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Homologation of α-amino acids to β-amino acids using Fmoc-amino acid pentafluorophenyl esters

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Abstract: The homologation of α-amino acids to β-amino acids by the two-step Arndt–Eister method is achieved by using Fmoc-α-amino acid pentafluorophenyl esters for the acylation of diazomethane, synthesizing the key intermediates Fmoc-aminoacyldiazomethanes as crystalline solids in good yields and purity.

There has been an increasing interest in the development of new synthetic routes to β-amino acids, mainly due to their role as structural units of modified peptides. Recent results from the groups of Seebach (1, 2) and Gellman (3–5) revealed that β-peptides also have stable secondary structures like their α-peptide counterparts. Some β-peptides are also found to be stable towards α-peptidases. They are also good candidates for protein folding (6). The building blocks for the synthesis of such peptides are β-amino acids (β-substituted β-amino acids). The homologation of the commercially available crystalline, optically pure α-amino acids to β-amino acids by the Arndt–Eister method is accomplished by employing α-aminoacyldiazomethanes as the key reactive intermediates (7–10). These optically active substrates are then converted to the corresponding β-amino acids by the Wolff rearrangement with retention of configuration (7–10). The acylation of diazomethane remains the single most important route for the preparation of α-aminoacyldiazomethanes (7–10). N^{α}-Boc and Z-protected α-aminoacyldiazomethane derivatives were synthesized earlier by an *in situ* mixed anhydride procedure using isobutyloxycarbonyl chloride or ethyl chlorocarbonate (11–13). This method is being followed in spite of several known

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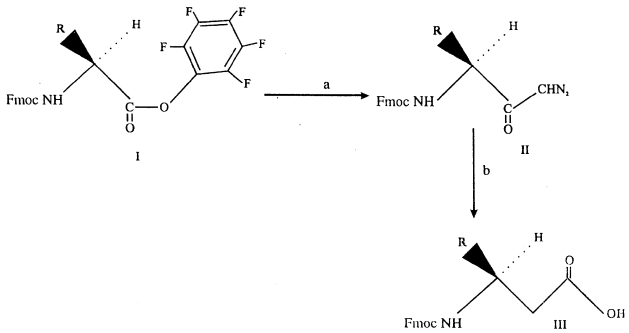
difficulties concerning their preparation and use (14). As the instability of Boc-/Z-amino acid chlorides is well known, the acid chloride method was utilized when a ethoxycarbonyl group was employed for N-protection earlier (15). However, Leggio *et al*. have recently described the synthesis of five β-amino acids employing Fmoc-amino acid chlorides (16). We have also accomplished the synthesis of several β-amino acids including nipecotic acid and isonipecotic acid through acid chloride method (17).



Compound No.	R	Compound No.	R
a	CH_3	g	$(CH_2)_2CH_3$
b/c	$CH_2CH(CH_3)_2$	h	CH_2Ph
d/e	$(CH_2)_3CH_3$	i	$(CH_2)_4NH(Boc)$
f	$CH(CH_3)_3$		

Results and Discussion

In continuation of our studies on the development of new methodologies for the preparation of α-aminoacyldiazomethanes, 'active esters' of protected amino acids are explored as starting materials.

Fmoc-amino acid pentafluorophenyl esters (18–21) can be made easily and are also commercially available and crystalline compounds. Their utility for peptide bond formation in both solution as well as in solid-phase methods is well documented (22–25). They have been used for the incorporation of Gln/Asn and several other sterically hindered amino acids also with or without the use of HOBt and/or a base (26). This paper describes the use of the pentafluorophenyl esters of Fmoc-amino acids for the synthesis of β-amino acids (Fig. 1). It is found that the acylation of diazomethane can be achieved by using N^{α}-Fmoc-α-amino acid pentafluorophenyl esters in dry THF in presence of an equimolar quantity of a tertiary base like triethylamine or N-methylmorpholine (Fig. 1). The reaction is complete in about 45 min. All the resulting Fmoc-α-aminoacyldiazomethane derivatives (**IIa-i**) are obtained in almost quantitative yields. They are converted to β-amino acids (**IIIa-i**) in presence of silver benzoate.

Although N-nitroso-N-methylurea was recommended as the precursor for the generation of diazomethane (27, 28), N-methyl-N-nitroso toluene-p-sulphonamide was used (29). The former is known to decompose in an explosion-like fashion when stored for several hours at ambient temperature. It is also reported that N-methyl-N-nitrosourea does not allow the complete removal of water from ethereal solution (7–10). The formation of the acid–base type HOH———CH_2N_2 adduct can promote several side reactions. N-Methyl-N-nitroso-toluene-p-sulphonamide (m.p., 58–60°) was prepared by nitrosation of N-methyl-toluene-p-sulphonamide (m.p., 80°), which was obtained using 40% methylamine and p-toluenesulphonyl chloride. It was heated as and when required, in the presence of alcoholic KOH to generate diazomethane.

