Indian Journal of Chemistry
Vol. 45B, August 2006, pp. 1880-1886

Synthesis of Fmoc-protected *β*-amino alcohols and peptidyl alcohols from Fmoc-amino acid / peptide acid azides

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Received 10 May 2005; accepted (revised) 13 October 2005

An efficient synthesis of N^{α}-9*H*-fluoren-9-ylmethoxycarbonyl(Fmoc)-*β*-amino alcohols by the reduction of Fmoc-*α*-amino acyl azides employing aqueous $NaBH_4$ as a reducing agent has been described. The reduction is found to be simple and almost complete. All the Fmoc-*β*-amino alcohols prepared are fully characterized by ^1H and ^{13}C NMR and mass spectrometry. Further, the method is extended for the reduction of seven Fmoc-dipeptidyl acids to the corresponding alcohols. Their reduction is also found to be smooth and complete.

Keywords: Fmoc-*β*-amino alcohols, Fmoc-*α*-amino acyl azides

IPC Code: Int.Cl.[8] C07D

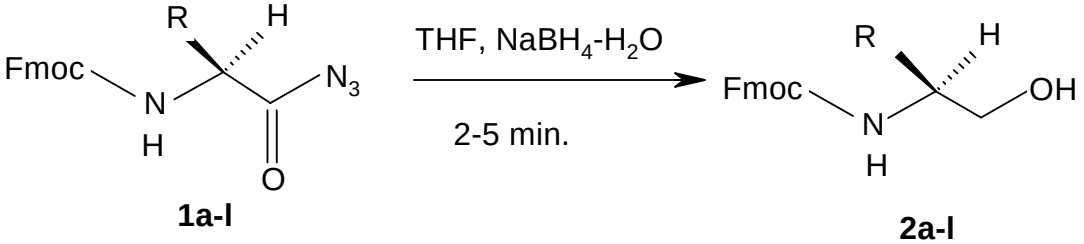
Enantiomerically pure *β*-amino alcohols are in great demand as chiral synthons for a number of organic reactions namely, as chiral auxiliaries in asymmetric C-C-bond formation[1], chiral 4-substituted oxazolidine-2-ones[2] and in the synthesis of insecticidal compounds[3]. Further, they are also used to obtain peptide bond surrogates and peptidomimetics and as chiral auxiliaries in the resolution of primary amines[4]. Thus, the selective reduction of carboxylic acids to alcohols is still an important task in organic synthesis. For the reduction of *α*-amino acids, a useful approach is to reduce the unprotected amino acid to *β*-amino alcohol followed by protection of the amino group[5]. When this protocol is not possible, the carboxyl group can be activated using the mixed carbonic anhydride approach followed by reduction with $NaBH_4$ (ref.6). Although this procedure is in use, Falorni *et al.*[7] reported the formation of different amounts of the ester derived from decarboxylation of the intermediate carbonic-carbonic mixed anhydride (generated from ethyl or butyl chloroformate) that occurs before the reduction step. The resulting ester cannot be reduced by $NaBH_4$. Hence, it has to be separated from the product *β*-amino alcohol using column chromatography, which is tedious and results in loss of the product. The chemoselective reduction of carboxylic acids to alcohols by activation of the carboxylic group with BOP (benzotriazole-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate) followed by reduction with $NaBH_4$ has also been described[8]. The high cost of BOP reagent naturally restricts its utility for the synthesis of *β*-amino alcohols in large scale. Prasad *et al.*[9] employed $NaBH_4$ / I_2 system for the reduction of acids to alcohols. This method was extended for the reduction of amino acids to alcohols. Essentially, this method involves refluxing the reaction mixture for 18-24 hr in an appropriate solvent and hence not suitable for amino acids having side chain functionalities[10]. Naquvi *et al.*[11] prepared *β*-amino alcohols starting from *N*-protected amino acid pentachlorophenyl esters using the $NaBH_4$ / I_2 system for reduction. Other methods reported for reduction of *N*-protected amino acids and peptides to alcohols include the reagents NBTU [2-(6-nitro-1-oxybenzotriazol-3-yl)-1, 1, 3, 3-tetramethyluranium hexafluorophosphate], HBTU[12] {*N*-[(1*H*-benzotriazol-1-yl) (dimethylamino)methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide)} and cyanuric chloride[7] for the activation of carboxyl group. This paper describes the synthesis of Fmoc-*β*-amino alcohols by the reduction of Fmoc-*α*-amino acid azides employing $NaBH_4$-H_2O as a reducing agent.

