Amino alcohols as C-Terminal Protecting Groups in Peptide Synthesis

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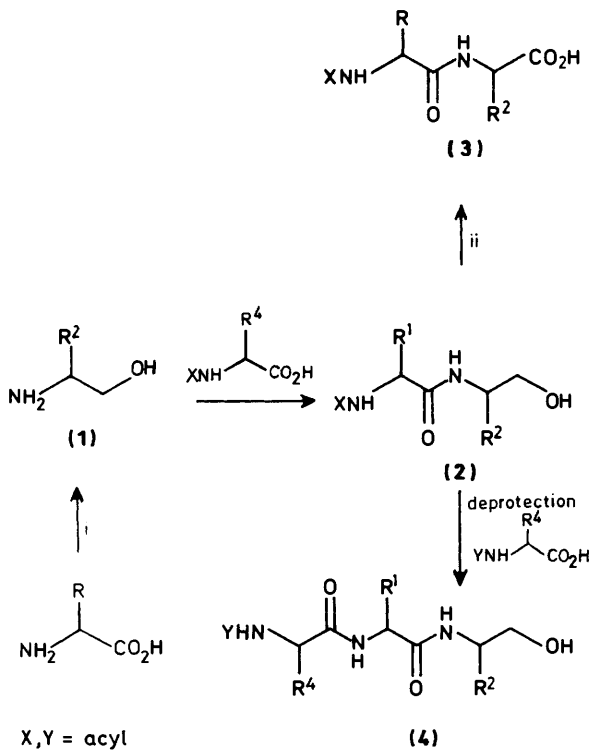
The synthesis of peptides using amino alcohols as C-terminal protecting groups is described. C-Terminal protection of amino acid could be accomplished by reduction of the terminal carboxyl group to a hydroxymethyl group, and regeneration of the carboxyl group could be achieved by Jones' oxidation. This method was applied to the formation of di-and tripeptides.

In recent years, optically active 2-substituted 2-aminoethanols, which can be prepared readily by lithium aluminum hydride reduction of amino acids,[1] have been used as chiral auxiliaries in asymmetric synthesis. Oxidation of the hydroxymethyl entity of such amino alcohols to the carboxylic group can be accomplished, after protection of the amino group by a phthaloyl group,[2] a benzoyl group,[3] or a benzyloxycarbonyl group,[4] with oxidants such as potassium dichromate, potassium permanganate, and chromium trioxide. Although the preparation and the oxidation of amino alcohols proceed in fair yields, these reactions have not been applied to peptide synthesis.

Kashima *et al.* have studied the alkylation and acylation of amino alcohols (**1**),[5] and have found that the amino group of (**1**) can be selectively acylated to afford the (N-protected amino-acyl) amino alcohol (**2**) on condensation with N-protected amino acids. Regeneration of the carboxyl group could then be accomplished by oxidation of the hydroxymethyl entity of compound (**2**), to yield an N-protected dipeptide (**3**). Alternatively, an N-deprotected amino acid could also be coupled at the N-terminal of compound (**2**) to form compound (**4**) (Scheme 1).

Hitherto, various groups have been used for the protection of the N- and/or C-termini of amino acids in peptide synthesis. In particular, benzyloxycarbonyl, t-butoxycarbonyl, phthaloyl, and toluene-*p*-sulphonyl groups have been used as amino protecting groups, and methyl, benzyl, and t-butyl esters have been used as carbonyl protecting groups. These protecting groups are generally introduced by acylation and esterification, and removed by reduction, acidic or basic hydrolysis, and thermolysis. However, by using amino alcohols as C-terminal protecting groups, protection and deprotection should proceed by reduction and oxidation respectively, processes different from normal protection and deprotection reactions, and hence useful for chemoselectivity. The scope and limitations of the use of amino alcohols as C-terminal protecting groups was clarified.

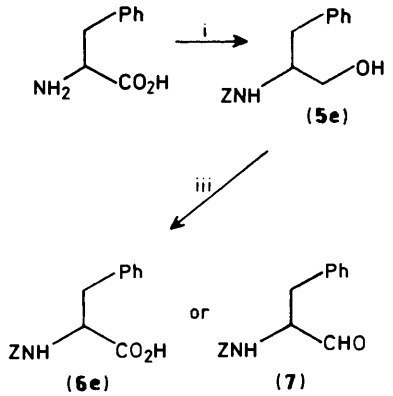


Scheme 1. *Reagents:* i, LAH; ii, [O]

Results and Discussion

Synthesis of N-*Benzyloxycarbonyl Amino Acids by Oxidation of* N-*Benzyloxycarbonyl Amino Alcohols.*—The oxidation of amino alcohols protected by a benzyloxycarbonyl (*Z*-) group, which has been used extensively as an amino protecting group in peptide synthesis, was investigated. *N*-Z-Amino alcohols were prepared by benzyloxycarbonylation of 2-substituted 2-amino-ethanols, which were prepared by lithium aluminium hydride (LAH) reduction of amino acids. Under normal conditions using sodium hydrogen carbonate, the amino acids glycine, alanine, valine, leucine, and phenylalanine gave the 2-substituted *N*-Z-2-aminoethanols (**5**).