Our initial attempts to acylate diazomethane using 2,4,5-trichlorophenyl esters of Fmoc-amino acids (30, 31) with diazomethane in the presence of a base, even after stirring for several hours were unsuccessful (as monitored by TLC and IR). On the other hand, it was found that pentafluorophenyl esters of Fmoc-amino acids react with diazomethane vigorously. As the reaction proceeds the pH of the reaction mixture becomes acidic. The liberated pentafluorophenol probably reacts with diazomethane. Consequently the product formation stopped at one stage (as monitored by TLC) and did not result in any further progress. Although the IR analysis (presence of a characteristic CO stretching frequency of $COCHN_2$ around 2100 cm^{-1}) clearly indicated the formation of α-aminoacyldiazomethanes, it resulted in poor yields even after adding an additional quantity of diazomethane and then extending the reaction duration. Finally, Fmoc-amino acid pentafluorophenyl esters were added to the saturated solution of diazomethane in dry THF in the presence of an equimolar quantity of triethylamine. It was found that the reaction proceeded to completion satisfactorily.

There were no detectable amounts of amino free substances in any of the acylation reactions. All the Fmoc-amino acid diazoketones (**IIa-i**) prepared were obtained as crystalline solids. As the reaction was carried out in dry THF, none of the products were found to contain the corresponding methyl esters. This was indicated by the absence of peaks at around 1740 cm^{-1} in IR. The Fmoc-α-aminoacyldiazomethane derivatives were converted to the corresponding Fmoc-β-amino acids using catalytic amounts

of silver benzoate in dioxane/water by refluxing the mixture for nearly 3–4 h. Employing these conditions, all Fmoc-β-amino acids were isolated in good yields.

Thus the commercially available, optically pure, crystalline, Fmoc-amino acid pentafluorophenyl esters can be used as substrates for the synthesis of optically active Fmoc-α-amino acid diazomethanes in good yields and purity.

Experimental Procedures

Solvents and reagents were purified by standard procedures and were distilled prior to use. The melting points were determined using a Lietz-Wetzlar melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet model Impact 400D FTIR spectrometer (KBr pellets, 3 cm^{-1} resolution). ^1H NMR spectra were recorded on a Brucker ACF 200 MHz spectrometer using Me_4Si as an internal standard. Optical rotations were measured with an automatic AA-10 polarimeter (Optical Activity, UK). Elemental analyses were recorded using a Perkin Elmer Analyser and the samples were dried for 24 h under vacuum before analysis. The TLC analysis was carried on precoated silica gel plates using solvent systems. (i) ethyl acetate/hexane (35 : 65, v/v) (ii) $CHCl_3$/methanol/acetic acid (40 : 2:1, v/v) and (iii) $CHCl_3$/methanol (9 : 1, v/v) and R_f values designated as R_fA, R_fB and R_fC, respectively. N-Fmoc-α-amino acid pentafluorophenyl esters were prepared from the corresponding N-Fmoc-α-amino acid and pentafluorophenol in dry THF, followed by addition of dicyclohexylcarbodiimide at 0°C and the products were isolated in the usual manner (32). The diazomethane solution in dry THF was prepared from N-methyl-N-nitroso-toluene-p-sulphonamide, using reported procedures (29).

Synthesis of N-Fmoc-α-amino acyldiazomethanes

General method

Diazomethane gas was passed into an ice-cold solution of N-Fmoc-α-amino acid pentafluorophenyl ester (1 mmol) and triethylamine (TEA, 1 mmol) in anhydrous THF (50 mL) until saturation. The reaction mixture was stirred at room temperature for about 45 min. The course of the reaction was monitored by TLC. The mixture was washed with 5% $NaHCO_3$, 5% HCl and water and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure. The resulting oily residue was precipitated using ethyl acetate/hexane.

N-Fmoc-L-alanyldiazomethane (IIa)

Diazomethane gas was passed through a cold solution of N-Fmoc-L-alanylpentafluorophenyl ester (0.49 g, 1 mmol) and TEA (0.15 mL, 1 mmol) in THF (50 mL). Yield, 0.3 g, (93%); m.p., 110–112°C; R_fA, 0.58; R_fB, 0.84; $[\alpha]^{25}{}_D$ – 32.0° (c = 1, $CHCl_3$); Anal. Calc. for $C_{19}H_{17}N_3O_3$ (335.3): C, 68.05; H, 5.11; N, 12.53; Found: C, 68.11; H, 5.28; N, 12.48%. IR ν_{max} (KBr disk)/cm^{-1}: 3314 (NH), 2121 (CHN_2), 1692 (CO urethane) and 1636 (COCH); ^1H NMR (δ, $CDCl_3$): 1.32 (3H, d, CH_3CH), 4.1 (2H, br, $CHCH_3$ and CH Fmoc), 4.5 (2H, d, CH_2O), 5.25 (1H, s, CHN_2), 5.49 (1H, br, NH) and 7.2–7.7 (8H, m, aryl).