Unlike Boc-/*Z*-protected amino acids, the use of Fmoc-group for the protection of amino group of amino acids had led to the synthesis of stable Fmoc-amino acid azides. Far from the possibility of formation of numerous side products during the preparation of Boc-/*Z*-amino acid azides[13,14]. Fmoc-amino acid azides were prepared by the mixed anhydride method or acid chloride method in a straight forward manner. Several N^{α}-Fmoc-bifunctional amino acid azides bearing a *t*-butyl group were also prepared by our group[15]. Similar results were obtained in the case of Fmoc-peptidyl acyl azides as well[16]. All the Fmoc-amino acid/peptide acid azides prepared have been isolated as crystalline solids. They can be stored for long periods without any decomposition. Our group recently demonstrated the utility of these azides for the synthesis of various peptidylureas via isocyanates[17] as well as pentafluorophenyl[18], *p*-nitrophenyl[19] and 2,4,5-trichlorophenyl-(9-fluorenylmethoxycarbonylamino)methylcarbamates[20].

As a part of our work directed towards the development of new methods for the synthesis of alcoholic building blocks for the construction of peptidomimetics, in the present study, the reduction of Fmoc-amino acid azides to the corresponding *β*-amino alcohols is developed. The Fmoc-amino acid azides required for the present study have been prepared by the mixed anhydride method. The acyl azides made have been used directly without further purification. The reaction of Fmoc-amino acid azides with $NaBH_4$-H_2O at 0ºC was found to be smooth and rapid (**Scheme I**). The course of the reaction was monitored by TLC (followed by the disappearance of the starting material) and also by the IR analysis (the absence of peak at around 2147-2152 cm^{-1} corresponding to the acyl azide functionality). It was found that the reaction was complete within 5 min. In most of the cases, the products were obtained in pure form without column chromatography purification. All the compounds **2a-l** made were characterized by IR, ^{1}H NMR and mass spectrometry. Their yields were also satisfactory (**Table I**).

Encouraged with the above results, the procedure was then extended for the reduction of Fmoc-dipeptide acid azides. The peptide acids were made by the mixed anhydride method using *bis*-TMS amino acid as an amino component. They were then converted to the corresponding acid azides by mixed anhydride method. All the peptide acid azides **5a-g** made were purified and characterized. They were reduced using $NaBH_4$-H_2O to the corresponding alcohols (**Scheme II**). In a typical procedure, to Fmoc-peptide acid azide in THF solution at 0°C $NaBH_4$ in water was added and stirred. The reaction, as monitored by TLC (followed by the disappearance of the starting material) and IR analysis (the absence of peak at around 2145-2152 cm^{-1} corresponding to the acyl azide functionality), was complete within 5 min. All the compounds **6a-g** were isolated as crystalline white solids in good yields. The reduction of Fmoc-amino acid azides to the corresponding Fmoc-*β*-amino alcohols has been found to be free from racemization. This has been confirmed by measuring the optical rotations of several *β*-amino alcohols and comparing with the literature values (see **Table I**). The reduction of carboxylic acid using $NaBH_4$-I_2 requires its pentachlorophenyl esters, which have to be prepared in the precursor step using DCC. Further, the reduction took about 2.5 to 5 hr at room temperature. In the present study, Fmoc-amino acid azides were reduced to the corresponding *β*-amino alcohols using $NaBH_4$ at 0°C, which were found to be complete within 10 min.

In summary, it has been demonstrated that the synthesis of Fmoc-*β*-amino alcohols and peptide alcohols can be carried out using $NaBH_4$-H_2O starting from Fmoc-amino acid/peptide acid azides. The reaction is rapid and efficient and results in good yields of products with high purity.



