Convenient and stereospecific homologation of *N*-fluorenylmethoxycarbonyl-α-amino acids to their β-homologues

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A very simple approach to the enantioselective homologation of α-amino acids is presented which is based on the formation of *N*-Fmoc-aminoacyldiazomethanes with nearly quantitative yields and on the complete retention of both chiral configuration and N-terminal protecting group in the overall transformation.

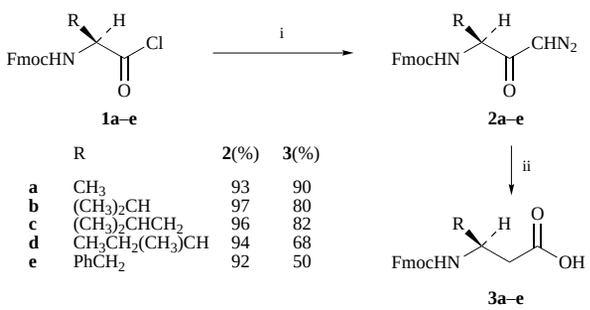
Introduction

α-Aminoacyldiazomethanes are reactive intermediates widely used in organic synthesis.[1] Benzyloxycarbonyl (Z), *tert*-butoxycarbonyl (Boc) and fluoren-9-ylmethoxycarbonyl (Fmoc)-L-phenylalanyldiazomethanes are substrates in the formation of phenylalanyl epoxides, which are potential precursors of hydroxyethylene dipeptides.[2] The Wolff rearrangement to β-homoamino acids[3] represents, however, the most valuable and well known application of α-aminoacyldiazomethanes in the design of modified peptides as well as in the synthesis of some β-lactam antibiotics. Unfortunately, the synthesis of the Z- or Boc-protected aminoacyldiazomethanes faces many drawbacks when performed as reported[4] from an ethereal solution of diazomethane.[5] The instability of the acyl chloride intermediates and their ready tendency to undergo racemization at the α-carbon has favoured the use of the mixed anhydrides obtained from the protected α-amino acids with ethyl[6] or isobutyl chloroformate.[7,8] The yields of aminoacyldiazomethanes are often poor[8] whereas racemic starting products and their methyl esters are present as co-products in reaction mixtures whose purification is often tedious. The different physical data reported for the same compound[7–9] are probably an indication of the problems encountered in the isolation of the pure compounds.

Results and discussion

In the course of our studies aimed at obtaining modified biological molecules with potential pharmacological activity[10,11] a useful approach to β-homoamino acids was needed; the formation of these compounds requires the development of an effective and simple strategy for preparing Fmoc-α-aminoacyldiazomethane substrates since literature procedures[6–8] based on the conversion of mixed anhydrides of Z- or Boc-protected amino acids into the corresponding acyldiazomethane derivatives did not give satisfactory results. The main limitation of this procedure is represented by the isolation of relevant quantities of the methyl esters of the starting amino acids. The sequential treatment of Fmoc-L-alanine with isobutyl chloroformate and then with an ethereal solution of diazomethane[5] gives rise, in fact, to *N*-Fmoc-alanyldiazomethane and *N*-Fmoc-alanine methyl ester in 51 and 38% isolated yield, respectively, after flash chromatography. The previously reported[9] 2-(fluoren-9-ylmethoxy)-4-methyl-5(4*H*)-oxazolone was not present in the crude mixture. Similar results were obtained when the same procedure was applied to *N*-Fmoc-α-aminoacyl chlorides. The lack of success of the aforementioned procedures is clearly due to the hydrolysis undergone by both the highly activated acid derivatives in the adopted experimental conditions. Moreover the need for gram quantities of aminoacyldiazomethane substrates requires fairly dry concentrated solutions of diazomethane which cannot be obtained with the classic distillation method.[12]

0.66 M Solutions of diazomethane in dichloromethane[13] can be obtained from *N*-methyl-*N*-nitrosourea and are kept sufficiently dry over potassium hydroxide pellets. The target aminoacyldiazomethanes **2a–e** were then prepared with 92–97% yield by reaction of the *N*-Fmoc-α-aminoacyl chlorides **1a–e**[14] with dichloromethane solutions of the nucleophile (Scheme 1).