N-Fmoc-L-leucyldiazomethane (IIb)

Diazomethane was passed through a cold solution of N-Fmoc-L-leucylpentafluorophenyl ester (0.519 g, 1 mmol) and TEA (0.15 mL, 1 mmol) in THF (50 mL). Yield, 0.36 g (96%); m.p., 91–92°C; R_fA, 0.60; R_fB, 0.81; $[\alpha]^{25}{}_D$ – 42.50 (c = 1, $CHCl_3$); Anal. Calc. for $C_{22}H_{23}N_3O_3$ (377.4): C, 70.0; H, 6.14; N, 11.13; Found: C, 70.04; H, 6.19; N, 11.20%. IR ν_{max} (KBr disk)/cm^{-1}: 3307 (NH), 2107 (CHN_2), 1709 (CO urethane) and 1547 (COCH); ^1H NMR. (δ, $CDCl_3$): 0.93 [6H, d, $CH(CH_3)(CH_3)$], 1.3–1.5 (3H, m, CH_2CH), 4.2 (2H, m, CHCO and CH Fmoc), 4.53 (2H, d, CH_2O), 5.2 (1H, s, CHN_2), 5.5 (1H, br, NH), 7.2–7.7 (8H, m, aryl).

N-Fmoc-D-leucyldiazomethane (IIc)

Diazomethane gas was passed through a cold solution of N-Fmoc-D-leucylpentafluorophenyl ester (0.51 g, 1 mmol) and TEA (0.15 mL, 1 mmol) in THF (50 mL). Yield, 0.35 g, (92%); m.p., 92–93°C; R_fA, 0.61; R_fB, 0.79; $[\alpha]^{25}{}_D$ + 42.1° (c = 1, $CHCl_3$); Anal.Calc. for $C_{22}H_{23}N_3O_3$ (377.4): C, 70.0; H, 6.14; N, 11.13; Found: C, 70.09; H, 6.08; N, 11.24%. IR ν_{max} (KBr disk)/cm^{-1}: 3328 (NH), 2102 (CHN_2), 1699 (CO urethane and 1647 (COCH); ^1H NMR (δ, $CDCl_3$): 0.9 [6H, d, $CH(CH_3)(CH_3)$], 1.3–1.5 (3H, m, CH_2CH), 4.2 (2H, m, CHCO and CH Fmoc), 4.4 (2H, d, CH_2O), 5.1 (1H, s, CHN_2), 5.5 (1H, br, NH), 7.2–7.7 (8H, m, aryl).

N-Fmoc-L-norleucyldiazomethane (α-amino-*n*-L-caproic acid, IId)

Diazomethane gas was passed through a cold solution of N-Fmoc-L-norleucyl pentafluorophenyl ester (0.53 g, 1 mmol) and TEA (0.15 mL, 1 mmol) in THF (50 mL). Yield 0.31 g, (93%), m.p., 120–122°; R_fA, 0.66; R_fB, 0.83; $[\alpha]^{25}{}_D$ – 37.8° (c = 1, $CHCl_3$); Anal. Calc. for $C_{22}H_{23}N_3O_3$ (377.4): C, 70.0; H, 6.14; N, 11.13; Found: C, 70.12; H, 6.19; N, 11.24%. IR ν_{max} (KBr disk)/cm^{-1}: 3317 (NH), 2112 (CHN_2), 1698 (CO urethane) and 1641 (COCH); ^1H NMR (δ, $CDCl_3$): 0.90 [9H, m $(CH_2)_3CH_3$], 3.9 (1H, d, NHCH), 4.1 (2H, m, CHCO and

CH Fmoc), 4.5 (2H, d, CH_2O), 5.1 (1H, s, CHN_2), 5.6 (1H, br, NH), 7.2–7.8 (8H, m, aryl).

