Homologation of α-amino acids to β-amino acids using Boc_2O

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The use of Boc_2O as a coupling agent in the homologation of *N*-urethane protected-α-amino acid to its β-homomers by the Arndt–Eistert method is described. The homologation gives good yields without racemization. The use of Boc_2O as a coupling agent not only allows the easy scale up of the process but also it is cost effective.

Recently, unnatural polymers with well defined folding propensities have attracted a great deal of attention.[1] Oligomers of β-amino acids (β-peptides) can adopt a variety of secondary structures including helices,[2] sheets[3] and reverse turns[4] depending upon the residue substitution pattern in organic solvents as well as in the solid state. Furthermore, β-peptides are also found to be chemically stable and resistant to enzymatic degradation which may ultimately be useful for the construction of biomimetic polymers.[5] It was recently demonstrated that a β-amino acid analogue of Tat 47–57 translocates across human cell membranes with efficiency comparable to HIV Tat 47–57 itself.[6] Thus, peptides composed of β-amino acids hold particular promise in molecular design.

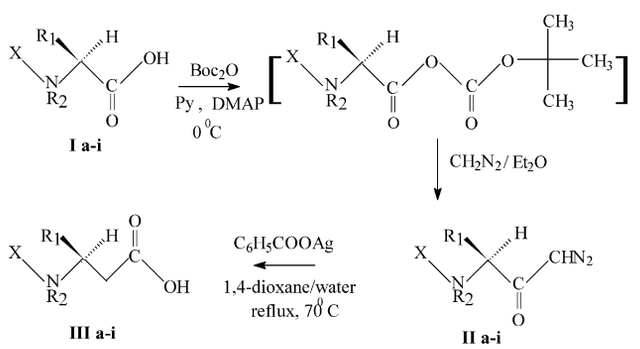
β-Amino acids can be synthesized by homologation of α-amino acids as well as by other routes.[7] The homologation of an α-amino acid to its higher homologue (β^3-amino acid) can be very conveniently carried out using the Arndt–Eistert method in a two step process.[8] The use of mixed anhydride method[9] is now routinely employed, under careful conditions for the synthesis of α-aminodiazoketone derivatives with moderate yields. Unlike the acid chlorides,[10] the utility of acid fluorides[11] and pentafluorophenyl esters[12] led to not only Fmoc-β-amino acids but also Boc- and Z-β-amino acids in good yields. All these routes involve the activation of the carbonyl group of the urethane protected α-amino acid employing either preformed, isolated, and activated derivatives or an *in situ* generated, activated species for acylation of diazomethane.

Alternatively, the use of DCC and related coupling agents like DIC, EDC, *etc.*, as coupling agents has several advantages including activation and acylation to be achieved in a single step.[13] Its employment in peptide synthesis is still particularly relevant in the large scale production of peptides.[14] However, its use for the acylation of diazomethane resulted in only about 30–70% of Pht-/Z-/Boc-aminoacyldiazoketone.[15]

Results and discussion

As a part of our aim to find the effect of incorporation of β-amino acids into the sequential bioelastic polypeptides[16] of the repeating pentamers VPGVG, PGVGV, GVGVP, VGVGP, GVPGV, *etc.*, a cost effective and efficient approach to β-amino acids was required. The use of Boc_2O as a *tert*-butoxy carbonylating agent for the protection of amino groups,[17] alcohols and thiols,[18] *etc.*, and for the synthesis of six Boc-protected dipeptide esters,[19] *etc.*, is well documented. This report deals with its applicability in stereo specific homologation of commercially available urethane protected α-amino acids to their β-homomers.