Scheme I — Synthesis of *β*-amino alcohols from acid azide

Table I — Physical and spectral data of Fmoc-protected *β*-amino alcohols

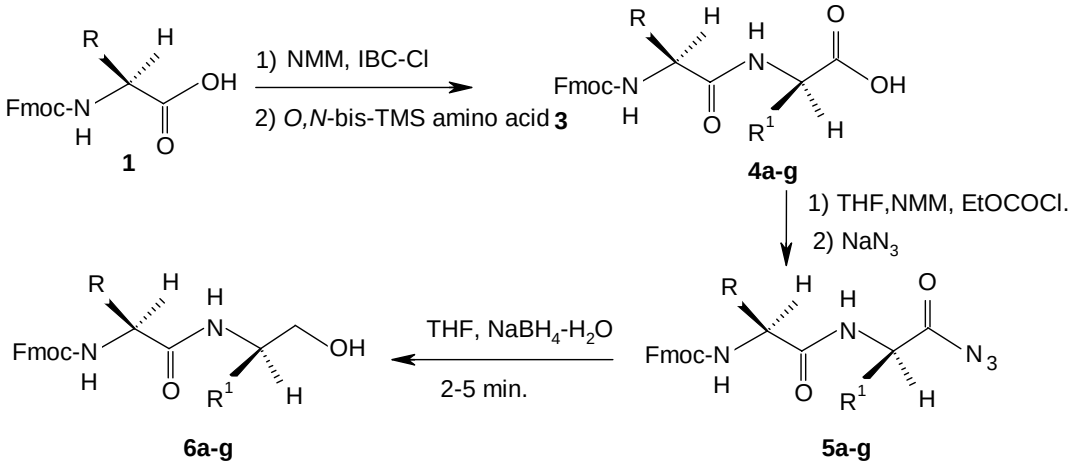
Sl No.	Fmoc-*β*-amino alcohols	Yield (%)	m.p (°C) (rep.[21])	m.p (°C) obs.	$[\alpha]_D^{25}$ (c1, $CHCl_3$) (rep.[21])	$[\alpha]_D^{25}$ (c1, $CHCl_3$) obs.	^{1}H NMR (δ, $CDCl_3$)	^{13}C NMR (δ, $CDCl_3$)	ES = MS (m/z) $[M+Na]^+$
2a	Phe-ol	87	(129-30)	127-29	(-23.2)	-22.8	2.0 (1H, s), 2.8 (2H, d, *J* = 6.2 Hz), 3.62(2H, m), 3.94 (1H, m), 4.2 (1H, t, *J* = 6.5 Hz), 4.38 (2H, m), 5.8 (1H, s), 7.1-7.4 (9H, m), 7.5 (2H, m), 7.8 (2H, d, *J* = 7.2 Hz).	37.2, 47.1, 53.6, 62.0, 67.0, 120.0, 124.2, 126.6, 127.0, 127.8, 128.4, 129.1, 137.2, 140.8, 144.0, 154.8.	396.0
2b	Val-ol	89	(107-08)	106-07	(-18.4)	-17.9	0.9 (6H, t), 1.9 (1H, m), 2.2 (1H, s), 3.4(2H, m), 18.2, 19.4, 28.9, 47.1, 58.2, 63.4, 3.7 (1H, m), 4.2 (1H, t, *J* = 6.5 Hz), 4.36(2H, m), 5.1 (1H, d, *J* = 7.8 Hz), 7.2-7.4 (4H, m), 7.6 (2H, d), 7.8 (2H, d).	66.8, 120.0, 124.5, 127.0, 127.8, 141.1, 143.4, 157.0,	348.1
2c	Gly-ol	90	138-40		-		2.2 (1H, br), 3.2-3.4 (4H, m), 4.2-4.4(3H,m), 5.2 (1H,d, *J* =8.0 Hz), 7.2-7.4 (4H,m), 7.6 (2H,d), 7.8 (2H, d, *J* = 7.5 Hz).	47.0, 65.2, 66.4, 120.2, 124.6, 127.0, 127.8, 141.2, 143.2, 157.0.	306.6
2d	Leu-ol	91	(112-13)	110-12	(-20.8)	-20.5	0.92 (6H, d, *J* = 5.2 Hz), 1.2 (2H, m), 1.6 (1H, m), 1.78 (1H, br), 3.5 (2H, m), 3.8 (1H, m), 4.2-4.45 (3H, m), 5.2 (1H, d, *J* = 8.6 Hz), 7.3-7.42 (4H, m), 7.6 (2H, m), 7.8 (2H, d).	21.2, 22.7, 40.1, 47.0, 50.4, 64.2, 66.8, 119.8, 124.6, 126.8, 127.8, 141.6, 143.8, 157.0.	362.2
2e	Ile-ol	88	(114-15)	114-15	(-20.0)	-21.0	0.9(6H, m), 1.12(1H, m), 1.6(2H, m), 2.1(1H, s), 3.5 (3H, m), 4.2 (1H, t, *J* = 6.4 Hz), 4.38 (2H, m), 5.2 (1H, d, *J* = 8.8 Hz), 7.2-7.4(4H, m), 7.6 (2H, d), 7.8 (2H, d).	11.2, 15.6, 25.8, 35.6, 47.2, 57.2, 64.0, 67.0, 120.0, 125.0, 127.0, 127.9, 141.4, 143.4, 156.8.	362.0
2f	Phg-ol	89	144-46		-18.2		1.9(1H,s), 2.2 (1H,s), 3.4(2H, m), 3.9(1H,m), 4.2-4.4 (3H,m), 5.0(1H,br), 7.18-7.5(9H,m), 7.7(2H,m), 7.84(2H,d, *J* = 7.2 Hz).	46.8, 53.4, 64.2, 65.8, 120.0, 125.0, 126, 127.0, 128.8, 130.0, 136.8, 141.0, 143.2, 157.2.	382.1
2g*	D-Phg-ol	88	145-47		+18.2		1.9(1H,s), 2.2 (1H,s), 3.4(2H, m), 3.9(1H,m), 4.2-4.4 (3H,m)5.0(1H,br), 7.18-7.5(9H,m), 7.7(2H,m), 7.84(2H,d, *J* = 7.3 Hz).	46.8, 53.4, 64.2, 65.8, 120.0, 125.0, 126, 127.0, 128.8, 130.0, 136.8, 141.0, 143.2, 157.2.	382.0