N-Fmoc-D-norleucyldiazomethane (α-amino-*n*-D-caproic acid, **IIe**)

Diazomethane gas was passed through a cold solution of N-Fmoc-D-norleucylpentafluorophenyl ester (0.53 g, 1 mmol) and TEA (0.15 mL, 1 mmol) in THF (50 mL). Yield, 0.3 g, (90%). m.p., 120–122°C; R_fA, 0.64; R_fB, 0.85; $[\alpha]^{25}{}_D$ + 38.2° (c = 1, $CHCl_3$); Anal. Calc. for $C_{22}H_{23}N_3O_3$ (377.4): C, 70.0; H, 6.14; N, 11.13; Found: C, 70.28; H, 5.98; N, 11.31%. IR ν_{max} (KBr disk)/cm^{-1}: 3294 (NH), 2122 (CHN_2), 1713 (CO urethane) and 1641 (COCH); ^1H NMR (δ, $CDCl_3$): 0.8–0.9 [9H, m $(CH_2)_3CH_3$], 4.0 (1H, d, NHCH), 4.2 (2H, m, CHCO and CH Fmoc), 4.6 (2H, d, CH_2O), 5.1 (1H, s, CHN_2), 5.5 (1H, br, NH), 7.2–7.8 (8H, m, aryl).

N-Fmoc-L-valyldiazomethane (**IIf**)

Diazomethane gas was passed through a cold solution of N-Fmoc-L-valylpentafluoropehenyl ester (0.50 g, 1 mmol) and TEA (0.15 mL, 1 mmol) in THF (50 mL). Yield, 0.40 g, (97%); m.p., 123–125°; R_fA, 0.68; R_fB, 0.82; $[\alpha]^{25}{}_D$ – 23.0° (c = 1, $CHCl_3$); Anal. Calc. for $C_{21}H_{21}N_3O_3$ (365.42): C, 69.41; H, 5.81; N, 11.56; Found: C, 69.53; H, 5.88; N, 11.62%. IR ν_{max} (KBr disk)/cm^{-1}: 3298 (NH), 2102 (CHN_2), 1686 (CO urethane) and 1631 (COCH); ^1H NMR (δ, $CDCl_3$): 0.90 [6H, d, $CH(CH_3)(CH_3)$], 1.75 (1H, m, NHCH), 4.25 (1H, m, CH Fmoc), 4.45 (2H, m, CH_2O), 5.30 (1H, s, CHN_2), 5.4 (1H, d, NH) and 7.3–7.9 (8H, m, aryl).

N-Fmoc-D-norvalyldiazomethane (α-aminovaleric acid, **IIg**)

Diazomethane gas was passed through a cold solution of N-Fmoc-D-norvalylpentafluorophenyl ester (0.50 g, 1 mmol) and TEA (0.15 mL, 1 mmol) in THF (50 mL). Yield, 0.32 g, (95%); m.p., 111–115°; R_fA, 0.59; R_fB, 0.78; $[\alpha]^{25}{}_D$ + 27.2° (c = 1, $CHCl_3$); Anal. Calc. for $C_{21}H_{21}N_3O_3$ (365.42): C, 69.41; H, 5.81; N, 11.56; Found: C, 69.38; H, 5.89; N, 11.48%. IR ν_{max} (KBr disk)/cm^{-1}: 3328 (NH), 2112 (CHN_2), 1690 (CO urethane) and 1647 (COCH); ^1H NMR (δ, $CDCl_3$): 0.85–1.4 [7H, m $(CH_2)_2CH_3$], 3.2 (1H, d, NHCH), 4.1 (2H, t, CH Fmoc), 4.2 (2H, d, CH_2O), 5.1 (1H, s, CHN_2), 5.6 (1H, br, NH), 7.2–7.8 (8H, m, aryl).

N-Fmoc-L-phenlalanyldiazomethane (**IIh**)

Diazomethane gas was passed through a cold solution of N-Fmoc-L-phenylalanylpentafluorophenyl ester (0.57 g, 1 mmol) and TEA (0.15 mL, 1 mmol) in THF (50 mL). Yield, 0.38 g, (92%); m.p., 136–137°; R_fA, 0.61; R_fB, 0.79; $[\alpha]^{25}{}_D$ + 16.3° (c = 1, $CHCl_3$) Anal. Calc. for $C_{25}H_{23}N_3O_3$ (413.46): C, 72.60; H, 5.60; N, 10.16; Found: C, 71.89; H, 5.57; N, 10.21%. IR ν_{max} (KBr disk)/cm^{-1}: 3302 (NH), 2108 (CHN_2), 1690 (CO urethane) and 1640 (COCH); ^1H NMR (δ, $CDCl_3$): 2.6 (4H, m, CH_2CH_2), 4.2 (2H, m, $CHCH_2$ and CH Fmoc), 4.5 (2H, d, CH_2O), 5.2(1H, s, CHN_2), 5.4 (1H, br, NH) and 7.2–7.7 (13H, m, aryl).