It has been found that the reaction of diazomethane with Boc-/Z-/Fmoc-α-amino acids could be carried out using Boc_2O at 0 °C in the presence of an equimolar quantity of pyridine and a catalytic amount of 4-dimethylaminopyridine (DMAP). The reaction (Scheme 1) proceeds through the formation of a



	X	R_1	R_2
a:	Fmoc	H	H
b:	Fmoc	$CH(CH_3)_2$	H
c:	Fmoc	CH_2COO^tBu	H
d:	Fmoc	$(CH_2)_4NHBoc$	H
e:	Boc	R_1-R_2 = $(CH_2)_3$	
f:	Boc	$CH(CH_3)CH_2CH_3$	H
g:	Boc	$CH(CH_3)CH_2CH_3$	H
h:	Z	$CH_2C_6H_5$	H
i:	Z	C_6H_5	H

Scheme 1

carbonic–carbonic mixed anhydride which has been identified by the characteristic carbonyl vibrational stretching frequency of the anhydride at 1820 cm^{-1} in the IR spectra. The addition of DMAP results in formation of the reactive *tert*- butoxycarbonyl-4-dimethylaminopyridinium *tert*-butylcarbonate, which facilitates the nucleophilic addition of the amino acid carboxylate anion at the *tert*-butoxy carbonyl group of the pyridinium system, and consequently activates the amino acid carbonyl toward acylation of diazomethane. It is also observed that the rate of reaction is sluggish in the absence of DMAP. A freshly prepared 0.66 M solution of diazomethane in diethyl ether was added to N^{α}-protected amino acid, Boc_2O, pyridine, DMAP mixture in THF at 0 °C, and then the reaction mixture was stirred for 30 min and allowed to warm up to r.t. before workup. The acylation reaction with two equivalents excess of diazomethane results in complete conversion. The course of the reaction was monitored by TLC using chloroform–methanol–acetic acid (45 : 2 : 1, v/v/v) as well as using IR. All the resulting Boc-/Z-/Fmoc-aminoacyldiazoketones (**II a–i**) are isolated as crystalline solids in 85–94% yield. The purity of the com-

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pounds, as checked by HPLC, is satisfactory. They have been fully characterized by using IR which contains characteristic stretching vibrational frequencies at 2100–2108 cm^{-1} of the CHN_2 group and by ^1H NMR.

The compounds **II a**–**i** were then converted to the corresponding β-amino acids by Wolff rearrangement using silver benzoate–1,4-dioxane–water by refluxing the mixture for 6 h at 70 °C. The resulting β-amino acids **III a**–**i** were also characterized.

The acylation of diazomethane using Boc_2O was found to be free from racemization. This was confirmed by comparing the specific rotations of **II f**: $[\alpha]_D^{25}$ (*c* 1, $CHCl_3$ − 60.4), **III f**: $[\alpha]_D^{25}$ (*c* 1, $CHCl_3$ − 24.2) and **II g**: $[\alpha]_D^{25}$ (*c* 1, $CHCl_3$ + 60.14), **III g**: $[\alpha]_D^{25}$ (*c* 1, $CHCl_3$ + 24.8). Furthermore, the HPLC analysis of **II b** (R_t for the L-isomer 17.48 min, R_t for racemic mixture 17.44 min and 18.18 min) and **III b** (R_t for the L-isomer 15.42 min, R_t for racemic mixture 15.36 min and 16.12 min) derived from Fmoc-Val-OH and comparison with the analysis of racemic mixture specifically prepared to test the possible extent of racemization reveals that both acylation of diazomethane using Boc_2O and Wolff rearrangement are free from racemization.

Thus, Boc_2O, a commonly used reagent for the introduction of the Boc group in peptide synthesis, can also conveniently be used for the homologation of urethane protected α-amino acids to β-amino acids with good yield and without racemization. In contrast to the method with DCC, the removal of side products (CO_2 and ^{t}BuOH) in the present method poses no practical problems. This is a simple procedure, which allows the easy scale up of the process to make large quantities of β-amino acids.

