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An Efficient Method for the Preparation of Peptide Alcohols

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Starting materials and solvents were purchased from commercial sources and used without further purification. Melting points were determined on a Fisher melting apparatus and are uncorrected. Column chromatography was carried out using silica gel 200-425 mesh. HPLC analyses were performed on Shimadzu SPD-20-A using a Whelk-O1 column with detection at 254 nm, a flow rate of 1.0 ml/min and hexanes/isopropanol (9:1) as the eluting solvent. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a 300 MHz NMR spectrometer with $CDCl_3$ or DMSO-d_6 as solvents. *J* values are given in Hz. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Elemental analyses were performed on a Carlo Erba-1106 instrument.

Preparation of Dipeptide alcohols 3a-p, (3d + 3d'); General Procedure

To a mixture of *N*-protected(α-aminoacyl)benzotriazoles **1** (1 mmol) in dry THF (10 mL) was added the α-aminoalcohol **2** (1 mmol) and the mixture was stirred for 6 hours at room temperature. The solvent was evaporated under vacuum and the residue was dissolved in ethyl acetate (15 mL), washed with Na_2CO_3 (3x5 mL), brine (1x5 mL), water (1x5 mL) dried over Na_2SO_4. The solvent was evaporated and the solid obtained was crystallized from ethyl acetate/hexanes to afford the corresponding dipeptide alcohols **3**.

***N*-Boc-L-Val-L-Phenylalaninol (3a)**[1a]. (0.301 g, 86%). White microcrystals; mp 145.0─146.0 °C (EtOAc/Hexanes). $[\alpha]_D^{24}$ -49.4 (*c* 1.0 in MeOH). (Found: C, 65.26; H, 8.94; N, 7.99. Calcd for $C_{19}H_{30}N_2O_4$: C, 65.12; H, 8.63; N, 7.99%). δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.37-7.26 (5 H, m, 5H, Ar*H*), 6.32 (1 H, d, *J* 7.2, N*H*), 4.98 (1 H, br s, N*H*), 4.24 (1 H, br s, O*H*), 3.89 (1 H, t, *J* 6.0, CH_2CH), 3.77-3.59 (2 H, m, $PhCH_2$), 3.00-2.86 (2 H, m, OCH_2), 2.22-2.11 (1 H, m, $(CH_3)_2CH$), 1.82 (1 H, br s, O*H*), 1.50 (9 H, s, 3 x CCH_3), 0.96 (3 H, d, *J* 6.9, $CH(CH_3)$) and 0.87 (3 H, d, *J* 5.7, $CH(CH_3)$); δ_C (75 MHz; $CDCl_3$;

Me_4Si) 172.0, 156.2, 137.8, 129.3, 128.6, 126.6, 80.2, 63.4, 60.6, 52.9, 37.0, 30.6, 28.4, 19.3 and 17.9.

***N*-Boc-L-Val-L-Leucinol (3b)**[1a]. (0.257 g, 77%). White microcrystals; mp 122.0─123.0 °C (EtOAc/Hexanes). $[\alpha]_D^{24}$ -42.5 (*c* 1.0 in MeOH). (Found: C, 59.35; H, 10.44; N, 8.61. Calcd for $C_{16}H_{32}N_2O_4 \cdot H_2O$: C, 59.05; H, 10.22; N, 8.61%). δ_H (300 MHz; $CDCl_3$; Me_4Si) 6.16 (1 H, br s, N*H*), 5.05 (1 H, br s, N*H*), 4.10-3.98 (1 H, m, NHC*H*CO), 3.81 (1 H, t, *J* 7.2, O*H*), 3.70-3.63 (1 H, m, $CH_3)_2CHCH_2$), 3.55-3.48 (1 H, m, $(CH_3)_2CHCH_2$), 2.90-2.81 (1 H, m, C*H*), 2.18-2.06 (1 H, m, C*H*), 1.68-1.54 (1 H, m, C*H*), 1.43 (9 H, s, $(CH_3)_3C$), 1.40-1.28 (2 H, m, CH_2) and 0.98-0.89 (12 H, m, 2 x $(CH_3)_2CH$); δ_C (75 MHz; $CDCl_3$; Me_4Si) 172.3, 156.2, 80.2, 65.8, 60.7, 50.1, 40.0, 30.5, 28.4, 24.9, 23.2, 22.2, 19.4 and 18.2.