N^{α}-Fmoc-N^{ε}-Boc-L-lysinyldiazomethane (**IIi**)

Diazomethane gas was passed through a cold solution of N-Fmoc-L-lysinyl(Boc)pentafluorophenyl ester (0.689 g, 1 mmol) and TEA (0.15 mL, 1 mmol) in THF (50 mL). Yield, 0.62 g, (92%); m.p., 95–97°; R_fA, 0.53; R_fB, 0.69; $[\alpha]^{25}{}_D$ – 26.8° (c = 1, $CHCl_3$); Anal. Calc. for $C_{27}H_{32}N_4O_5$ (492.52): C, 65.8; H, 6.54; N, 11.37; Found: C, 64.90; H, 6.58; N, 11.41%. IR ν_{max} (KBr disk)/cm^{-1} 3341 (NH), 2109 (CHN_2), 1700, 1698 (CO urethane) and 1631 (COCH). ^1H NMR (δ, $CDCl_3$): 1.4 [9H, s, $C(CH_3)_3$], 2.2 [8H, m $(CH_2)_4$], 4.1 (2H, m, CHCO and CH Fmoc), 4.2 (2H, d, CH_2O), 5.2 (1H, s, CHN_2), 5.6 (1H, br, NH), 6.0 (1H, br, NH), 7.2–7.8 (8H, m, aryl).

Synthesis of N-Fmoc-β-homoamino acids

General method

A solution of an N-Fmoc-α-aminoacyldiazomethane (1 mmol) in 1,4-dioxane (10 mL) and water (5 mL) was treated with silver benzoate (2 mg, 0.08 mmol). The reaction mixture was refluxed at 70°C for 1–5 h and then filtered. The solvent was evaporated off under reduced pressure. The residue was redissolved in saturated aqueous sodium carbonate (20 mL) and stirred for 1 h. The solution was washed with ether (2 × 30 mL). The aqueous layer was acidified to pH 2 with 6 N HCl and extracted with ethyl acetate (3 × 25 mL). The combined organic layer was washed with water (20 × 20 mL), dried over Na_2SO_4 and evaporated to get the corresponding N-Fmoc-β-homoamino acid.

N-Fmoc-L-β-homoalanine (**IIIa**)

Prepared from compound **Iia** (0.348 g, 1 mmol) in 1,4-dioxane–water (13 : 7 mL) and silver benzoate (0.13 g, 0.01 mmol). Yield, 0.27 g, (84%); m.p., 96–98°; R_fB, 0.59; R_fC, 0.76; $[\alpha]^{25}{}_D$ – 21.0° (c = 1, $CHCl_3$); Anal. Calc. for $C_{19}H_{19}NO_4$ (325.33): C, 70.14; H, 5.89; N, 4.30; Found: C, 70.30; H, 5.72; N, 4.52%. IR ν_{max} (KBr disk)/cm^{-1} 3324 (NH) and 1689 (CO urethane); ^1H NMR ($CDCl_3$); 1.10 (3H, d, 3 Me), 2.31 (1H, d, 2-H), 2.45 (1H, d, 2 -H), 3.85 (1 H, m, 3-H), 4.15–4.35 (3H, m, CH Fmoc and CH_2O) and 7.30–7.90 (9H, m, Aryl and NH).

N-Fmoc-L-β-homoleucine (**IIIb**)

Prepared from compound **IIb** (0.3 73 g, 1 mmol) in 1,4-dioxane–water (13: 7 mL) and silver benzoate (0.13 g, 0.01 mmol). Yield, 0.29 g, (79%); m.p., 106–108°; R_fB, 0.60; R_fC, 0.74; $[\alpha]^D{}_{25}$– 39.2° (c = 1, CH Cl_3); Anal. Calc. for $C_{22}H_{25}NO_4$ (367.30): C, 71.37; H, 6.56; N, 3.96; Found; C, 71.24; H, 6.38; N, 3.78%; IR ν_{max} (KBr disk)/cm^{-1}: 3334 (NH) and 1696 (CO urethane); ^{1}H NMR (δ, $CDCl_3$): 0.85 (6H, d, 5-Me_2), 1.15 (2H, m, 4-H_2), 1.4 (1H, m, 5-H), 2.35 (2H, m, 2-H_2) and 3.80 (1H, m, 3-H), 4.20 (3H, m, CH Fmoc and CH_2O), 7.3–7.0 (9H, m, aryl and NH).

N-Fmoc-D-β-homoleucine (**IIIc**)

Prepared from compound **IIc** (0.37 g, 1 mmol) in 1,4-dioxane–water (13 : 7 mL) and silver benzoate (0.13 g, 0.01 mmol). Yield, 0.29 g, (79%); m.p., 105–108°; R_fB, 0.61; R_fC, 0.78; $[\alpha]^{25}{}_D$ + 38.0° (c = 1, $CHCl_3$); Anal, Calc. for $C_{22}H_{25}NO_4$ (367.30): C, 71.37; H, 6.56; N, 3.96; Found: C, 71.39; H, 6.51; N, 3.89%; IR ν_{max} (KBr disk)/cm^{-1}: 3320 (NH) and 1688 (CO urethane); 1H NMR (δ, $CDCl_3$): 0.80 (6H, d, 5-Me_2) 1.10 (2H, m, 4-H_2), 1.4 (1H, m, 5-H), 2.30 (2H, m, 2-H_2), 3.8 (1H, m, 3-H), 4.1 (3H, m, CH Fmoc and CH_2O), 7.2–7.8 (9H, m, aryl and NH).