N-Phenylalaninol (**5e**) did not yield *N*-Z-phenylalanine (**6e**) on oxidation with potassium permanganate due to its low solubility in aqueous sodium hydroxide. However, treatment of compound (**5e**) with Jones' reagent produced (**6e**) in a quantitative yield without racemization. Oxidation of (**5e**) with chromium trioxide and pyridine, or with dimethylsulphoxide (DMSO) and *N*,*N*'-dicyclohexylcarbodi-imide (DCC), however, gave the corresponding aldehyde (**7**), but racemization of (**7**) occurred rapidly in solution owing to keto-enol isomerization (Scheme 2). From these observations Jones' oxidation was



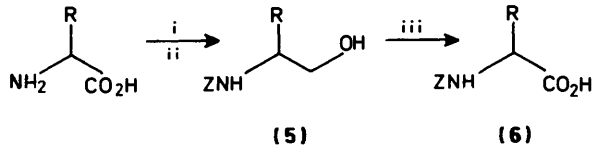
Scheme 2. *Reagents:* i, LAH; ii, Z-Cl; iii, [O]

Table 1.

R	(5) Yield (%)	Yield (%)	(6) M.p. (lit.) (°C)	Optical purity (%)
a H	38	95	118—119 (120)[6]	
b Me	33	95	83—84 (87)[7]	99[7]
c Pr^i	38	96	114—115 (116—117)[8,*]	97[8,*]
d Bu^i	52	85	(Oil)[9]	97[9]
e $PhCH_2$	70	92	87—87.5 (88—89)[10]	97[10,†]

* The m.p. and optical purity values are those of the *N*-hydroxy succinimide ester of benzyloxycarbonyl valine. † Compound (**10e**) showed $[\alpha]_D$ +2.8° (*c* 2.3, CH_3CO_2H). The lit. value indicated $[\alpha]_D$ +5.1° (*c* 2, CH_3CO_2H), however, the $[\alpha]_D$ of commercially available Z-phenylalanine was +2.8°.

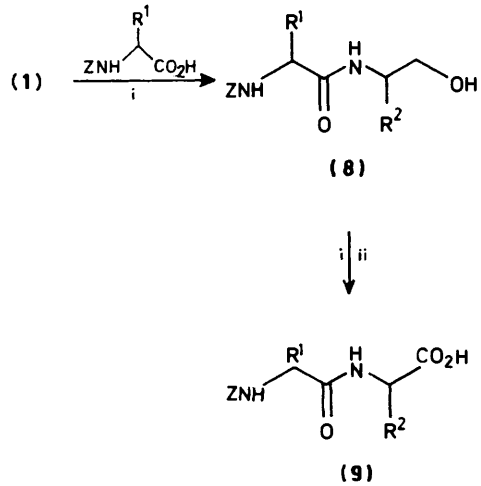
found to be preferable for the synthesis of *N*-Z-amino acids and was used in subsequent oxidations. Under these conditions, the 2-substituted *N*-Z-2-aminoethanols (**5**) gave glycine, alanine, valine, and leucine (**6**) in good yields and fair optical purities as shown in Table 1 (Scheme 3).



Scheme 3. *Reagents:* i, LAH; ii, Z-Cl; iii, Jones' oxidation

N-Z-Tyrosinol (**5f**; R = *p*-$HOC_6H_4CH_2$) was prepared by sodium borohydride reduction after esterification of *N*-Z-tyrosine (**6f**; R = *p*-$HOC_6H_4CH_2$) in poor yield (12%). On oxidation with Jones' reagent *N*-Z-tyrosine (**6f**) was regenerated in a low yield (9%).

Peptide Synthesis using Amino Alcohols as C-Terminal Protecting Groups.—The *N*-Z-Amino acids were treated with 2-substituted 2-aminoethanols (**1**) in the presence of DCC as a coupling reagent. After work-up, the *N*-Z-aminoacylaminoethanol (**8**) was obtained in the yields shown in Table 2 (Scheme 4).



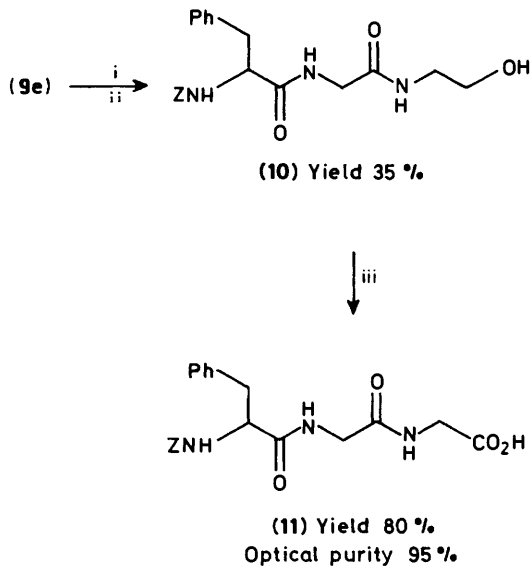
Scheme 4. *Reagents:* i, DCC; ii, Jones' oxidation

Table 2.