Experimental

All the solvents were freshly distilled prior to use. Melting points were recorded by capillary method and are uncorrected. TLC analysis was carried out on precoated silica gel plates using solvent system chloroform–methanol–acetic acid (45 : 2 : 1, v/v/v). IR spectra were recorded on a Nicolet model impact 400D FT-IR spectrometer (KBr pellets). HPLC analysis was performed with a Waters LC-3000 system consisting of a 484 tunable absorbance UV detector and a Millipore 745 data modulae using a C18 Bondapack (3.9 × 300 mm, 10μ) and chiralcel OD (4.6 × 250 mm, 10μ) columns with a linear gradient of water (0.1% TFA) and acetonitrile (0.1% TFA), with acetonitrile from 20% to 90% over 25 min. Optical rotations were determined using automatic AA-10 polarimeter (Optical Activity, UK) and are given in 10^{-1} deg cm^2 g^{-1}. Elemental analyses were carried out on a Perkin-Elmer analyzer. ^1H NMR spectra were recorded using a Bruker AMX 400 MHz spectrometer. The diazomethane solution in dry diethyl ether was prepared from *N*-methyl-*N*-nitrosotoluene-*p*-sulfonamide using a reported procedure.[20,21] The concentration of diazomethane solution was estimated by back-titration with benzoic acid solution.[22]

General procedure for the synthesis of N^{α}-urethane protected aminodiazoketone

To a stirred solution of N^{α}-protected amino acid (5 mmol), pyridine (0.4 mL, 5 mmol), Boc_2O (1.05 g, 5.5 mmol) and a catalytic amount of DMAP (0.012 g) in THF (15 mL), diazomethane in diethyl ether (15 mL) was added at 0 °C and stirred for about 30 min. The solvent was evaporated and the residue was dissolved in $CHCl_3$. It was washed thrice using 5 mL portions of 5% $NaHCO_3$, 5% HCl or citric acid and water, and then the organic phase was dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure and recrystallization of the resulting residue from hexane gave the title compound as a crystalline solid.

Fmoc-glycyldiazomethane (II a). 1.5 g (5 mmol) of **I a**, after the reaction gave 1.44 g (89%) of **II a**; mp 148 °C; Anal. Calc. for $C_{18}H_{15}N_3O_3$ (321.29): C, 67.28; H, 4.67; N, 13.08; Found C, 67.35; H, 4.62; N, 13.15%; IR $\nu_{max.}$ cm^{-1} 2104 (CHN_2), 1690 (CO urethane); ^1H NMR (δ, $CDCl_3$): 2.7 (2H, t), 4.25 (1H, *J* = 6.5, t), 4.60 (2H, d), 5.42 (1H, d), 5.5 (1H, *J* = 8.3, d) and 7.26–7.8 (8H, m).

Fmoc-L-valyldiazomethane (II b). 1.70 g (5 mmol) of **I b**, after the reaction gave 1.72 g (94%) of **II b**; mp 123–124 °C; Anal. Calc. for $C_{21}H_{21}N_3O_3$ (365.42): C, 69.41; H, 5.81; N, 11.56; Found C, 69.48; H, 5.82; N, 11.65%; IR $\nu_{max.}$ cm^{-1} 2106 (CHN_2), 1690 (CO urethane); ^1H NMR (δ, $CDCl_3$): 0.90 (3H, *J* = 6.5, d), 1.10 (3H, *J* = 6.5, d), 2.15 (1H, m), 4.10 (1H, m), 4.25 (1H, *J* = 6.6, t), 4.4 (2H, d), 5.25 (1H, s), 5.4 (1H, d) and 7.30–7.8 (8H, m).

Fmoc-L-aspartyl-(O^{t}Bu)-diazomethane (II c). 2.05 g (5 mmol) of **I c**, after the reaction gave 1.92 g (88%) of **II c**; mp 73 °C; Anal. Calc. for $C_{24}H_{25}N_3O_5$ (435.42): C, 66.20; H, 5.74; N, 9.65; Found C, 66.28; H, 5.64; N, 9.73%; IR $\nu_{max.}$ cm^{-1} 2105 (CHN_2), 1745 (O^{t}But), 1703 (CO urethane); ^1H NMR (δ, $CDCl_3$): 1.4 (9H, s), 2.0 (1H, m), 2.45 (2H, m), 4.32 (2H, d), 4.5 (1H, *J* = 6.6, m), 5.4 (1H, s), 5.5 (1H, *J* = 7.8, d) and 7.3–7.8 (8H, m).