Contd

Table I — Physical and spectral data of Fmoc-protected *β*-amino alcohols—(*Contd*)

Sl No.	Fmoc-*β*-amino alcohols	Yield (%)	m.p (°C) (rep.[21])	m.p (°C) obs.	$[\alpha]_D^{25}$ (c1, $CHCl_3$) (rep.[21])	$[\alpha]_D^{25}$ (c1, $CHCl_3$) obs.	^{1}H NMR (δ, $CDCl_3$)	^{13}C NMR	ES = MS (m/z) $[M+Na]^+$
2h	Ala-ol	92	(120)	119-20	(-0.58)	-1.2	1.1(3H, d, *J* = 6.2 Hz), 2.4(1H, s), 3.6(2H, m), 3.8 (1H, m), 4.2(1H, t), 4.34(2H, d, *J* = 5.8 Hz), 127.0, 127.4, 141.2, 143.6, 157.2. 5.1(1H, d, *J* = 7.6 Hz), 7.2-7.34 (4H, m), 7.5(2H, d), 7.7(2H, d).	17.0, 47.6, 49.1, 65.8, 120.1, 124.6,	320.4
2i	Pro-ol	86	(89-90)	87-89	(-30.3)	-28.2	1.1-1.3(4H, m), 2.5 (1H, s), 3.1-3.4(4H, m), 4.1-4.36 (4H, m), 7.2-7.42(4H, m), 7.6(2H, d, *J* = 7.2 Hz), 7.78 (2H, d).	24.1, 28.2, 47.5, 47.8, 61.0, 66.8, 120.0, 124.8, 127.0, 127.9, 141.6, 143.6, 157.2.	346.0
2j	Ser(O^{t}Bu)-ol	86	(97-98)	96-98	(+12.3)	+12.8	1.2(9H, s), 3.2-3.4(4H, m), 4.2(1H, t, *J* = 6.4 Hz), 4.4 (2H, m), 5.6(1H, m), 7.2-7.4(4H, m), 7.54 (2H.d), 7.75(2H, d).	26.8, 45.8, 51.2, 62.4, 64.0, 67.0, 72.6, 119.8, 124.2, 126.9, 127.5, 140.6, 143.2, 157.0.	392.0
2k	Glu(O^{t}Bu)-ol	86	(55-57)	57-59	(-10.0)	-9.2	1.4(9H, s), 2.2(2H, m), 2.5(2H, t), 2.8(1H, s), 3.6 (2H, d), 4.2-4.4(4H, m), 5.8(1H, br), 7.2-7.4(4H, m), 7.6(2H, d), 7.8 (2H, d).	27.2, 37.0, 46.8, 50.2, 64.2, 67.2, 81.0, 120.0, 124.6, 127.0, 128.0, 141.2, 143.2, 155.8, 172.2.	434.6
2l	Asp(OBn)-ol	88	76-78		-7.8		2.2(2H,br), 2.8(1H,s), 3.6(2H,d, *J* = 4.4 Hz), 4.2-4.4(4H,m), 4.8(2H,s), 7.2-7.45(9H, m), 7.6(2H,d), 7.74(2H,d, *J* = 7.7 Hz).	27.2, 37.0, 46.8, 50.2, 64.2, 67.2, 81.0, 120.0, 124.6, 127.0, 128.0, 141.2, 143.2, 155.8, 172.2.	453.2