R^1	R^2	(9) Yield (%)	Yield (%)	(10) M.p. (lit.) (°C)	Optical purity (%)
a H	$PhCH_2$	63	91	126.5—127.7 (126.5—127.5)	96[11]
b Me	H	35	80	127—129 (134—135)	92[11]
c Pr^i	H	61	99	160—161 (156—157)	87[11,*]
d Bu^i	H	57	100	115.5—116 (112—113)	100[12]
e $PhCH_2$	H	99	99	147—148 (154—155)	100[11]
f *p*-$HOC_6H_4CH_2$	H	29	†		
g Indol-3-yl-CH_2	H	39	†		
h H	H	52			

* The m.p. and optical purity values are those of the *N*-Z-valylglycine methyl ester. † An intractable mixture.

Deprotection of the C-terminal hydroxymethyl group of (**8**) to form the *N*-1-dipeptide (**9**) was accomplished by oxidation with Jones' reagent. The amino acids possessing alkyl substituents gave the *N*-Z-dipeptides (**9**) in good yield, but those sensitive to oxidation, such as tyrosine and tryptophan, failed to yield the *N*-Z-dipeptides (**9**) by Jones' oxidation. The results are summarized in Table 2. Furthermore, the reaction of *N*-Z-phenylalanylglycine (**9e**) with 2-aminoethanol in the presence of DCC produced *N*-Z-phenylalanylglycylaminoethanol (**10**). Oxidation of the C-terminal hydroxymethyl entity with Jones' reagent produced the tripeptide, *N*-Z-phenylalanylglycylglycine (**11**) (Scheme 5). Thus amino alcohols are excellent C-terminal

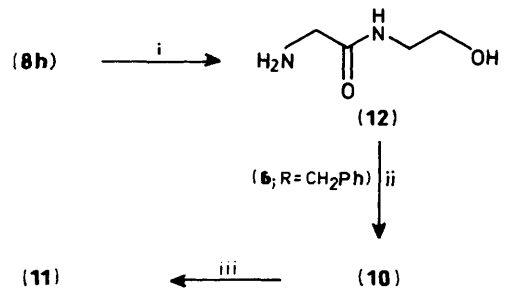


Scheme 5. *Reagents:* i, NH_2⌒⌒OH; ii, DCC; iii, Jones' oxidation

protecting groups for peptide bond formation of amino acids possessing alkyl substituents, and it is expected that this series of reactions could be applied to the formation of polypeptides.

Deprotection of the N-terminal of *N*-Z-glycylaminoethanol (**8h**) and coupling with *N*-Z-phenylalanine using DCC, also gave *N*-Z-phenylalanylglycylaminoethanol (**10**), which again gave the tripeptide (**11**) by Jones' oxidation (Scheme 6).

The *N*-Z-aminoacylaminoethanols (**8**) and (**10**) were readily crystallized, were easy to handle, and could be stored indefinitely.



Scheme 6. *Reagents:* i, H_2/Pd; ii, DCC; iii, Jones' oxidation

Experimental

M.p.s were measured on a Yanagimoto Micro m.p. apparatus, and are uncorrected. I.r. spectra were measured on a Jasco IRA-1 i.r. spectrometer, and ^1H and ^{13}C n.m.r. spectra were recorded using Hitachi R-24 and a JOEL-100 spectrophotometers, respectively, with tetramethylsilane as an internal standard. Elemental analysis was performed on a Perkin-Elmer Model 240 elemental analyzer. Specific rotations were measured on a Jasco DIP-360 Digital Polarimeter, and optical purity was determined by comparison with the values in the literature or the values of an authentic sample obtained independently by known methods. Ether refers to diethyl ether.

Preparation of 2-Substituted 2-Aminoethanols (**1**).—2-Substituted 2-aminoethanols were prepared from the corresponding L-amino acids by the method of Enders[12] using lithium aluminum hydride.

Preparation of 2-Substituted N-Z-2-Aminoethanols (**5**).—Method A: A solution of the 2-aminoethanol (**1**) (10 mmol) in dichloromethane was added to a solution of sodium hydrogen carbonate (26 mmol) in water (15 ml) at room temperature. Benzyloxycarbonyl chloride (6.5 ml) in dichloromethane was added to the well stirred reaction mixture. When the reaction was complete (2 h), benzyloxycarbonyl chloride (6.5 ml) and sodium hydrogen carbonate (13 mmol) were added, and the reaction mixture stirred for a further 3 h. The mixture was washed with ether to remove the excess of benzyloxycarbonyl chloride. The aqueous phase was acidified with 6M hydrochloric acid and extracted with ethyl acetate. The combined organic phase was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (chloroform–acetone–ethanol).