Fmoc-L-lysyl-(N^{ε}Boc)-diazomethane (II d). 2.34 g (5 mmol) of **I d**, after the reaction gave 2.23 g (90.6%) of **II d**; mp 96 °C; Anal. Calc. for $C_{27}H_{32}N_4O_5$ (492.52): C, 65.8; H, 6.54; N, 11.37; Found C, 64.86; H, 6.64; N, 11.45%; IR $\nu_{max.}$ cm^{-1} 2106 (CHN_2), 1700, 1690 (CO urethanes); ^1H NMR (δ, $CDCl_3$): 1.3 (9H, s), 2.22 (8H, m), 4.16 (2H, *J* = 6.5, t), 4.24 (2H, d), 5.25 (1H, s), 5.63 (1H, br), 6.0 (1H br) and 7.25–7.8 (8H, m).

Boc-L-prolyldiazomethane (II e). 1.075 g (5 mmol) of **I e**, after the reaction gave 1.03 g (86%) of **II e**; mp 44 °C; Anal. Calc. for $C_{11}H_{17}N_3O_3$ (239.24): C, 55.22; H, 7.5; N, 17.56; Found C, 55.68; H, 7.34; N, 17.48%; IR $\nu_{max.}$ cm^{-1} 2105 (CHN_2), 1690 (CO urethane); ^1H NMR (δ, $CDCl_3$): 1.4 (9H, s), 2.4 (4H, m), 3.45 (2H, t), 4.2 (1H, q) and 5.30 (1H, s).

Boc-L-isoleucyldiazomethane (II f). 1.55 g (5 mmol) of **I f**, after the reaction gave 1.12 g (87.8%) of **II f**; mp 86 °C; Anal. Calc. for $C_{12}H_{21}N_3O_3$ (255.28): C, 56.45; H, 8.28; N, 16.45; Found C, 56.28; H, 8.34; N, 16.48%; IR $\nu_{max.}$ cm^{-1} 2107 (CHN_2), 1700 (CO urethane); ^1H NMR (δ, $CDCl_3$): 0.9 (3H, *J* = 7.5, t), 0.93 (3H, *J* = 7.1, d), 1.32 (11H, m), 1.5 (1H, m), 4.24 (1H, m), 5.3 (1H, s) and 5.42 (1H, *J* = 8.3, d).

Boc-D-isoleucyldiazomethane (II g). 1.55 g (5 mmol) of **I g**, after the reaction gave 1.18 g (92.5%) of **II g**; mp 85–86 °C; Anal. Calc. for $C_{12}H_{21}N_3O_3$ (255.28): C, 56.45; H, 8.28; N, 16.45; Found C, 56.32; H, 8.30; N, 16.50%; IR $\nu_{max.}$ cm^{-1} 2107 (CHN_2), 1700 (CO urethane); ^1H NMR (δ, $CDCl_3$): 0.9 (3H, *J* = 7.5, t), 0.93 (3H, *J* = 7.1, d), 1.3 (11H, m), 1.55 (1H, m), 4.24 (1H, m), 5.35 (1H, s) and 5.45 (1H, *J* = 8.3, d).

Z-L-phenylalanyldiazomethane (II h). 1.5 g (5 mmol) of **I h**, after the reaction gave 1.54 g (95%) of **II h**; mp 82 °C; Anal. Calc. for $C_{18}H_{17}N_3O_3$ (315.30): C, 66.86; H, 5.29; N, 12.99; Found C, 66.3; H, 5.8; N, 13.28%; IR $\nu_{max.}$ cm^{-1} 2107 (CHN_2), 1700 (CO urethane); ^1H NMR (δ, $CDCl_3$): 2.9 (2H, d), 4.6 (1H, m), 5.05 (2H, s), 5.1 (1H, s), 5.4 (1H, *J* = 5.9, d) and 7.3–7.8 (10H, m).