* Phg = Phenylglycine



Scheme II — Reduction of Fmoc-dipeptide acids to peptidyl alcohols

Experimental Section

Unless stated otherwise, the chemicals were obtained from commercial sources and used without further purification. Melting points were determined by capillary method and are uncorrected. TLC analysis was carried out on precoated silica gel plates using solvent systems: (a) chloroform - methanol - acetic acid (40:2:1) and (b) chloroform - methanol (9:1). Column chromatography was perfomed on Merck Kieselgel 60 (40-60 μm). IR spectra were recorded on a Nicolet model impact 400D FT-IR spectrometer. HPLC analysis was performed using Waters LC-3000 system consisting of a 484 tunable absorbance UV detector and a Millipore 745 data modulae using a C18 Bondapak (3.9 × 300 mm, 10 μ) column using the mobile phase acetonitrile - water : (95:5) with flow rate 1.0 mL/min, monitoring at 215 nm. Optical rotations were determined using automatic AA-10 polarimeter (Optical Activity, U.K.). ^{1}H NMR spectra in $CDCl_3$ were recorded on a Bruker AMX 400 MHz spectrometer (chemical shifts in δ, ppm). Mass spectra were recorded on ESMS and MALDI-TOF (KRATOS). Fmoc-amino acid azides as well as peptide acid azides, prepared by the reported procedures[15, 16], were isolated and characterized prior to use.

General procedure for the synthesis of Fmoc-*β*-amino alcohols 2. A stirred solution of Fmoc-protected amino acyl azide **1** (1 mmole) in THF (5 mL) was cooled to -10ºC and a solution of $NaBH_4$ (75.6 mg, 2 mmoles) in water (0.5 mL) was added in one portion and stirred till the completion of the reaction. The reaction mixture was concentrated under reduced pressure and residue was taken in dichloromethane (15 mL). The organic layer was successively washed with dil. HCl, aq. $NaHCO_3$ and then brine solution. It was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Addition of hexane (5 mL) precipitated pure alcohols. The resulting compounds were filtered and dried to obtain the alcohols **2a-l** as white solids (**Table I**).

Synthesis of *O,N-bis*-trimethylsilyl-amino acids 3. To a suspension of amino acid (1 mmole) in CH_2Cl_2 (5 mL) was added DIEA (0.35 mL, 2 mmoles, diisopropyl ethylamine) and TMS-Cl (0.15 mL, 2 mmoles, trimethylsilyl chloride) and refluxed under N_2 for 2 hr. The resulting solution was cooled to r.t. and used directly.

General procedure for the synthesis of N^{α}-protected peptide acids[22] 4. To a chilled solution of Fmoc-amino acid (1 mmole) and *N*-methylmorpholine (NMM, 0.11 mL, 1 mmole) in dry THF (5 mL) was added isobutoxycarbonyl chloride (IBC-Cl, 0.135 mL, 1 mmole) and stirred at 0°C for 20 min. Then, the freshly prepared solution containing *O,N-bis*-trimethylsilyl-amino acid was added directly in one portion. The stirring was continued till the completion of the reaction. The organic layer was evaporated and the resulting residue was partitioned between 10% aqueous Na_2CO_3 solution (10 mL) and washed with diethyl ether (3 × 10 mL) and acidified using 5% HCl. The precipitated solid was filtered, washed thoroughly with water and recrystallized using suitable solvent to obtain the peptide acid as a crystalline solid.

Fmoc-Phg-Phe-OH 4a: Yield 84 %; m.p. 170-72ºC; $[\alpha]^{25}_D$ -44.0 (c1, DMF); ^{1}H NMR (DMSO): δ 2.9 (2H, d, J = 6.3 Hz), 3.8 (2H, m), 4.2-4.35 (3H, m), 5.2 (1H, d, J = 8.4 Hz), 7.1-7.5 (14H, m), 7.55 (2H, d), 7.8 (2H, d, J = 7.2 Hz), 8.0 (1H, d, J = 8.6 Hz).

Fmoc-D-Phg-Phe-OH 4b: Yield 82%; m.p. 175-77 ºC; $[\alpha]^{25}_D$ +43.6 (c1, DMF); ^{1}H NMR (DMSO) : δ 2.9 (2H, d, J = 6.3 Hz), 3.75 (2H, m), 4.2-4.35 (3H, m), 5.3 (1H, d, J = 8.6 Hz), 7.1-7.5 (14H, m), 7.55 (2H, d, J = 7.0 Hz), 7.8 (2H, d), 8.0 (1H, d, J = 8.4 Hz).