1a–e **2a–e** **3a–e**

	R	2(%)	3(%)
a	CH_3	93	90
b	$(CH_3)_2CH$	97	80
c	$(CH_3)_2CHCH_2$	96	82
d	$CH_3CH_2(CH_3)CH$	94	68
e	$PhCH_2$	92	50

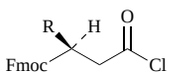
Scheme 1 *Reagents and conditions:* i, CH_2N_2, CH_2Cl_2; ii, $PhCO_2Ag$, aq. 1,4-dioxane, 70 °C

The formation of compounds **2a–e** in a nearly pure state was important for the use of these substrates in further applications without any purification. Accordingly, the absence of significant amounts of the previously observed co-products was investigated and confirmed spectroscopically. No IR absorbances in the region of 1750 cm^{-1} or NMR resonances in the interval δ_H 3.60–3.65, typical of pure samples of the methyl esters of *N*-Fmoc-amino acids, were detected in the crude mixtures of products **2a–e**, which were satisfactorily pure by TLC. An important aspect related to the use of diazoketones **2a–e** in the homologation of α-amino acids is the conservation of the chiral homogeneity of substrates **1a–e** throughout their transformation. The lack of a detectable amount of racemization in the conversion of the acyl chloride substrates into the diazomethane derivatives was confirmed by NMR spectroscopy using (2*S*,3*S*)-isoleucine as test compound. The ^{13}C NMR spectrum of the crude product displayed carbon resonances which can be attributed to a single diastereomeric aminoacyldiazomethane **2d**.

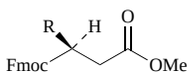
The acyldiazomethane intermediates thus produced preserve, therefore, sufficient chemical and optical purity for their direct use in the homologation of α-amino acids. With reference to literature procedures,[15] a 1,4-dioxane–water solution of silver benzoate catalyst and *N*-Fmoc-aminoacyldiazomethanes **2a–e** was heated at 70 °C for 1–3 h; work-up afforded the *N*-Fmoc-

β-homoamino acids **3a–e** in 50–90% isolated yield. The basicity of the reaction medium did not affect the integrity of the N-terminal protecting group, as would occur if the classical basic treatment of the Wolff rearrangement were used.[3]

The stereospecificity of the overall process was monitored with the model system *N*-Fmoc-isoleucyldiazomethane **2d**. The configuration of the α-carbon was preserved during the rearrangement and a single diastereoisomer **3d** of *N*-Fmoc-β-homoisoleucine was obtained, as shown by the appropriate resonances of its ^{13}C NMR spectrum. The Fmoc-protected β-homoamino acids thus obtained were converted, in quantitative yields, by using the same procedure as for the α homologues, into the corresponding acyl chlorides **4a–d**. The chemical and optical purity of the latter was determined spectroscopically after their conversion into the corresponding methyl esters[16] **5a–d**. Compounds **4a–d** are extremely useful as intermediates in synthetic organic chemistry and as building blocks for their incorporation in modified peptide chains.



4a–d



5a–d

A nearly direct conversion of *N*-Fmoc-α-amino acids into their acid chloride β-homologues can, therefore, be achieved by routine operations, by setting properly experimental conditions. The high yields, lack of racemization, and preservation of the integrity of the N-protecting group in the transformation of compounds **1a–d** into the *N*-Fmoc-β-homoaminoacyl chlorides **4a–d** can be considered the major achievements of the procedure reported above.