N-Fmoc-L-β-homonorleucine (**IIId**)

Prepared from compound **IId** (0.38 g, 1 mmol) in 1,4-dioxane–water (13 : 7 mL) and silver benzoate (0.13 g, 0.01 mmol). Yield, 0.30 g, (82%); m.p., 108–110°; R_fB, 0.65; R_fC, 0.77; $[\alpha]^{25}{}_D$ – 22.0° (c = 1, $CHCl_3$); Anal. Calc. for $C_{22}H_{22}NO_4$ (364.38): C, 71.9; 4, 6.81; N, 3.81; Found: C, 71.8; H, 6.69; N, 3.84%; IR ν_{max} (KBr disk)/cm^{-1}: 3441 (NH) and 1693 (CO urethane); ^{1}H NMR (δ, $CDCl_3$): 0.9–1.5 [9H, m $(CH_2)_3CH_3$], 2.4 (1H, d, $CHCH_2$), 3.7 (1H, d, NHCH), 4.3 (3H, m, CH Fmoc and CH_2O), 7.2–7.8 (9H, m, aryl and NH).

N-Fmoc-D-β-homonorleucine (**IIIe**)

Prepared from compound **IIe** (0.384 g, 1 mmol) in 1,4-dioxane–water (13 : 7 mL) and silver benzoate (0.13 g, 0.01 mmol). Yield, 0.29 g, (80%); m.p., 109–111°; R_fB, 0.66; R_fC, 0.80; $[\alpha]^{25}{}_D$ + 21.2° (c = 1, $CHCl_3$); Anal. Calc. for $C_{22}H_{25}NO_4$ (364.38): C, 71.9; H, 6.81; N, 3.81; Found: C, 70.90; H, 6.84; N, 3.86%; IR ν_{max} (KBr disk)/cm^{-1}: 3369 (NH) and 1690 (CO urethane); ^{1}H NMR (δ, $CDCl_3$): 0.8–1.4 [9H, m $(CH_2)_3CH_3$], 2.3 (1H, d, $CHCH_2$), 3.75 (1H, d, NHCH), 4.3 (3H, m, CH Fmoc and CH_2O), 7.2–7.8 (9H, m, aryl and NH).

N-Fmoc-L-β-homovaline (**IIIf**)

Prepared from compound **IIf** (0.354 g, 1 mmol) in 1,4-dioxane–water (13 : 7 mL) and silver benzoate (0.13 g, 0.01 mmol). Yield, 0.28 g, (80%); m.p., 153–154°; R_fB, 0.59; R_fC, 0.77; $[\alpha]^{25}{}_D$ – 36.2° (c = 1, $CHCl_3$); Anal.calc. $C_{21}H_{23}NO_4$ (353.38): C, 70.14; H, 5.89; N, 4.20; Found: C, 71.24; H, 6.38; N, 3,78%; IR ν_{max} (KBr disk)/cm^{-1}: 3343 (NH) and 1706 (CO urethane); ^{1}H NMR (δ, $CDCl_3$): 0.85 (6H, d, 4-Me_2), 1.75 (1H, m, 4-H), 2.30 (1H, d, 2-H), 2.45 (1H, d, 2-H), 3.75 (1H, m, 3-H), 4.30 (3H, m, CH Fmoc and CH_2O) and 7.30–7.80 (9H, m, Aryl and NH).

N-Fmoc-D-β-homonorvaline (**IIIg**)

Prepared from compound **IIg** (0.35 g, 1 mmol) in 1,4-dioxane–water (13 : 7 mL) and silver benzoate (0.13 g, 0.01 mmol). Yield, 0.27 g, (79%); m.p., 109–112°; R_fB, 0.58; R_fC, 0.69; $[\alpha]^D{}_{25}$ + 31.2° (c = 1, $CHCl_3$); Anal. Calc. for $C_{21}H_{23}NO_4$ (353.38): C, 70.14; H, 5.89; N, 4.30; Found: C, 70.09; H, 5.79; N, 4.32%; IR ν_{max} (KBr disk)/cm^{-1}: 3328 (NH) and 1690 (CO urethane). ^{1}H NMR (δ, $CDCl_3$): 0.9–2.0 [7H m $(CH_2)_2CH_3$], 2.4 (1H, d, $CHCH_2$), 3.75 (1H, m, CHNH), 4.30 (3H, m, CH Fmoc and CH_2O), 7.3–7.9 (9H, m, aryl and NH).