Method B: A solution of the 2-aminoethanol (**1**) (10 mmol) and triethylamine (10 mmol) in dichloromethane (40 ml) was cooled to 0 °C, benzyloxycarbonyl chloride (10 mmol) in dichloromethane was added dropwise and the mixture was stirred for 4 h at 0 °C. The organic layer was washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (chloroform–acetone–ethanol).

N-*Benzyloxycarbonylaminoethanol* (**5a**).[13] Yield 38% (method A), m.p. 62—63 °C (lit., 53—55 °C).

N-*Benzyloxycarbonyl-L-alaninol* (**5b**).[14] Yield 33% (method B), m.p. 80.5—81.5 °C; $[\alpha]_D$ −6.55° (*c* 1.91, $CHCl_3$) [lit., −5.42 °C (*c* 1.5, $CHCl_3$)].

N-*Benzyloxycarbonyl-D-valinol* (**5c**). Yield 38% (method A), m.p. 57—59 °C (from benzene–hexane) (Found: C, 65.85; H, 8.1; N, 5.9. $C_{13}H_{19}NO_3$ requires C, 65.80; H, 8.07; N, 5.90%); $[\alpha]_D$ −16.1° (*c* 1.03, methanol); $\nu_{max.}$(KBr) 3 410br, 3 300, 1 680, and 1 530 cm^{-1}; $\delta_H(CDCl_3)$ 0.89 (d, 3 H, *J* 6.8 Hz), 0.92 (d, 3 H, *J* 6.8 Hz), 1.79 (sept, 1 H, *J* 6.4 Hz), 2.98 (br s, 1 H), 3.58 (br s, 1 H), 3.3—3.7 (m, 2 H), 5.07 (s, 2 H), 5.0—5.3 (m, 1 H), and 7.31 (s, 5 H); $\delta_C(CDCl_3)$ 18.4 (q), 19.4 (q), 29.2 (d), 53.5 (d), 63.4 (t), 66.8 (t), 127.9 (d), 128.4 (d × 2), 136.4 (s), and 157.0 p.p.m. (s).

N-*Benzyloxycarbonyl-L-leucinol* (**5d**) Yield 52% (method B), b.p. 140 °C/5 mmHg (Found: C, 66.25; H, 8.45; N, 5.55. $C_{14}H_{21}NO_3$ + 0.1 H_2O requires C, 66.42; H, 8.46; N, 5.53%); $\nu_{max.}$(film) 3 260, 1 680, and 1 500 cm^{-1}; $\delta_H(CDCl_3)$ 0.90 (d, 6 H, *J* 6.4 Hz), 1.2—1.8 (m, 3 H), 3.04 (br s, 1 H), 3.4—4.0 (m, 3 H), 5.08 (s, 2 H), 5.1—5.3 (br s, 1 H), and 7.32 (s, 5 H); $\delta_C(CDCl_3)$ 22.1 (q), 23.0 (q), 24.7 (d), 40.5 (t), 51.4 (d), 65.6 (t), 66.7 (t), 70.6 (s), 127.9 (d), 128.0 (d), 128.4 (d), 136.4 (s), and 157.0 p.p.m. (s).

N-*Benzyloxycarbonyl-L-phenylalaninol* (**5e**). Yield 70% (method B), m.p. 92—94 °C (from benzene–hexane) (Found: C, 71.55; H, 6.7; N, 4.9. $C_{17}H_{19}NO_3$ requires C, 71.55; H, 6.71; N, 4.90%); $[\alpha]_D$ −42.7° (*c* 1.24, methanol); $\nu_{max.}$(KBr) 3 320, 3 230br, 1 680, and 1 520 cm^{-1}; $\delta_H(CDCl_3)$ 2.78 (br s, 1 H), 2.82 (d, 2 H, *J* 7.3 Hz), 3.5 (br s, 2 H), 3.8—4.1 (m, 2 H), 5.03 (s, 2 H), 5.21 (d, 1 H, *J* 7.8 Hz), and 6.9—7.4 (m, 10 H); $\delta_C(CDCl_3)$ 37.4 (t), 54.2 (d), 63.7 (t), 66.8 (t), 126.5 (d), 127.9 (d), 128.0 (d), 128.5 (d × 2), 129.2 (d), 136.3 (s), 137.6 (s), and 156.5 p.p.m. (s).

N-*Benzyloxycarbonyl-L-tyrosinol* (**5f**). A solution of the *N*-Z-tyrosine dicyclohexylamine salt in methanol was neutralized with 12M hydrochloric acid, and refluxed. After two days, the mixture was extracted with ethyl acetate, and the organic layer dried ($MgSO_4$), and concentrated to give *N*-Z-tyrosine methyl ester. Sodium borohydride was added to a methanol solution of the crude product and the mixture refluxed for 12 h. The mixture was diluted with ethyl acetate, washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (chloroform–acetone–ethanol) to yield Z-tyrosinol (**5f**) in 12% yield.