Z-L-phenylglycyldiazomethane (II i). 1.45 g (5 mmol) of **I i**, after the reaction gave 1.38 g (89%) of **II i**; mp 88 °C; Anal. Calc. for $C_{17}H_{15}N_3O_3$ (309.27): C, 66.01; H, 4.88; N, 13.58; Found C, 66.08; H, 4.9; N, 13.60%; IR $\nu_{max.}$ cm^{-1} 2106 (CHN_2), 1690 (CO urethane); ^1H NMR (δ, $CDCl_3$): 4.5 (1H, br), 5.03 (2H, s), 5.3 (1H, s), 5.42 (1H, *J* = 5.8, d) and 7.3 (10H, m).

General procedure for the synthesis of N^{α}-protected-β-homo-amino acids

N^{α}-Protected aminoacyldiazoketone (**II a**–**i**) (5 mmol) in 1,4-dioxane (15 mL) and water (10 mL) was treated with silver benzoate (20 mg, 0.08 mmol). The reaction mixture was refluxed at 70 °C for 6 h and then filtered. The solvent was evaporated under reduced pressure. The residue was dissolved in saturated aqueous Na_2CO_3 solution (50 mL) and stirred, the mixture was washed with diethyl ether (3 × 30 mL). The aqueous layer was acidified to pH 2 using HCl–citric acid and extracted using EtOAc (3 × 30 mL). The organic layer was washed with water, dried over Na_2SO_4 and evaporated to get the title compound in good yield.

Fmoc-β-homoglycine (III a). 1.625 g (5 mmol) of **II a**, after the rearrangement gave 1.26 g (80%) of **III a**; mp 148 °C; Anal. Calc. for $C_{18}H_{17}NO_4$ (311.29): C, 69.45; H, 5.46; N, 4.50; Found C, 69.52; H, 5.42; N, 4.58%; ^{1}H NMR (δ, $CDCl_3$): 2.75 (2H, t), 3.46 (2H, m), 4.3 (1H, J = 6.6, t), 4.6 (2H, d), 5.52 (1H, J = 8.4, d), 7.2–7.8 (8H, m) and 8.6 (1H, br).

Fmoc-L-β-homovaline (III b). 1.826 g (5 mmol) of **II b**, after the rearrangement gave 1.35 g (76%) **III b**; mp 155 °C; Anal. Calc. for $C_{21}H_{23}NO_4$ (353.38): C, 70.14; H, 5.89; N, 4.30; Found C, 70.23; H, 5.76; N, 4.38%; ^{1}H NMR (δ, $CDCl_3$): 0.9 (6H, J = 6.2, d), 1.8 (1H, m), 2.32 (1H, d), 2.45 (1H, d), 3.8 (1H, m), 4.2 (1H, J = 6.6, t), 4.42 (2H, J = 6.6, d), 5.9 (1H, J = 9.2, d) and 7.3–7.8 (8H, m).

Fmoc-L-β-homoaspartic(O^{t}Bu) acid (III c). 2.175 g (5 mmol) of **II c**, after the rearrangement gave 1.684 g (79%) of **III c**; mp 85 °C; Anal. Calc. for $C_{24}H_{27}NO_6$ (425.41): C, 67.76; H, 6.35; N, 3.29; Found C, 67.64; H, 6.48; N, 3.43%; ^{1}H NMR (δ, $CDCl_3$): 1.4 (9H, s), 2.6 (2H, J = 5.2, d), 2.73 (2H, d), 4.2 (1H, t), 4.4 (3H, m), 6.5 (1H, J = 9.2, d) and 7.2–7.8 (8H, m).

Fmoc-L-β-(N^{ε}-Boc)-homolysine (III d). 2.462 g (5 mmol) of **II d**, after the rearrangement gave 1.82 g (75%) of **III d**; mp 95 °C; Anal. Calc. for $C_{27}H_{34}N_2O_6$ (482.52): C, 64.6; H, 6.53; N, 5.38; Found C, 64.42; H, 6.48; N, 5.32%; ^{1}H NMR (δ, $CDCl_3$): 1.5 (9H, s), 2.1 (8H, m), 2.32 (2H, J = 5.0, d), 2.45 (1H, d), 4.2 (1H, J = 6.8, t), 4.35 (2H, d), 5.62 (1H, br) and 7.25–7.8 (9H, m).