Experimental

Solvents and reagents were purified by standard procedures and were distilled prior to use. Mps were recorded on a Reichert Thermovar Kofler apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT Paragon 1000 PC spectrometer. Fast-atom bombardment (FAB) spectra were recorded on a VG-micromass ZAB 2F mass spectrometer equipped with an M-SCAN steerable gun, using a beam of 9.5 keV Xe atoms and *m*-nitrobenzyl alcohol as liquid matrix.

^1H NMR and ^{13}C NMR spectra were recorded on a Bruker ACP 300 (300 MHz) spectrometer using tetramethylsilane as internal standard and deuteriochloroform and hexadeuteriodimethyl sulfoxide as solvents. *J*-Values are given in Hz.

Optical rotations were measured on a Perkin-Elmer 141 polarimeter (1.0 dm cell) for chloroform solutions at 20 °C. $[\alpha]_D$-Values are given in units of 10^{-1} deg cm^2 g^{-1}.

Elemental analyses were obtained using a Perkin-Elmer Elemental Analyzer.

The TLC systems employed glass plates precoated with silica gel 60 F254 (Merck) as the absorbent, and either chloroform–methanol (9:1) or diethyl ether–light petroleum (distillation range 40–60 °C) (7:3) as the developing solvent.

N-Fmoc-α-amino acid chlorides were prepared from the corresponding *N*-Fmoc-α-amino acid and thionyl dichloride in dichloromethane chloride as solvent.[14]

N-Fmoc-β-homoamino acid chlorides were obtained in accordance with the procedure used for *N*-Fmoc-α-amino acid chlorides.

The diazomethane solution in dry dichloromethane was prepared from *N*-methyl-*N*-nitrosourea using a classical procedure.[5] 0.66 M Dichloromethane stock solutions were kept dry with potassium hydroxide pellets. The concentration of diazomethane solution was obtained by back-titration with benzoic acid solution.[5]

Preparation of *N*-Fmoc-α-aminoacyldiazomethanes 2a–e

General method. A solution of *N*-Fmoc-α-amino acid chloride **1a–e** (2 mmol) in dry dichloromethane (40 ml) was added dropwise to a stirred 0.66 M dichloromethane solution of diazomethane (9 ml, 6 mmol). The reaction mixture was stirred at room temperature for 1 h. Solvent was evaporated off under reduced pressure to afford the *N*-Fmoc-α-aminoacyldiazomethane **2a–e** in 92–97% yield.

***N*-Fmoc-L-alanyldiazomethane 2a.** Prepared from *N*-Fmoc-L-alanine chloride **1a** (0.8 g, 2.4 mmol) in dry dichloromethane (45 ml) and diazomethane solution (11.0 ml, 7.3 mmol) in 93% yield; mp 110–112 °C (Found: C, 67.85; H, 4.95; N, 12.65. $C_{19}H_{17}N_3O_3$requires C, 68.05; H, 5.11; N, 12.53%); ν_{max}(KBr disk)/cm^{-1} 3314 (NH), 2121 (CHN_2), 1692 (CO urethane) and 1636 (COCH); δ_H($CDCl_3$) 1.30 (3 H, d, *J* 7, 2-Me), 4.20 (2 H, m, 2-H and CH Fmoc), 4.50 (2 H, m, CH_2O), 5.30 (1 H, s, CHN_2), 5.50 (1 H, d, *J* 7, NH) and 7.20–7.90 (8 H, m, ArH); *m/z* 336 [$(MH)^+$, 22%], 179 (100), 178 (64) and 165 (20).