Oxidation of 2-Subtituted N-Z-2-Aminoethanols.—(i) Jones' oxidation. Jones' reagent was prepared by dissolving chromium trioxide (2.67 g) in concentrated sulphuric acid (2.3 ml) and diluting to 10 ml with water. The 2-substituted *N*-Z-2-aminoethanol (**5**) (1 mmol) was dissolved in acetone (1.5—5 ml) and added dropwise to a stirred solution of Jones' reagent (0.7 ml) in acetone (1.9 ml) at 0 °C. The mixture was stirred for 3 h at 0 °C then isopropyl alcohol (0.3 ml) was added, and stirring continued for a further 0.5 h. The organic layer was concentrated, diluted with water, and extracted with ethyl acetate. The organic phase was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure to give the 2-substituted *N*-Z-2-amino acids (**6**). An analytical sample was prepared by dissolving (**6**) in dichloromethane and washing with 5% aqueous potassium hydroxide. Acidification of the aqueous layer, re-extraction, and solvent evaporation gave pure compound (**6**). Similarly, the *N*-Z-aminoacylaminoethanols (**8**) and (**10**) gave the *N*-Z-dipeptides (**9**) and the *N*-Z-tripeptides (**11**), respectively.

(ii) Potassium permanganate oxidation.[15] *N*-Z-L-Phenylalaninol (**5e**) (1 mmol) was added to a 5% aqueous solution of potassium permanganate (12 ml), and acetone was added to the solution until compound (**5e**) dissolved. Potassium permanganate (214 mg) was added in small portions at room temperature. After 1 h, sodium hydrogen sulphite was added, and the mixture stirred for a few minutes. The reaction mixture was filtered, and the filtrate extracted with ethyl acetate. The organic layer was dried ($MgSO_4$), and evaporated under reduced pressure.

(iii) Pfitzner-Moffatt oxidation.[16] *N,N'*-Dicyclohexylcarbodiimide (DCC) (3 mmol) in DMSO (5 ml) was added to a solution of *N*-Z-L-phenylalaninol (**5e**) (1 mmol) and phosphoric acid (0.5 mmol) in DMSO (5 ml) and the solution stirred at room temperature for 10 h. The reaction mixture was extracted with dichloromethane, dried ($MgSO_4$), and concentrated under reduced pressure to give the corresponding aldehyde (**7**). The aldehyde (**7**) was purified by column chromatography on florisil

(chloroform–acetone–ethanol), and crystallized from benzene–hexane.

(iv) Oxidation with Collins' reagent:[17] Collins' reagent was prepared by adding chromium trioxide (6 mmol) in small portions to a solution of pyridine (12 mmol) in dichloromethane. After 15 min, *N*-Z-L-phenylalaninol (**5e**) in dichloromethane was added to the solution of Collins' reagent and the mixture stirred for 15 min. The reaction mixture was filtered and the residue washed with ether. The organic phase was washed with 5% sodium hydroxide solution, 5% hydrochloric acid, 5% sodium hydrogen carbonate solution, and saturated aqueous sodium chloride, dried ($MgSO_4$), and evaporated under reduced pressure to give compound (**7**). The product was purified as described above.

(S)-2-(N-*Benzyloxycarbonyl*)*amino*-3-*phenylpropanal* (**7**). Yield 58% m.p. 78.5—80 °C (from benzene) (Found: C, 71.95; H, 6.05; N, 4.95. $C_{17}H_{17}NO_3$ requires C, 72.06; H, 6.04; N, 4.94%); $\nu_{max.}$(KBr) 3 320, 1 730, and 1 670 cm^{-1}; $\delta_H(CDCl_3)$ 3.10 (d, 2 H, *J* 6.8 Hz), 4.48 (dt, 1 H, *J* 6.8 and 6.8 Hz), 5.09 (s, 2 H), 5.38 (d, 1 H, *J* 6.4 Hz), 7.0—7.4 (m, 10 H), and 9.58 (s, 1 H); $\delta_C(CDCl_3)$ 35.3 (t), 61.1 (d), 67.1 (t), 127.1 (d), 128.1 (d), 128.2 (d), 128.5 (d), 128.7 (d), 129.2 (d), 135.4 (s), 136.0 (s), 155.8 (s), and 198.8 p.p.m. (d).

Oxidation of Aldehyde (**7**) *with Hydrogen Peroxide.*—A mixture of 5% aqueous sodium hydroxide (3 ml) and 3% aqueous hydrogen peroxide (4.5 ml) was added to a solution of aldehyde (**7**) (1 mmol) in ethanol (7 ml), and the mixture stirred for 15 min at 65 °C. 3% Aqueous hydrogen peroxide was added (1.5 ml), and after 5 min, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure to yield the corresponding *N*-Z-amino acid (**6**).