N-Fmoc-L-β-homophenylalanine (**IIIh**)

Prepared from compound **IIh** (0.42 g, 1 mmol) in 1,4-dioxane–water (13 : 7 mL) and silver benzoate (0.13 g, 0.01 mmol). Yield, 0.32 g (80%); m.p., 110–112°; R_fB, 0.62; R_fC, 0.75; $[\alpha]^D{}_{25}$– 26.0° (c = 1, $CHCl_3$); Anal. Calc. for $C_{25}H_{23}NO_4$ (401.42): C, 75.05; H, 5.58; N, 3.70; Found: C, 74.81; H, z5.78; N, 3.49%; IR ν_{max} (KBr disk)/cm^{-1}: 3344 (NH) and 1698 (CO urethane); ^{1}H NMR (δ, $CDCl_3$): 2.43 (1H, d, 2-H), 2.52 (2H, m, 4-H_2), 2.71 (1H, d, 2-H), 3.6 (1H, m, 3-H), 4.10 (1H, m, CH Fmoc), 4.2 (2H, m, CH_2O) and 7.30–7.80 (14H, m, Aryl and NH).

N^{α}-Fmoc-N^{ε}-Boc-L-β-homolysine (**IIIi**)

Prepared from compound **IIi** (0.543 g, 1 mmol) in 1,4-dioxane–water (13 : 7 mL) and silver benzoate (0.13 g, 0.01 mmol). Yield, 0.35 g, (60%); m.p., 97–98°C; R_fB, 0.58; R_fC, 0.63; $[\alpha]^{25}{}_D$ – 18.2° (c = 1, $CHCl_3$); Anal. Calc. for $C_{27}H_{34}N_2O_6$ (482.52): C, 64.6; H,6.53; N,5.38; Found: C, 63.92; H, 6.48; N, 5.29%; IR ν_{max} (KBr disk)/cm^{-1}: 3400, 3450 (NH) and 1703, 1690 (C = o of Fmoc and Boc); ^{1}H NMR (δ, $CDCl_3$): 1.5 (9H, s, $C(CH_3)_3$), 2.0 [8H, m $(CH_2)_4$], 2.4 (1H, d, $CHCH_2$), 4.1 [3H, m, CH Fmoc and CH_2O], 5.6 (1H, br NH), 7.2–7.8 (9H, m, aryl and NH).