***N*-Boc-L-Val-L-tert-Leucinol (3c)**. (0.263 g, 81%). White microcrystals; mp 72.0─74.0 °C (EtOAc/Hexanes). $[\alpha]_D^{24}$ -25.7 (*c* 1.0 in MeOH). (Found: C, 59.35; H, 10.44; N, 8.61. Calcd for $C_{16}H_{32}N_2O_4 \cdot \frac{1}{2}H_2O$: C, 59.05; H, 10.22; N, 8.61%). δ_H (300 MHz; $CDCl_3$; Me_4Si) 6.17 (1 H, d, *J* 7.2, N*H*), 5.01 (1 H, br m, N*H*), 3.86-3.79 (3 H, m, CH_2 overlapped with C*H*), 3.53-3.47 (1 H, m, C*H*), 2.60 (1 H, br m, O*H*), 2.24-2.17 (1 H, m, C*H*), 1.44 (9 H, s, $(CH_3)_3C$) and 1.01-0.94 (15 H, m, $(CH_3)_3C$ overlapped with $(CH_3)_2CH$); δ_C (75 MHz; $CDCl_3$; Me_4Si) 172.8, 156.3, 80.3, 62.7, 61.1, 59.7, 33.6, 30.0, 28.4, 27.0, 19.5, 18.2.

***N*-Z-L-Ala-L-Phenylalaninol (3d)**[3g]**.** (0.313 g. 88 %). White microcrystals; mp 118─120.0 °C. (from ethyl acetate/hexanes). $[\alpha]_D^{24}$ -51.0 (*c* 1.0 in MeOH). (Found: C, 67.53; H, 6.95; N, 7.73. Calc. for $C_{20}H_{24}N_2O_4$: C, 67.40; H, 6.79; N, 7.86.); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.19-7.36 (10 H, m, Ar*H)*, 6.62-6.64 (1 H, m, N*H*), 5.50 (1 H, d, *J* 6.6,

N*H*), 5.06-5.15 (2 H , m, CH_2), 4.14-4.22 (2 H , m, CH_2), 3.64 (1 H, br s, *CH*), 3.58 (1 H, br s, *CH*), 3.14 (1 H, br s, *OH*), 2.85 (2 H, d, *J* 6.6, CH_2) and 1.31 (3 H, d, *J* 6.9, CH_3). δ_C (75 MHz; $CDCl_3$; Me_4Si) 172.8**,** 156.3, 137.8, 136.2**,** 129.4, 128.8, 128.7, 128.5, 128.3, 126.8, 67.3, 63.6, 53.0, 51.0, 37.0 and 18.6 .

***N*-Z-DL-Ala-L-Phenylalaninol (3d + 3d')**. (0.317 g, 89 %). White microcrystals; mp 118─120.0 °C (from ethyl acetate/hexanes). (Found: C, 67.42; H, 6.97; N, 7.73. Calc. for $C_{20}H_{24}N_2O_4$: C, 67.40; H, 6.79; N, 7.86.). δ_H (300 MHz; $CDCl_3$; Me_4Si) (Diastereomeric mixture) 7.12-7.44 (10 H, m, Ar*H)*, 6.50-6.78 (1 H, m, N*H*), 5.68 (1 H, d, *J* 7.2, N*H*), 5.45 (1 H , br s, C*H*), 4.96-5.20 (2 H , m, CH_2), 4.02-4.25 (2 H , m, CH_2), 3.60-3.78 (1 H, br m, C*H*), 3.46-3.59 (1 H, m, C*H*), 2.84 (2 H, br s, C*H, OH*) and 1.20-1.34 (3 H , m, CH_3). δ_C (75 MHz; $CDCl_3$; Me_4Si) δ 173.0**,** 156.4, 137.8, 136.2**,** 129.4, 128.8, 128.7, 128.5, 128.4, 128.3, 128.2, 126.7, 67.3, 67.2, 63.8, 63.6, 53.0, 52.8, 50.9, 37.1, 37.0, 31.1, 18.6 and 18.8.