Reaction of N-*Z-Amino Acids with* 2-*Substituted* 2-*Aminoethanols* (**1**).—DCC (1 mmol) in dichloromethane (10 ml) was added to a solution of an *N*-Z-amino acid (1 mmol), and the mixture stirred for 20 min at 0 °C. *N*-Z-2-aminoethanol (1 mmol) in dichloromethane (10 ml) was added to the reaction mixture and stirring was continued for 10 h at room temperature. The reaction mixture was filtered, the filtrate was washed with water and aqueous saturated sodium hydrogen carbonate dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (chloroform–acetone–ethanol) and recrystallized to yield the corresponding alcohol (**8**).

N-(N'-*Benzyloxycarbonylglycyl*)-L-*phenylalaninol* (**8a**). Yield 63%, m.p. 102—103.5 °C (from ethyl acetate) (Found: C, 66.6; H, 6.5; N, 8.15. $C_{19}H_{22}N_2O_4$ requires C, 66.65; H, 6.47; N, 8.18%); $[\alpha]_D$ −16.5° (*c* 2.14, methanol); $\nu_{max.}$(KBr) 3 370, 3 240, 1 680, 1 650, and 1 530 cm^{-1}; $\delta_H(CDCl_3)$ 2.80 (d, 2 H, *J* 6.8 Hz), 3.4—3.6 (m, 2 H), 3.71 (d, 2 H, *J* 1.0 Hz), 3.9—4.3 (m, 1 H), 5.09 (s, 1 H), and 7.1—7.4 (m, 10 H); $\delta_C(CDCl_3)$ 43.9 (t), 45.9 (t), 52.4 (d), 62.4 (t), 66.8 (t), 126.1 (d), 127.6 (d), 127.9 (d), 128.2 (d × 2), 128.9 (d), 135.9 (s), 137.5 (s), 156.9 (s), and 169.6 p.p.m. (s).

N-*Benzyloxycarbonyl*-L-*alanylaminoethanol* (**8b**). Yield 35%, m.p. 114—115 °C (from ethyl acetate) (Found: C, 58.55; H, 6.9; N, 10.5. $C_{13}H_{18}N_2O_4$ requires C, 58.63; H, 6.81; N, 10.51%); $[\alpha]_D$ −12.8° (*c* 0.93, methanol); $\nu_{max.}$(KBr) 3 260br, 1 660, 1 620, and 1 510 cm^{-1}; $\delta_H(CDCl_3)$ 1.34 (d, 3 H, *J* 6.9 Hz), 3.2—3.7 (m, 5 H), 4.1—4.4 (m, 1 H), 5.00 (d, 1 H, 12.7 Hz), 5.19 (d, 1 H, 12.7 Hz), 5.88 (d, 1 H, *J* 4.9 Hz), 7.00 (br s, 1 H), and 7.31 (s, 5 H); $\delta_C(CDCl_3)$ 18.7 (q), 42.2 (t), 50.8 (d), 61.4 (t), 67.1 (t), 128.0 (d), 128.2 (d), 128.5 (d), 136.1 (s), 156.2 (s), and 173.5 p.p.m. (s)

N-*Benzyloxycarbonyl*-L-*valylaminoethanol* (**8c**). Yield 61%, m.p. 150—151 °C (from ethyl acetate) (Found: C, 61.05; H, 7.65; N, 9.4. $C_{15}H_{22}N_2O_4$ requires C, 61.20; H, 7.53; N, 9.51%); $[\alpha]_D$ 12.0° (*c* 1.14, methanol); $\nu_{max.}$(KBr) 3 270br, 1 660, 1 620, and 1 515 cm^{-1}; $\delta_H(CDCl_3)$ 0.92 (d, 3 H, *J* 6.8 Hz), 0.95 (d, 3 H, *J* 6.8 Hz), 2.04 (sept, 1 H, *J* 6.8 Hz), 3.2—3.8 (m, 4 H), 3.9—4.2 (m, 1 H), 4.99 (d, 1 H, *J* 12 Hz), 5.13 (d, 1 H, *J* 12 Hz), 5.82 (d, 1 H, *J* 8.3 Hz), 6.8—7.2 (m, 1 H), and 7.31 (s, 5 H); $\delta_C(CDCl_3)$ 18.0 (q), 19.3 (q), 31.1 (d), 42.2 (t), 60.8 (d), 61.6 (t), 67.1 (t), 127.9 (d), 128.2 (d), 128.5 (d), 136.1 (s), 156.7 (s), and 172.4 p.p.m. (s).

