1); **1l** (pentane/ethyl acetate 1/1).

t-Butyl 2-(benzyloxycarbonylamino-2-(diethoxyphosphinyl)-acetate (**1h**): A stirred solution of compound **1n** (4.3 g, 12.5 mmol), 4-dimethylaminopyridine (200 mg), and *t*-butanol (3 g) in dichloromethane (13 ml) is cooled to 0 °C and dicyclohexylcarbodiimide (3.1 g) is added. The mixture is allowed to come to room temperature and is stirred overnight. The precipitated urea is filtered off and the filtrate concentrated in vacuo to afford product **1h** which is pure enough for the subsequent reactions; yield: 4.9 g (80%). An analytically pure sample is prepared by recrystallization from ethyl acetate; m.p. 63 °C.

N-[2-(N-t-Butoxycarbonyl(S)-isoleucylamino)-2-(dimethoxyphosphinyl)-acetyl]-glycine Methyl Ester (1m):

N-[2-Benzyloxycarbonylamino-2-(dimethoxyphosphinyl)-acetyl]-glycine Methyl Ester: A stream of dry gaseous ammonia is passed through a stirred ice-cooled suspension of methyl glycinate hydrochloride (2.51 g, 20 mmol) in dichloromethane (80 ml). The precipitate is filtered off and the solvent is carefully removed under reduced pressure. The residue and 2-benzyloxycarbonylamino-2-dimethoxyphosphinylacetic acid (**1o**; 6.34 g, 20 mmol) are dissolved in dimethylformamide/acetonitrile (1/1; 20 ml) and dicyclohexylcarbodiimide (4.54 g, 22 mmol) is added with stirring at 0 °C. Stirring is continued for 5 h at room temperature, the precipitated urea is filtered off, and the filtrate is concentrated in vacuo. The residue is redissolved in ethyl acetate (150 ml), and the solution is washed with 1 normal potassium hydrogen sulfate (30 ml) and with saturated sodium hydrogen carbonate solution (30 ml), dried with sodium sulfate, and evaporated. The crude product is purified by filtration through silica gel (eluent: ethyl acetate); yield: 6.28 g (81%).

Tripeptide Ester **1m**: A solution of *N*-[2-benzyloxycarbonylamino-2-(dimethoxyphosphinyl)-acetyl]-glycine methyl ester (6.28 g, 16.2 mmol) in methanol (30 ml) is hydrogenated at 3 atm in the presence of palladium on charcoal (5%; 0.8 g). After 1.5 h, hydrogenation is complete (checked by T.L.C.) and the filtrate is concentrated. The unstable *N-(2-amino-2-dimethoxyphosphinylacetyl)-glycine methyl ester* is immediately *N*-acylated by reaction with *N-t*-butoxycarbonyl-(*S*)-isoleucine (4.03 g, 17 mmol) and dicyclohexylcarbodiimide (4.1 g, 20 mmol) in dichloromethane (30 ml) as described for the *N*-acylation **1c** → **1f**. The crude product **1m** is purified by column chromatography on silica gel using ethyl acetate as eluent; yield: 5.67 g (75%); m.p. 59–60 °C.

Condensation of Alkyl Phosphonoglycinates (1) with Aldehydes (2) to give 2-Amino-2-alkenoic Esters (3); Typical Procedures:

Method A:

Ethyl 2-Benzyloxycarbonylamino-3-phenylpropenoate (**3a**): A solution of ethyl 2-ethoxycarbonylamino-2-(diethoxyphosphinyl)-acetate (**1a**; 3 g, 8 mmol) in tetrahydrofuran (7 ml) is added dropwise to a stirred slurry of sodium hydride (50% in oil; 0.43 g, 9 mmol) in tetrahydrofuran (5 ml) at 20 °C. After gas evolution has ceased, a solution of benzaldehyde (0.85 g, 8 mmol) in tetrahydrofuran (2 ml) is added and stirring is continued for 2 h. Then, tetrahydrofuran/water (a few ml) is added to decompose excess sodium hydride. The solvent is removed and the residue taken up in ether (~50 ml). This solution is washed with water (10 ml), dried with sodium sulfate, and concentrated in vacuo to give product **3a** as an (*E/Z*)-mixture which is separated by medium-pressure chromatography (eluent: pentane/ethyl acetate 9/1).