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References

1. Seebach, D. & Matthews, J.L. (1997) β-peptides: a surprise at every turn. *Chem. Commun.*, 2015.
2. Hintermann, T. & Seebach, D. (1997) The biological stability of β-peptides: no interactions between α- and β-peptidic structures? *Chimia* **50**, 244.
3. Appella, D.H., Christianson, L.A., Klein, D.A., Powell, D.R., Huang, X., Barchi, J.J. Jr & Gellamn, S.H. (1997) Residue-based control of helix shape in β-peptide oligomers. *Nature* **387**, 381.
4. Krauthauser, S., Christianson, L.A., Powell, D.R. & Gellman, S.H. (1997) Antiparallel sheet formation in β-peptide foldamers: Effects of β-amino acid substitution on conformational preference. *J. Am. Chem. Soc.* **119**, 11719.
5. Gellman, S.H. (1998) Foldamers: a manifesto. *Acc. Chem. Res.* **31**, 173.
6. Koert, U. (1997) β-peptides. Novel secondary structures take shape. *Angew. Chem. Int. Ed. Engl.* **36**, 1836.
7. Cole, D.C. (1994) Recent stereoselective synthetic approaches to β-amino acids. *Tetrahedron* **32**, 9517.
8. Matthews, J.L., Seebach, C., Guibourdenche, C., Overhead, M., Seebach, D. (1997) *Enantioselective Synthesis of β-Amino Acids* (Juaristi, E., ed). Wiley–VCH, New York, pp. 105–126.
9. Seebach, D., Beck, A.K., Studer, A. (1995) *Modern Synthetic Methods,* Vol. 7 (Ernst, B., Leumann, C., eds). VCHA, Basel, pp. 1–178.
10. Ye, T. & McKervey, M.A. (1994) Organic synthesis with α-diazocarbonyl compounds. *Chem. Rev.* **94**, 1091.
11. Carsal, J.-M., Furst, A. & Meier, W. (1976) Synthese der enatiomeren 2-pyrrolidinessigsauren. *Helv. Chim. Acta.* **59**, 1917.
12. Balaspiri, L., Penke, B., Dombi, Gy, & Kovacs, K. (1975) Synthese von diazoketonen aus acylaminosauren unter verwendung von gemischten anhydriden bzw. *N,N*[1]-dicyclohexyl-carbodiimid. *Helv. Chim. Acta.* **58**, 969.
13. Podleska, J. & Seebach, D. (1995) The Arndt–Eistert reaction in peptide chemistry: a facile access to homopeptides. *Angew. Chem. Int. Ed. Engl.* **34**, 471.
14. Plucinska, K. & Liberek, B. (1987) Synthesis of diazoketones derived from α-amino acids; problem of side reactions. *Tetrahedron* **43**, 3509 and references cited therein.
15. Ye, T. & McKervey, M.A. (1992) Synthesis of chiral N-protected α-amino-β-diketones from α-diazoketones derived from natural amino acids. *Tetrahedron* **48**, 8007.
16. Leggio, A., Liguori, A., Procopio, A. & Sindona, G. (1997) Convenient and stereospecific homologation of N-fluorenylmethoxycarbonyl-α-amino acids to their β-homologues. *J. Chem. Soc., Perkin Trans.* **1**, 1969.
17. Gopi, H.N. & Suresh Babu, V.V. (in press) Homologation of α-amino acids β–amino acids using Fmoc-amino acid chlorides. *Indian J. Chem.,* (in press).
18. Kovacs, J., Mayers, G.L., Johnson, R.H., Cover, R.E. & Ghatak, U.R. (1970) Rates of racemization and coupling of cysteine active ester derivatives. *Chem. Commun.,* 53.
19. Kovacs, J., Mayers, G.L., Johnson, R.H., Cover, R.E. & Ghatak, U.R. (1970) Racemization of amino acid derivatives. Rate of racemization and peptide bond formation of cysteine active esters. *J. Org. Chem.* **35**, 1810.
20. Kisfaludy, L. & Schon, I. (1983) Preparation and applications of pentafluorophenyl esters of 9-fluorenylmethoxycarbonyl amino acids for peptide synthesis. *Synthesis,* 325.
21. Schon, I. & Kisfaludy, L. (1986) 9-Fluorenylmethylpentafluorophenyl carbonate as a useful reagent for the preparation of N-9-fluorenylmethyloxycarbonyl amino acids and their pentafluorophenyl esters. *Synthesis,* 303.
22. Atherton, E., Carmeron, L.R. & Sheppard, R.C. (1988) Peptide synthesis Part 10. Use of pentafluorophenyl esters of fluorenylmethoxycarbonyl amino acids in solid phase peptide synthesis. *Tetrahedron* **44**, 843.
23. Atherton, E. & Sheppard, R.C. (1985) Solid phase peptide synthesis using N^{α}-fluorenylmethyloxycarbonyl amino acid pentafluorophenyl esters. *Chem. Commun.,* 165.
24. Hudson, D. (1990) Methodological implications of simultaneous solid-phase peptide synthesis: a comparison of active esters. *Peptide Res.* **3**, 51.
25. Carey, R.I., Bordas, L.W., Slaughter, R.A., Meadows, B.C., Wadsworth, J.L., Huang, H., Smith, J.J. & Furusjo, E. (1997) Preparation and properties of N^{α}-Bpoc-amino acid pentafluorophenyl esters. *J. Peptide Res.* **49**, 570.
26. Beyermann, M., Bienert, M., Niedrich, H., Carpino, L.A. & Sadat-Aalaee, D. (1990) Rapid continuous peptide synthesis via Fmoc-amino acid chloride coupling and 4-(aminomethyl) piperidine deblocking. *J. Org. Chem.* **55**, 721.
27. Arndt, F. (1943) Diazomethane. *Org. Synth., Coll.* **2**, 165.
28. Neeman, M. & Johnson, S. (1973) Cholestanyl methyl ether. *Org. Synth., Coll.* **V**, 245.
29. Furniss, B.S., Hannaford, A.J., Smith, P.W.G. & Tatchell, A.R. (1994) *Vogel's Textbook of Practical Organic Chemistry*. Longman Scientific & Technical, p.430.
30. Sivanandaiah, K.M. & Gurusiddappa, S. (1981) Fmoc-amino acid active esters in solid phase peptide synthesis using, p-alkoxybenzyl alcohol resin: synthesis of [Leu-NH_2]^5-enkephalin. *Synthesis* **7**, 565.
31. Sivanandaiah, K.M. & Gurusiddappa, S. (1984) Fluorenylmethloxycarbonyl amino acid trichlorophenyl esters. *Indian J. Chem.* **23B**, 372.
32. Atherton, E. & Sheppard, R.C. (1989) *Solid Phase Peptide Synthesis, a Practical Approach*. IRL Press, UK.