N-*Benzyloxycarbonyl*-L-*leucylaminoethanol* (**8d**). Yield 57%, m.p. 125.5—127 °C (from ethyl acetate) (Found: C, 62.25; H, 7.9; N, 9.05. $C_{16}H_{24}N_2O_4$ requires C, 62.31; H, 7.84; N, 9.09%). $[\alpha]_D$ 17.6° (*c* 1.04, methanol); $\nu_{max.}$(KBr) 3 220, 1 640, 1 615, and 1 500 cm^{-1}; $\delta_H(CDCl_3)$ 0.90 (d, 6 H, *J* 4.9 Hz), 1.57 (d, 2 H, *J* 4.9 Hz), 1.4—1.8 (br s, 1 H), 3.2—3.8 (m, 4 H), 4.0—4.4 (m, 1 H), 4.96 (d, 1 H, *J* 12.2 Hz), 5.12 (d, 1 H, *J* 12.2 Hz), 5.99 (d, 1 H, *J* 8.3 Hz), and 7.29 (s, 5 H); $\delta_C(CDCl_3)$ 21.8 (q), 22.9 (q), 24.7 (d), 41.6 (t), 42.2 (t), 53.7 (d), 61.4 (t), 66.9 (t), 127.8 (d), 128.1 (d), 128.4 (d), 136.0 (s), 156.5 (s), and 173.5 p.p.m. (s).

N-*Benzyloxycarbonyl*-L-*phenylalanylaminoethanol* (**8e**). Yield 99%, m.p. 128—129 °C (from ethyl acetate) (Found: C, 66.6; H, 6.5; N, 8.15. $C_{19}H_{22}N_2O_4$ requires C, 66.65; H, 6.47; N, 8.18%); $[\alpha]_D$ −5.8° (*c* 2.045, methanol); $\nu_{max.}$(KBr) 3 270, 1 675, 1 630, and 1 515 cm^{-1}; $\delta_H(CDCl_3)$ 3.00 (br s, 1 H), 3.02 (d, 2 H, *J* 6.8 Hz), 3.26 (t, 2 H, *J* 4.6 Hz), 3.47 (t, 2 H, *J* 4.6 Hz), 4.43 (dt, 1 H, *J* 7.8 and 7.3 Hz), 4.93 (d, 1 H, *J* 12.7 Hz), 5.07 (d, 1 H, *J* 12.7 Hz), 5.81 (d, 1 H, *J* 8.3 Hz), 6.7 (br s, 1 H), 7.21 (s, 5 H), and 7.28 (s, 5 H); $\delta_C(CDCl_3)$ 38.9 (t), 41.2 (t), 56.5 (d), 61.4 (t), 67.0 (t), 126.9 (d), 127.9 (d), 128.1 (d), 128.4 (d), 128.5 (d), 129.2 (d), 136.0 (s), 136.4 (s), 156.1 (s), and 171.8 p.p.m. (s).

N-*Benzyloxycarbonyl*-L-*tyrosylaminoethanol* (**8f**). Yield 29%, m.p. 139—140 °C (from ethyl acetate–benzene) (Found: C, 63.6; H, 6.2; N, 7.8. $C_{19}H_{22}N_2O_5$ requires C, 63.67; H, 6.18; N, 7.81%); $[\alpha]_D$ −1.04° (*c* 1.05, methanol); $\nu_{max.}$(KBr) 3 275, 1 675, 1 625, 1 525, and 1 510 cm^{-1}; $\delta_H(CDCl_3$–$CD_3OD)$ 2.8 (dd, 1 H, *J* 8.3 and 13.9 Hz), 3.0 (dd, 1 H, *J* 6.4 and 13.9 Hz), 4.2—4.7 (m, 4 H), 4.31 (dd, 1 H, *J* 6.4 and 8.3 Hz), 4.94 (d, 1 H, *J* 12.2 Hz), 5.09 (d, 1 H, *J* 12.2 Hz), 6.72 (d, 2 H, *J* 8.8 Hz), 7.03 (d, 2 H, *J* 8.3 Hz), and 7.28 (s, 5 H); $\delta_C(CDCl_3$–$CD_3OD)$ 38.3 (t), 42.5 (t), 57.6 (d), 61.1 (s), 67.3 (t), 115.9 (d), 137.2 (s), 156.5 (s), 157.5 (s), and 173.7 p.p.m. (s).

N-*Benzyloxycarbonyl*-L-*tryptophylaminoethanol* (**8g**). Yield 39%, m.p. 127—128 °C (from ethyl acetate–benzene) (Found: C, 66.0; H, 6.05; N, 10.95. $C_{21}H_{23}N_3O_4$ requires C, 66.12; H, 6.07; N, 11.01%); $[\alpha]_D$ −3.61 ° (*c* 1.16, methanol); $\nu_{max.}$(KBr) 3 240, 1 660, 1 620, 1 600, and 1 510 cm^{-1}; $\delta_H(CDCl_3$–$CD_3OD)$ 4.1—4.4 (m, 6 H), 4.43 (t, 1 H, *J* 6.8 Hz), 5.00 (s, 2 H), 6.9—7.7 (m, 4 H), 7.05 (s, 1 H), and 7.26 (s, 5 H); $\delta_C(CDCl_3$–$CD_3OD)$ 29.0 (t), 42.5 (t), 57.0 (d), 61.1 (t), 67.4 (t), 110.3 (s), 111.9 (d), 118.9 (d), 119.5 (d), 122.1 (d), 124.2 (d), 128.2 (s), 128.3 (d), 128.6 (d), 129.0 (d), 137.3 (s), 157.5 (s), and 174.8 p.p.m. (s).