Boc-L-β-homoproline (III e). 1.195 g (5 mmol) of **II e**, after the rearrangement gave 0.92 g (80%) of **III**; gum; Anal. Calc. for $C_{11}H_{19}NO_4$ (229.23): C, 57.87; H, 8.38; N, 6.13; Found C, 57.64; H, 8.58; N, 5.92%; ^{1}H NMR (δ, $CDCl_3$): 1.30 (9H, s), 2.0 (4H, m), 2.4 (2H, d), 3.42 (2H, t), 3.85 (1H, m) and 8.3 (1H, br).

Boc-L-β-homoisoleucine (III f). 1.275 g (5 mmol) of **II f**, after rearrangement gave 0.98 g (80%) of **III f**; mp 86 °C; Anal. Calc. for $C_{12}H_{23}NO_4$ (245.28): C, 58.99; H, 9.48; N, 5.73; Found C, 58.86; H, 9.56; N, 5.68%; ^{1}H NMR (δ, $CDCl_3$): 0.9 (3H, J = 7.2, t), 0.93 (3H, J = 6.8, d), 1.32 (11H, m), 1.5 (1H, m), 2.35 (2H, d), 3.5 (1H, m), 5.4 (1H, br) and 8.3 (1H, br).

Boc-D-β-homoisoleucine (III g). 1.275 g (5 mmol) of **II g**, after rearrangement gave 1.02 g (83%) **III g**; mp 87 °C; Anal. Calc. for $C_{12}H_{23}NO_4$ (245.28): C, 58.99; H, 9.48; N, 5.73; Found C, 58.92; H, 9.52; N, 5.8%; ^{1}H NMR (δ, $CDCl_3$): 0.89 (3H, J = 7.2, d), 0.92 (3H, J = 6.8, d), 1.32 (11H, m), 1.5 (1H, m), 2.3 (2H, d), 3.55 (1H, m), 5.42 (1H, br) and 8.32 (1H, br).

Z-L-β-homophenylalanine (III h). 1.62 g (5 mmol) of **II h**, after rearrangement gave 1.32 g (84%) of **III h**; mp 84 °C; Anal. Calc. for $C_{18}H_{19}NO_4$ (313.31): C, 69.21; H, 6.13; N, 4.48; Found C, 68.92; H, 6.18; N, 4.35%; ^{1}H NMR (δ, $CDCl_3$): 2.30 (2H, d), 2.75 (2H, d), 3.82 (1H, m), 5.01 (2H, s), 5.28 (1H, J = 5.9, d), 7.10 (5H, s), 7.28 (5H, s) and 9.4 (1H, br).

Z-L-β-homophenylglycine (III i). 1.55 g (5 mmol) of **II i**, after rearrangement gave 1.2 g (82%) of **III i**; mp 86–88 °C; Anal. Calc. for $C_{17}H_{17}NO_4$ (303.27): C, 68.44; H, 5.74; N, 4.95; Found C, 68.32; H, 5.82; N, 5.02%; ^{1}H NMR (δ, $CDCl_3$): 2.5 (2H, d), 4.3 (1H, m), 5.02 (2H, s), 5.4 (1H, J = 5.8, d), 7.2 (10H, s) and 8.6 (1H, br).