***N*-Fmoc-L-valyldiazomethane 2b.** Prepared from *N*-Fmoc-L-valine chloride **1b** (0.20 g, 0.56 mmol) in dry dichloromethane (11 ml) and diazomethane solution (2.6 ml, 1.3 mmol) in 97% yield; mp 123–125 °C (Found: C, 69.25; H, 5.76; N, 11.65. $C_{21}H_{21}N_3O_3$ requires C, 69.41; H, 5.82; N, 11.56%); ν_{max}(KBr disk)/cm^{-1} 3298 (NH), 2102 (CHN_2), 1686 (CO urethane) and 1631 (COCH); δ_H($CDCl_3$) 0.85 (3 H, d, *J* 7, 3-Me), 1.10 (3 H, d, *J* 7, 3-Me), 2.10 (1 H, m, 3-H), 4.10 (1 H, m, 2-H), 4.25 (1 H, m, CH Fmoc), 4.45 (2 H, m, CH_2O), 5.30 (1 H, s, CHN_2), 5.40 (1 H, d, *J* 8.5, NH) and 7.30–7.90 (8 H, m, ArH); *m/z* 364 [$(MH)^+$, 37%], 179 (100) and 178 (58).

***N*-Fmoc-L-leucyldiazomethane 2c.** Prepared from *N*-Fmoc-L-leucine chloride **1c** (1.5 g, 4.0 mmol) in dry dichloromethane (84 ml) and diazomethane solution (18 ml, 12 mmol) in 96% yield. *Oil* (Found: C, 70.21; H, 6.25; N, 10.85. $C_{22}H_{23}N_3O_3$ requires C, 70.01; H, 6.14; N, 11.13%); ν_{max}(film)/cm^{-1} 3454 (NH), 2104 (CHN_2), 1690 (CO urethane) and 1644 (COCH); δ_H($CDCl_3$) 0.90 (6 H, d, *J* 6, 4-Me_2), 1.30–1.50 (3 H, m, 3-H_2 and 4-H), 4.20 (1 H, m, 2-H), 4.40–4.70 (3 H, m, CH Fmoc and CH_2O), 5.30 (2 H, m, NH and CHN_2) and 7.30–7.90 (8 H, m, ArH); *m/z* 400 [$(M + Na)^+$, 13%], 378 [$(MH)^+$, 15], 179 (100), 178 (95) and 165 (92).

***N*-Fmoc-L-isoleucyldiazomethane 2d.** Prepared from *N*-Fmoc-L-isoleucine chloride **1d** (0.80 g, 2.15 mmol) in dry dichloromethane (43 ml) and diazomethane solution (9.70 ml, 6.46 mmol) in 94% yield; mp 143–144 °C (Found: C, 69.86; H, 6.34; N, 11.28%); ν_{max}(KBr disk)/cm^{-1} 3301 (NH), 2096 (CHN_2), 1691 (CO urethane) and 1634 (COCH); δ_H($CDCl_3$) 0.90 (6 H, m, 3- and 4-Me), 1.40 (2 H, m, 4-H_2), 1.80 (1 H, m, 3-H), 4.20 (2 H, m, 2-H and CH Fmoc), 4.50 (2 H, m, CH_2O), 5.30 (1 H, s, CHN_2), 5.50 (1 H, d, *J* 9, NH) and 7.30–7.90 (8 H, m, ArH); δ_C($CDCl_3$) 11.40, 15.63, 24.88, 29.66, 31.90, 37.58, 47.39, 66.84, 119.45, 124.97, 127.07, 127.69, 141.39, 143.85, 156.16 and 193.18; *m/z* 400 [$(M + Na)^+$, 4%], 378 [$(MH)^+$, 3], 179 (100), 178 (54) and 165 (16).

***N*-Fmoc-L-phenylalanyldiazomethane 2e.** Prepared from *N*-Fmoc-L-phenylalanine chloride **1e** (1.25 g, 3.00 mmol) in dry dichloromethane (60 ml) and diazomethane solution (13.5 ml, 9.0 mmol) in 92% yield; mp 136–137 °C (Found: C, 73.25; H, 5.25; N, 10.05. $C_{25}H_{21}N_3O_3$ requires C, 72.98; H, 5.14; N, 10.21%); ν_{max}(KBr disk)/cm^{-1} 3302 (NH), 2108 (CHN_2), 1690 (CO urethane) and 1640 (COCH); δ_H($CDCl_3$) 2.70 (1 H, dd, *J* 13.5 and 10.5, 3-H), 3.10 (1 H, dd, *J* 13.5 and 4, 3-H), 4.10–4.20 (2 H, m, 2-H and CH Fmoc), 4.40 (2 H, m, CH_2O), 5.10 (1 H, s, CHN_2), 5.35 (1 H, d, *J* 8.5, NH) and 7.10–7.50 (13 H, m, ArH); *m/z* 411 [$(M - H)^-$, 4%], 188 (100) and 179 (46).