N-*Benzyloxycarbonylglycylaminoethanol* (**8h**). Yield 52%, m.p. 113—114 °C (from ethyl acetate) (Found: C, 57.1; H, 6.4; N, 11.2. $C_{12}H_{16}N_2O_4$ requires C, 57.13; N, 6.39; N, 11.10%); $\nu_{max.}$(KBr) 3 300br, 3 270, 1 675, 1 640, and 1 530 cm^{-1}; $\delta_H(CDCl_3$–$CD_3OD)$ 3.33 (t, 2 H, *J* 4.9 Hz), 3.61 (t, 2 H, *J* 4.9 Hz), 3.80 (s, 2 H), 5.10 (s, 2 H), and 7.33 (s, 5 H); $\delta_C(CDCl_3$–$CD_3OD)$ 42.2 (t), 44.4 (t), 60.9 (t), 67.3 (t), 128.1 (d), 128.4 (d), 128.7 (d), 136.5 (s), 157.6 (s), and 171.0 p.p.m. (s).

N-*Benzyloxycarbonyl*-L-*phenylalanylglycylaminoethanol* (**10**).—Z-Phenylalanylglycine (**9e**) and 2-aminoethanol were coupled using DCC to yield compound (**10**) (35%), m.p. 123.5—124 °C (from ethyl acetate) (Found: C, 62.1; H, 6.25; N, 10.3. $C_{21}H_{25}N_3O_5$ + 0.4 H_2O requires C, 62.04; H, 6.35; N, 10.34%); $[\alpha]_D$ +1.48° (*c* 1.2, methanol); $\nu_{max.}$(KBr) 3 270, 1 670, 1 610, and 1 515 cm^{-1}; $\delta_H(CDCl_3$–$CD_3OD)$ 2.92 (dd, 1 H, *J* 7.8 and 13.7 Hz), 3.16 (dd, 1 H, *J* 6.4 and 13.7 Hz), 3.29 (t, 2 H, *J* 4.9 Hz), 3.61 (t, 2 H, *J* 4.9 Hz), 3.82 (d, 2 H, *J* 12.2 Hz), 4.36 (dd, 1 H, *J* 6.4 and 7.8 Hz), 4.97 (d, 1 H, *J* 12.6 Hz), 5.09 (d, 1 H, *J* 12.7 Hz), and 7.1—7.4 (m, 10 H); $\delta_C(CDCl_3$–$CD_3OD)$ 37.5 (t), 41.7 (t), 43.4 (t),

56.4 (d), 62.4 (t), 66.7 (t), 126.6 (d), 127.4 (d), 127.8 (d), 128.1 (d), 128.2 (d), 128.8 (d), 135.7 (s), 136.1 (s), 156.5 (s), 169.7 (s), and 172.4 p.p.m. (s).

N-*Benzyloxycarbonyl*-L-*phenylalanylglycylglycine* (**11**).—This was obtained from compound (**10**) by Jones' oxidation as described above in 80% yield. Physical properties were compared with those in the literature in the form of the ethyl ester. M.p. 92—94 °C, $[\alpha]_D$ −1.9° (*c* 1.46, methanol) {Lit.,[18] 89.5—91 °C, $[\alpha]_D$ +2.4° (*c* 1, methanol)}. However, an authentic sample obtained independently by coupling of Z-L-phenylalanine with glycylglycine ethyl ester showed m.p. 93—94 °C, $[\alpha]_D$ −1.9° (*c* 1.83, methanol).

Glycylaminoethanol (**12**).—*N*-Z-Glycylaminoethanol (**8h**) and 5% Pd–C (10%) was dissolved in methanol, and the mixture stirred at 90 atm under hydrogen at 70 °C. After 12 h, the catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to give glycylaminoethanol (**12**) as a white solid, which was purified by recrystallization (methanol–ether), m.p. 103—103.5 °C (Found: C, 40.65; H, 8.55; N, 23.5. $C_4H_{10}N_2O_2$ requires C, 40.66; H, 8.53; N, 23.71%); $\nu_{max.}$(KBr) 3 230, 1 640, and 1 540 cm^{-1}; δ_H($CDCl_3$–CD_3OD) 3.1—3.5 (m, 1 H), 3.31 (s, 2 H), 3.36 (t, 2 H, *J* 5.9 Hz), and 3.65 (t, 2 H, *J* 5.9 Hz); δ_C($CDCl_3$–CD_3OD) 42.1 (t), 44.6 (t), 61.1 (t), and 174.4 p.p.m. (s).

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