Fmoc-Val-Gly-OH 4c: Yield 80%; m.p. 173-75ºC; $[\alpha]^{25}_D$ -13.6 (c1, DMF); ^{1}H NMR (DMSO) : δ 0.92 (6H, t), 1.8 (1H, m), 2.9 (2H, m), 3.7 (1H, t, J = 9.35 Hz), 4.2-4.4 (3H, m), 5.2 (1H, d, J = 8.6 Hz), 7.1-7.45 (4H, m), 7.55 (2H, d, J = 7.4 Hz), 7.8 (2H, d), 8.05 (1H, d, J = 8.7 Hz).

Fmoc-Ala-Leu-OH 4d: Yield 78%; m.p. 168-70ºC; $[\alpha]^{25}_D$ -23.6 (c1, DMF); ^{1}H NMR (DMSO) : δ 0.93 (6H,d, J = 5.2 Hz), 1.14 (3H, d, J = 6.1 Hz), 1.32 (2H, m), 1.6 (1H, m), 3.8 (2H, m), 4.2-4.35 (3H, m), 5.1 (1H, d, J = 8.8 Hz), 7.1-7.45 (4H, m), 7.65 (2H, d, J = 7.1 Hz), 7.85 (2H, d), 8.0 (1H, d, J = 8.7 Hz).

Fmoc-Asp(OBn)-Ala-OH 4e: Yield 80%; m.p. 148-49ºC; $[\alpha]^{25}_D$ +38.6 (c1, DMF); ^{1}H NMR (DMSO): δ 1.2 (3H, d, J = 6.7 Hz), 2.6 (2H, br), 3.6-3.75 (2H, m), 4.25 (1H, t, J = 6.5 Hz), 4.35 (2H, d, J = 6.4 Hz), 4.8 (2H, s), 5.3 (1H, d, J = 8.9 Hz), 7.15-7.7 (13H, m), 8.0 (1H, d, J = 8.9 Hz).

Fmoc-Ser(OBn)-Val-OH 4f: Yield 78 %; m.p. 120-22ºC; $[\alpha]^{25}_D$ -28.4 (c1, DMF); ^{1}H NMR (DMSO): δ 0.93 (6H, t), 1.8 (1H, m), 3.4-3.7 (4H, m), 4.1 (1H, t, J = 6.45 Hz), 4.35 (2H, d, J = 6.0 Hz), 4.9 (2H, s), 5.2 (1H, d, J = 8.9 Hz), 7.2-7.8 (13H, m), 8.0 (1H, d, J = 8.8 Hz).

Fmoc-Val-Ala-OH 4g: Yield 84%; m.p. 204-06ºC; $[\alpha]^{25}_{D}$ -12.2 (c1, DMF); ^{1}H NMR (DMSO): δ 0.85-0.94 (6H, t, J = 6.2 Hz), 1.3 (3H, d, J = 6.5 Hz), 1.9 (1H, m), 3.9 (1H, t, J = 8.7 Hz), 4.1-4.3 (4H, m), 5.2 (1H, d, J = 8.6 Hz), 7.2-7.5 (4H, m), 7.6 (2H, d, J=7.4 Hz), 7.85 (2H, d, J = 7.2 Hz), 8.0 (1H, d, J = 8.9 Hz).

General procedure for the synthesis of N^{α}-Fmoc-peptide acid azide 5. N^{α}-Fmoc-peptide acid (1 mmole) was dissolved in dry THF (5 mL) and cooled in an ice-salt bath. EtOCOCl (0.1 mL, 1 mmole) and NMM (0.11 mL, 1 mmole) were added to the above cooled solution and stirred for 10 min., while maintaining the temperature at –10°C. The resulting reaction mixture was treated with aqueous NaN_3 (0.1 g, 1.5 mmoles in 1 mL of water) at the same temperature. The reaction, as monitored by TLC as well as IR analysis, was complete in about 15 min. The THF solution was evaporated under reduced pressure at r.t. and the residue was taken in CH_2Cl_2 (25 mL). The CH_2Cl_2 layer was washed with cold water (2×10 mL), dried over anhydrous Na_2SO_4 and concentrated to half of its volume and *n*-hexane (10 mL) was added to obtain pure N^{α}-Fmoc-peptide acid azide as a crystalline solid.

Fmoc-Phg-Phe-CON$_3$ 5a: Yield 88%; m.p. 162-64ºC; IR (neat, $CHCl_3$): 2145, 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$) : δ 2.9 (2H, d, J = 6.3 Hz), 3.8-3.9 (2H, m), 4.2-4.45 (3H, t, J = 6.5 Hz), 5.2 (1H, s), 6.2 (1H, d, J = 8.9 Hz), 7.1-7.5 (14H, m), 7.55 (2H, d), 7.8 (2H, d, J = 7.5 Hz).