Preparation of *N*-Fmoc-β-homoamino acids 3a–e

General method. A solution of an *N*-Fmoc-α-aminoacyldiazomethane **2a–e** (1 mmol) in distilled 1,4-dioxane (10 ml)–water (5 ml) was treated with silver benzoate (2 mg, 8.73×10^{-3} mmol). The reaction mixture was stirred at 70 °C

for 1–3 h and then was filtered. The solvent was evaporated off under reduced pressure, the residue was re-dissolved in saturated aq. sodium hydrogen carbonate (20 ml), and the solution was washed with diethyl ether (2 × 20 ml). The aqueous layer was acidified to pH 2 with hydrochloric acid (3 M) and extracted with ethyl acetate (3 × 20 ml). The combined organic layers were washed with water (2 × 20 ml), dried (Na_2SO_4), and evaporated *in vacuo* to give the corresponding *N*-Fmoc-β-homoamino acid **3a**–**e** in 50–90% yield.

***N*-Fmoc-L-β-homoalanine 3a.** Prepared from compound **2a** (0.24 g, 0.72 mmol) in 1,4-dioxane–water (7.2 : 3.6 ml) and silver benzoate (1.45 mg, 6.3×10^{-3} mmol) in 90% yield; mp 96–98 °C (Found: C, 70.30; H, 5.72; N, 4.52. $C_{19}H_{19}NO_4$ requires C, 70.14; H, 5.89; N, 4.30%); ν_{max}(KBr disk)/cm^{-1} 3324 (NH) and 1689br (CO urethane, CO); δ_H[$(CD_3)_2SO$] 1.10 (3 H, d, *J* 6.5, 3-Me), 2.31 (1 H, dd, *J* 7.5 and 15.5, 2-H), 2.45 (1 H, dd, *J* 6.5 and 15.5, 2-H), 3.85 (1 H, m, 3-H), 4.15–4.35 (3 H, m, CH Fmoc and CH_2O) and 7.30–7.90 (9 H, m, ArH and NH); *m/z* 326 [$(MH)^+$, 23%], 179 (100), 178 (75) and 165 (76).

***N*-Fmoc-L-β-homovaline 3b.** Prepared from compound **2b** (1.5 g, 4.2 mmol) in 1,4-dioxane–water (42 : 21 ml) and silver benzoate (8.4 mg, 0.036 mmol) in 80% yield; mp 153–154 °C (Found: C, 71.24; H, 6.38; N, 3.78. $C_{21}H_{23}NO_4$ requires C, 71.37; H, 6.56; N, 3.96%); ν_{max}(KBr disk)/cm^{-1} 3343 (NH) and 1706br (CO urethane, CO); δ_H[$(CD_3)_2SO$] 0.85 (6 H, d, *J* 6.5, 4-Me_2), 1.75 (1 H, m, 4-H), 2.30 (1 H, dd, *J* 9 and 15.5, 2-H), 2.45 (1 H, dd, *J* 5 and 15.5, 2-H), 3.75 (1 H, m, 3-H), 4.30 (3 H, m, CH Fmoc and CH_2O) and 7.30–7.80 (9 H, m, ArH and NH); *m/z* 376 [$(M + Na)^+$, 12%,], 354 [$(MH)^+$, 25], 179 (100), 178 (95) and 165 (40).