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References

1 (*a*) D. Seebach and J. L. Mathews, *Chem. Commun.*, 1997, 2015; (*b*) R. P. Cheng, S. H. Gellman and W. F. DeGrado, *Chem. Rev.*, 2001, **101**, 3219; (*c*) S. H. Gellman, *Acc. Chem. Res.*, 1998, **31**, 173.
2 (*a*) F. Lopez-Carrasquero, C. Aleman and S. Munoz-Guerra, *Biopolymers*, 1995, **36**, 263; (*b*) D. H. Apella, L. A. Christianson, D. A. Klein, D. R. Powell, X. Huang, J. J. Barchi and S. H. Gellman, *Nature*, 1997, **387**, 381.
3 (*a*) J. S. Nowick, E. M. Smith, J. W. Ziller and A. J. Shaka, *Tetrahedron*, 2002, **58**, 727; (*b*) C. K. Smith and L. Regan, *Acc. Chem. Res.*, 1997, **30**, 153; (*c*) J. H. Miwa, A. K. Patel, N. Vivatrat, S. M. Popek and A. M. Meyer, *Org. Lett.*, 2001, **3**, 3373.
4 B. R. Huck, J. D. Fisk and S. H. Gellman, *Org. Lett.*, 2000, **2**, 2607.
5 (*a*) D. Seebach, M. Overhand, F. N. M. Kuhnle, B. Martinoni, L. Oberer, U. Hommel and H. Widmer, *Helv. Chim. Acta*, 1996, **79**, 913; (*b*) Y. Hamuro, J. P. Schneider and W. F. DeGrado, *J. Am. Chem. Soc.*, 1999, **121**, 12200.
6 N. Umezawa, M. A. Gelman, M. C. Haigis, R. T. Rainer and S. H. Gellman, *J. Am. Chem. Soc.*, 2002, **124**, 368.
7 E. Juaristi, *Enantioselective synthesis of β-amino acids*, Wiley-VCH, New York, 1997.
8 (*a*) T. Ye and M. A. McKervey, *Chem. Rev.*, 1994, **94**, 1091; (*b*) D. C. Cole, *Tetrahedron*, 1994, **32**, 9517.
9 (*a*) G. Guichard, S. Abele and D. Seebach, *Helv. Chim. Acta*, 1998, **81**, 187; (*b*) S. Abele, G. Guichard and D. Seebach, *Helv. Chim. Acta*, 1998, **81**, 2141; (*c*) A. Heinsoo, G. Raidaru, K. Linask, J. Jarv, M. Zetterstruom and U. Langel, *Tetrahedron: Asymmetry*, 1995, **6**, 2245; (*d*) E. P. Ellmerer-Muller, D. Brossner, N. Maslouch and A. Tako, *Helv. Chim. Acta*, 1998, **81**, 59; (*e*) A. Muller, C. Vogt and N. Sewald, *Synthesis*, 1998, 837.
10 A. Leggio, A. Liguori, A. Procopio and G. Sindona, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1969.
11 K. Ananda, H. N. Gopi and V. V. Suresh Babu, *J. Pept. Res.*, 2000, **55**, 289.
12 (*a*) V. V. Suresh Babu, H. N. Gopi and K. Ananda, *J. Pept. Res.*, 1999, **53**, 308; (*b*) V. V. Suresh Babu and H. N. Gopi, *Lett. Pept. Sci.*, 1999, **6**, 173.
13 M. Bodanszky, *Principles of Peptide Synthesis*, Springer-Verlag, New York, 1984.
14 L. Andersson, L. Blomberg, M. Flegel, L. Lepsa, B. Nilsson and M. Verlander, *Biopolymers*, 2000, **55**, 227.
15 B. Penke, J. Czombos, L. Balaspiri, J. Petress and K. Kovacs, *Helv. Chim. Acta*, 1970, **53**, 1057.
16 D. W. Urry, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 819.
17 D. S. Tarbell, Y. Yamamoto and B. M. Pope, *Proc. Natl. Acad. Sci. USA*, 1992, **69**, 730.
18 M. Wakselman, *Encyclopedia of Reagents for Organic Synthesis*, ed. L. A. Paquette, John-Wiley and Sons, Inc., New York, 1995, vol. 3, pp. 1602–1608.
19 D. K. Mahapatra and A. Datta, *J. Org. Chem.*, 1999, **64**, 6879.
20 B. S. Furniss, A. J. Hannaford, P. W. G. Smith and A. R. Tatchell, *Vogel's Textbook of Practical Organic Chemistry*, Educational Low-Priced Books Scheme, ELBS, Longmann, UK, Fifth edn., 1994, p. 430.
21 **Caution**: The preparation of diazomethane solution should be carried out only in a fume cupboard with a powerful exhaust system.
22 F. Arndt, *Org. Synth.*, 1943, **Col. Vol. 2**, p. 165.