Fmoc-D-Phg-Phe-CON$_3$ 5b: Yield 89%; m.p. 165-67ºC; IR (neat, $CHCl_3$): 2150, 1708 cm^{-1}; ^{1}H NMR ($CDCl_3$) : δ 2.9 (2H, d, J=5.9 Hz), 3.9 (2H, m), 4.2-4.45 (3H, m), 5.3 (1H, d, J = 8.3 Hz), 6.3 (1H, d, J=9.0 Hz), 7.1-7.5 (14H, m), 7.55 (2H, d), 7.8 (2H, d, J = 7.2 Hz).

Fmoc-Val-Gly-CON$_3$ 5c: Yield 80 %; m.p. 154-56ºC; IR (neat, $CHCl_3$): 2152, 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$) : δ 0.92 (6H, t), 1.8 (1H, m), 2.9 (2H, m), 3.7 (1H, t), 4.2-4.4 (3H, m), 5.1 (1H, d, J = 7.9 Hz), 6.15 (1H, m), 7.1-7.45 (4H, m), 7.55 (2H, d), 7.8 (2H, d, J = 7.2 Hz).

Fmoc-Ala-Leu-CON$_3$ 5d: Yield 84%; m.p. 175-76ºC; IR (neat, $CHCl_3$): 2155, 1708 cm^{-1}; ^{1}H NMR ($CDCl_3$) : δ 0.93 (6H,d), 1.14 (3H, d, J = 6.1 Hz), 1.32 (2H, m), 1.6 (1H, m), 3.8 (2H, m), 4.2-4.35 (3H, m), 5.1 (1H, d, J = 8.5 Hz), 5.95 (1H, m), 7.1-7.45 (4H, m), 7.65 (2H, d), 7.85 (2H, d, J = 7.2 Hz).

Fmoc-Asp(OBn)-Ala-CON$_3$ 5e: Yield 86%; m.p. 165-67ºC; IR (neat, $CHCl_3$): 2145, 1755, 1708 cm^{-1}; ^{1}H NMR ($CDCl_3$) : δ 1.2 (3H, d, J = 6.1 Hz), 2.6 (2H, br), 3.6-3.7 (2H, m), 4.25-4.35 (3H, m), 4.8 (2H, s), 5.35 (1H, d, J = 8.6 Hz), 6.0 (1H, br), 7.1-7.5 (9H, m), 7.64 (2H, d), 7.85 (2H, d, J = 7.2 Hz).

Fmoc-Ser(OBn)-Val-CON$_3$ 5f: Yield 88%; m.p. 102-03ºC; IR (neat, $CHCl_3$): 2152, 1718 cm^{-1}; ^{1}H NMR ($CDCl_3$) : δ 0.93 (6H, t), 1.8 (1H, m), 3.4-3.7 (4H, m), 4.1 (1H, t), 4.35 (2H, d, J = 5.8 Hz), 4.9 (2H, s), 5.2 (1H, d, J = 7.8 Hz), 5.9 (1H, br), 7.1-7.45 (9H, m), 7.6 (2H, d), 7.85 (2H, d, J = 7.2 Hz).

Fmoc-Val-Ala-CON$_3$ 5g: Yield 88%; m.p. 175-76ºC; IR (neat, $CHCl_3$): 2155, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) : δ 0.88 (6H, m), 1.3 (3H, d, J = 6.4 Hz), 2.0 (1H, m), 3.9 (2H, m), 4.1-4.3 (3H, m), 5.2 (1H, d, J = 8.4 Hz), 5.9 (1H, br), 7.2-7.5 (4H, m), 7.6 (2H, d), 7.85 (2H, d, J = 7.1 Hz).

General procedure for the synthesis of Fmoc-peptidyl alcohols 6. A stirred solution of Fmoc-protected peptide acyl azide **5** (1 mmole) in THF (5 mL) was cooled to -10°C and a solution of $NaBH_4$ (75.6 mg, 2 mmoles) in water (0.5 mL) was added in one portion and stirred till the completion of the reaction. The reaction mixture was concentrated under reduced pressure and residue was taken in CH_2Cl_2 (15 mL). The organic layer was successively washed with dil. HCl, aq. $NaHCO_3$ and then brine solution. It was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Addition of hexane (about 5 to 10 mL) resulted in precipitation of pure alcohols. The resulting compounds were filtered and dried to obtain the alcohols **6a-g** as white solids.