***N*-Fmoc-L-β-homoleucine 3c.** Prepared from compound **2c** (1.80 g, 4.77 mmol) in 1,4-dioxane–water (48 : 24 ml) and silver benzoate (9.6 mg, 0.042 mmol) in 82% yield; mp 108–110 °C (Found: C, 71.75; H, 6.95; N, 3.74. $C_{22}H_{25}NO_4$ requires C, 71.91; H, 6.86; N, 3.81%); ν_{max}(KBr disk)/cm^{-1} 3334 (NH) and 1696br (CO urethane, CO); δ_H[$(CD_3)_2SO$], 0.85 (6 H, d, *J* 6.5, 5-Me_2), 1.15 (2 H, m, 4-H_2), 1.4 (1 H, m, 5-H), 2.35 (2 H, m, 2-H_2), 3.80 (1 H, m, 3-H), 4.20 (3 H, m, CH Fmoc and CH_2O), 7.30–7.90 (9 H, m, ArH and NH); *m/z* 390 [$(M + Na)^+$, 10%], 368 [$(MH)^+$, 29], 179 (100), 178 (94) and 165 (47).

***N*-Fmoc-L-β-homoisoleucine 3d.** Prepared from compound **2d** (0.50 g, 1.32 mmol) in 1,4-dioxane–water (13.5 : 6.6 ml) and silver benzoate (2.7 mg, 0.018 mmol) in 68% yield; mp 99–100 °C (Found: C, 72.12; H, 7.04; N, 3.68%); ν_{max}(KBr disk)/cm^{-1} 3324 (NH) and 1697br (CO urethane, CO); δ_H($CDCl_3$) 0.80 (6 H, m, 5- and 4-Me), 1.20–1.50 (3 H, m, 4-H, 5-H_2), 2.50 (2 H, m, 2-H_2), 3.90 (1 H, m, 3-H), 4.20 (1 H, t, *J* 7, CH Fmoc), 4.45 (2 H, d, *J* 7, CH_2O), 5.30 (1 H, d, *J* 9.5, NH) and 7.30–7.80 (8 H, m, ArH); *m/z* 390 [$(M + Na)^+$, 27%], 368 [$(MH)^+$, 9], 179 (100), 178 (80) and 165 (26).

***N*-Fmoc-L-β-homophenylalanine 3e.** Prepared from compound **2e** (1.50 g, 3.65 mmol) in 1,4-dioxane–water (37 : 18 ml) and silver benzoate (7.3 mg, 0.032 mmol) in 50% yield; *oil* (Found: C, 75.05; H, 5.58; N, 3.70. $C_{25}H_{23}NO_4$ requires C, 74.81; H, 5.78; N, 3.49%); ν_{max}(film)/cm^{-1} 3344 (NH) and 1698br (CO urethane, CO); δ_H[$(CD_3)_2SO$] 2.43 (1 H, dd, *J* 11.5 and 6, 2-H), 2.521 (2 H, m, 4-H_2), 2.71 (1 H, dd, *J* 11.5 and 4.5, 2-H), 3.60 (1 H, m, 3-H), 4.10 (1 H, m, CH Fmoc), 4.20 (2 H, m, CH_2O) and 7.30–7.80 (14 H, m, ArH and NH); *m/z* 424 [$(M + Na)^+$, 4%], 402 [$(MH)^+$, 12], 179 (100), 178 (80) and 165 (40).

N-Fmoc-L-β-homoamino acid methyl esters 5a–d

N-Fmoc-β-homoamino acid methyl esters, used to determine the purity of *N*-Fmoc-β-homoamino acid chlorides, were prepared from *N*-Fmoc-β-homoamino acid chlorides, methanol and triethylamine in dichloromethane as solvent as reported in the literature.[16]