(*E*)-**3a**; yield: 1.02 g (39%); R_f: 0.16.

(*Z*)-**3a**; yield: 1.09 g (42%); R_f: 0.06.

Method B:

Methyl 2-[N-t-Butoxycarbonyl-(S)-leucylamino]-3-(3,4,5-tribenzyloxyphenyl)-propenoate (**3t**): A solution of lithium diisopropylamide is prepared by adding butyllithium in hexane (17 mmol) to a solution of diisopropylamine (1.82 g, 18 mmol) in tetrahydrofuran (15 ml) at −60 °C. To this is added, dropwise and with stirring, a solution of methyl 2-[*N-t*-butoxycarbonyl-(*S*)-leucylamino]-2-(dimethoxyphosphinyl)-acetate (**1i**; 6.98 g, 17 mmol) in tetrahydrofuran (18 ml). During the addition of **1i**, the temperature should rise to about −10 °C to dissolve the precipitated salt. The resultant clear yellow solution is again cooled to −60 °C, and then a solution of 3,4,5-tribenzyloxybenzaldehyde (5.94 g, 14 mmol) in tetrahydrofuran (20 ml) is added dropwise. The mixture is allowed to come to room temperature, and stirred for a further 2 h. The solvent is evaporated under reduced pressure, the residue is redissolved in ethyl acetate (200 ml), this solution is washed with water (20 ml) and dried with sodium sulfate. The solution is concentrated in vacuo, and the remaining (*E/Z*)-isomer mixture is separated by medium-pressure chromatography on silica gel (eluent: pentane/ethyl acetate 7/3).

(*E*)-**3t**; yield: 5.35 g (54%); R_f: 0.42.

(*Z*)-**3t**; yield: 3.51 g (35%); R_f: 0.28.

Method C:

Methyl (Z)-2-Chloroacetylamino-3-(2-furyl)-propenoate (**3i**): Potassium *t*-butoxide (6.17 g, 55 mmol) is cooled to −60 °C and then slowly suspended in dichloromethane (10 ml). A solution of methyl 2-chloroacetylamino-2-(dimethoxyphosphinyl)-acetate (**1f**; 15 g, 55 mmol) in dichloromethane (80 ml) is added dropwise with stirring whereby the potassium *t*-butoxide is dissolved. Then, a solution of freshly destilled furfural (4.56 ml, 55 mmol) in dichloromethane (10 ml) is added and the almost clear solution allowed to come to room temperature and stirred for additional 2 h. During this time, a viscous precipitate forms. The mixture is concentrated in vacuo and the residue taken up in ethyl acetate (300 ml). This solution is washed with water (50 ml) and aqueous ammonium chloride (30 ml) and is dried with sodium sulfate. Removal of the solvent affords **3i** as a crystalline residue, which is recrystallized from ethyl acetate; yield: 12.46 g (93%); m.p. 109 °C.

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[1] For Part XLII, see: U. Schmidt, T. Beuttler, A. Lieberknecht, H. Griesser, *Tetrahedron Lett.* **24**, 3573 (1983).

[2] For Part XVIII, see: U. Schmidt et al., *Angew. Chem.* **94**, 797 (1982); *Angew. Chem. Int. Ed. Engl.* **21**, 770 (1982); *Angew. Chem. Suppl.* **1982**, 1682.

[3] For Part I, see Ref.[2].

[4] U. Schmidt, U. Schanbacher, *Angew. Chem.* **95**, 150 (1983); *Angew. Chem. Int. Ed. Engl.* **22**, 152 (1983).

[5] R. Kober, W. Steglich, *Liebigs Ann. Chem.* **1983**, 599.

[6] U. Zoller, D. Ben-Ishai, *Tetrahedron* **31**, 863 (1975).

[7] For other syntheses of amino-phosphonoglycinates, see Ref.[5]; and literature cited therein.

[8] B. Neises, W. Steglich, *Angew. Chem.* **90**, 556 (1978); *Angew. Chem. Int. Ed. Engl.* **17**, 522 (1978).

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