Fmoc-Phg-Phe-ol 6a: Yield 82%; m.p. 135-37ºC; $[\alpha]^{25}_{D}$ -24.6 (c1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) : δ 2.4 (1H, s), 2.9 (2H, d, J = 6.3 Hz), 3.55 (2H, m), 3.8 (2H, m), 4.2-4.45 (3H, m), 5.1 (1H, s), 6.2 (1H, d, J = 8.9 Hz), 7.1-7.5 (14H, m), 7.55 (2H, d), 7.8 (2H, d, J = 7.4 Hz).

Fmoc-D-Phg-Phe-ol 6b: Yield 78%; m.p. 139-41 ºC; $[\alpha]^{25}_{D}$ +23.6 (c1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) : δ 2.35 (1H, s), 2.9 (2H, d, J = 6.3 Hz), 3.55 (2H, m), 3.8 (2H, m), 4.2-4.45 (3H, m), 5.0 (1H, s), 6.3 (1H, d, J = 8.8 Hz), 7.1-7.5 (14H, m), 7.55 (2H, d), 7.8 (2H, d, J = 7.2 Hz).

Fmoc-Val-Gly-ol 6c: Yield 80%; m.p. 180-82ºC; $[\alpha]^{25}_{D}$ -10.6 (c1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) : δ 0.92 (6H, t), 1.8 (1H, m), 2.2 (1H, s), 2.9 (2H, m), 3.45 (2H, m), 3.7 (1H, m), 4.2-4.4 (3H, m), 5.1 (1H, s), 5.9 (1H, d, J = 8.9 Hz), 7.1-7.45 (4H, m), 7.55 (2H, d, J = 7.2 Hz), 7.8 (2H, d).

Fmoc-Ala-Leu-ol 6d: Yield 82%; m.p. 150-52ºC; $[\alpha]^{25}_{D}$ -20.6 (c1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) : δ 0.93

(6H,d), 1.14 (3H, d, *J* = 6.1 Hz), 1.32 (2H, m), 1.6 (1H, m), 2.4 (1H, s), 3.55 (2H, m), 3.8 (2H, m), 4.2-4.35 (3H, m), 5.3 (1H, d, *J* = 8.9 Hz), 5.95 (1H, m), 7.1-7.45 (4H, m), 7.65 (2H, d, *J* = 7.4 Hz), 7.85 (2H, d).

Fmoc-Asp(OBn)-Ala-ol 6e: Yield 76%; m.p. 108-09ºC; $[\alpha]^{25}_{D}$ +18.6 (c1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) : δ 1.2 (3H, d, *J* = 6.4 Hz), 2.3 (1H, s), 2.6 (2H, br), 3.6-3.7 (4H, m), 4.25- 4.35 (3H, m), 4.8 (2H, s), 5.3 (1H, m), 6.2 (1H, d, *J* = 8.2 Hz*)*, 7.1-7.5 (9H, m), 7.64 (2H, d), 7.85 (2H, d, *J* = 7.4 Hz).

Fmoc-Ser(OBn)-Val-ol 6f: Yield 74%; m.p. 135-37ºC; $[\alpha]^{25}_{D}$ -17.4 (c1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) : δ 0.93 (6H, t), 1.8 (1H, m), 2.7 (1H, s), 3.4-3.8 (6H, m), 4.1- 4.35 (3H, m), 4.9 (2H, s), 5.2 (1H, d, *J* = 8.9 Hz), 6.2 (1H, d, *J* = 8.9 Hz), 7.1-7.45 (9H, m), 7.6 (2H, d), 7.85 (2H, d, *J* = 7.2 Hz).

Fmoc-Val-Ala-ol 6g: Yield 80 %; m.p. 257-59ºC; $[\alpha]^{25}_{D}$ -12.2 (c1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) : δ 0.85 (6H, m), 1.3 (3H, d, *J* = 6.3 Hz), 2.0 (1H, m), 2.5 (1H, br), 3.55 (2H, m), 3.9 (1H, t, *J* = 8.9 Hz), 4.2-4.4 (4H, m), 4.9 (1H, d, *J* = 7.9 Hz), 6.1 (1H, d, *J* = 8.8 Hz), 7.2-7.5 (4H, m), 7.6 (2H, d), 7.8 (2H, d, *J* = 8.8 Hz).

Acknowledgement

Authors thank the Department of Biotechnology, Govt. of India for financial assistance. Authors also thank Prof. P Balaram, MBU, IISc, for mass spectra and Sophisticated Instruments Facility, IISc, for NMR data.

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