***N*-Fmoc-L-β-homoalanine methyl ester 5a.** Yield 90%; mp 75–77 °C (Found: C, 70.85; H, 6.06; N, 4.28. $C_{20}H_{21}NO_4$ requires C, 70.78; H, 6.24; N, 4.13%); $[\alpha]_D$ −27 (*c* 0.57, $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} 3318 (NH), 1738 (CO) and 1687 (CO urethane); δ_H($CDCl_3$) 0.80 (3 H, d, *J* 7, 3-Me), 2.55 (2 H, m, 2-H_2), 3.60 (3 H, s, OMe), 4.05 (1 H, m, 3-H), 4.15 (1 H, m, CH Fmoc), 4.35 (2 H, m, CH_2O), 5.15 (1 H, br s, NH) and 7.20–7.70 (8 H, m, ArH); *m/z* 362 [$(M + Na)^+$, 7%], 340 [$(MH)^+$, 20], 179 (86), 178 (100) and 165 (46).

***N*-Fmoc-L-β-homovaline methyl ester 5b.** Yield 86%; mp 70–72 °C (Found: C, 71.95; H, 7.05; N, 3.95. $C_{22}H_{25}NO_4$ requires C, 71.91; H, 6.86; N, 3.81%); $[\alpha]_D$ −26 (*c* 0.65, $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} 3320 (NH), 1748 (CO) and 1686 (CO urethane); δ_H($CDCl_3$) 0.90 (6 H, d, *J* 6.5, 4-Me_2), 1.85 (1 H, m, 4-H), 2.55 (2 H, m, 2-H_2), 3.65 (3 H, s, OMe), 3.85 (1 H, m, 3-H), 4.20 (1 H, t, *J* 7, CH Fmoc), 4.45 (2 H, d, *J* 7, CH_2O), 5.20 (1 H, d, *J* 9.5, NH) and 7.30–7.90 (8 H, m, ArH); *m/z* 390 [$(M + Na)^+$, 7%], 368 [$(MH)^+$, 28], 179 (100), 178 (96) and 165 (43).

***N*-Fmoc-L-β-homoleucine methyl ester 5c.** Yield 89%; mp 74–76 °C (Found: C, 72.61; H, 7.28; N, 3.55. $C_{23}H_{27}NO_4$ requires C, 72.42; H, 7.13; N, 3.67%); $[\alpha]_D$ −34 (*c* 0.85, $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} 3368 (NH) and 1718br (CO urethane, CO); δ_H($CDCl_3$) 0.80 (6 H, d, *J* 6.5, 5-Me_2), 1.20–1.50 (3 H, m, 4-H_2, 5-H), 2.60 (2 H, m, 2-H_2), 3.70 (3 H, s, OMe), 4.05 (1 H, m, 3-H), 4.20 (1 H, t, *J* 7, CH Fmoc), 4.40 (2 H, d, *J* 7, CH_2O), 5.2 (1 H, d, *J* 9, NH) and 7.3–7.9 (8 H, m, ArH); *m/z* 404 [$(M + Na)^+$ 10%], 382 [$(MH)^+$, 35], 179 (100), 178 (94) and 165 (25).

***N*-Fmoc-L-β-homoisoleucine methyl ester 5d.** Yield 87%; mp 72–74 °C (Found: C, 72.32; H, 6.95; N, 3.46%); $[\alpha]_D$ −21 (*c* 0.46, $CHCl_3$); ν_{max}(KBr disk)/cm^{-1} 3340 (NH) and 1720br (CO urethane, CO); δ_H($CDCl_3$) 0.80 (6 H, m, 4- and 5-Me), 1.20–1.50 (3 H, m, 4-H, 5-H_2), 2.50 (2 H, m, 2-H_2), 3.72 (3 H, s, OMe), 3.90 (1 H, m, 3-H), 4.21 (1 H, t, *J* 7, CH Fmoc), 4.40 (2 H, d, *J* 7, CH_2O), 5.25 (1 H, d, *J* 9.5, NH) and 7.30–7.80 (8 H, m, ArH); *m/z* 404 [$(M + Na)^+$, 10%], 382 [$(MH)^+$, 40] and 179 (100).

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