***N*-Z-L-Ala-L-Leucinol (3e)**. (0.270 g., 84%). White microcrystals; mp 89.0─90.0 °C (from ethyl acetate/hexanes) (lit.[13] 90.0 °C). $[\alpha]_D^{24}$ +21.0 (*c* 1.0 in MeOH). (Found: C, 63.48; H, 8.35; N, 8.65. Calc. for $C_{17}H_{26}N_2O_4$: C, 63.33; H, 8.13; N, 8.69.). δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.29-7.42 (5 H, m, Ar*H)*, 6.42 (1 H, br s, N*H*), 5.55 (1 H, br s, N*H*), 5.10 (2 H , s, CH_2), 4.18-4.30 (1 H, m, *CH*), 3.85-4.20 (1 H, m, C*H*), 3.63 (1 H, d, *J* 8.4, C*H*), 3.43-3.55 (1 H, m, C*H*), 3.03 (1 H, br s, OH), 1.51-1.62 (1 H, m, C*H*), 1.36 (3 H , d, *J* 7.2, CH_3), 1.30-1.44 (2 H, m, CH_2) and 0.70-0.95 (6 H , m, 2 x CH_3). δ_C (75 MHz; $CDCl_3$; Me_4Si). 173.0, 156.2, 136.2, 128.8, 128.5, 128.3, 67.3, 65.7, 51.0, 50.2, 40.1, 25.0, 23.2, 22.3 and 18.7.

***N*-Fmoc-L-Met-L-Phenylalaninol (3f)**. (0.302 g, 60%). White solid; mp 157─159 ºC (from hexanes). $[\alpha]_D^{24}$ -26.0 (*c* 1.0 in MeOH). (Found: C, 68.74; H, 6.63; N, 5.49. Calc. for $C_{29}H_{32}N_2O_4S$: C, 69.02; H, 6.39; N, 5.55%). δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.77 (2 H, d, *J* 7.6, 2 x N*H*), 7.58 (2 H, d, *J* 7.3, Ar*H*), 7.42 (2 H, t, *J* 7.3, Ar*H*), 7.32 (2 H, t, *J* 7.4, Ar*H*), 7.20-7.30 (7 H, m, Ar*H*), 6.40 (1 H, d, *J* 7.0, Ar*H*), 5.46 (1 H, d, *J* 7.0, OCH_2CH), 4.42 (2 H, t, *J* 7.1, OCH_2CH, OCH$_2$C*H*), 4.28 (1 H, d, *J* 7.1, C*H*), 4.21 (2 H, t, *J* 6.6, C*H*), 3.68-3.72 (1 H, m, CHCH_2OH), 3.55-3.61 (1 H, m, CHCH_2OH), 2.86 (2 H, d, *J* 7.0, CH_2), 2.47-2.49 (3 H, m, CH_2) and 2.07 (3 H, s, CH_3); δ_C (75 MHz, $CDCl_3$; Me_4Si) 171.2, 156.1, 143.6, 141.3, 137.4, 129.1, 128.6, 127.8, 127.1, 126.7, 125.0, 120.0, 67.0, 63.7, 54.0, 52.9, 47.1, 36.9, 31.3, 30.0 and 15.1.

***N*-Fmoc-L-Val-L-Phenylglycinol (3g)**. (0.247 g, 54%). White solid; mp 171─173 ºC (from hexanes). $[\alpha]_D^{24}$ -12.0 (*c* 1.0 in MeOH). (Found: C, 71.94; H, 6.63; N, 6.41. Calc. for $C_{28}H_{30}N_2O_4 \cdot ½H_2O$: C, 71.93; H, 6.68; N, 5.99%). δ_H (300 MHz; DMSO-d_6; Me_4Si) 8.25 (1 H, d, *J* 8.0, N*H*), 7.89 (3 H, d, *J* 7.1, Ar*H* and N*H*), 7.71-7.74 (2 H, m, Ar*H*), 7.16-7.51 (9 H, m, Ar*H*), 4.87 (2 H, br s, OCH_2CH), 4.11-4.36 (3 H, m, 3 x C*H*), 3.85-4.04 (1 H, m, CH$_2$O*H*), 3.55 (2 H, br s, CH_2OH), 1.85-2.10 (1 H, m, CH$_3$C*H*CH$_3$) and 0.88 (6H, t, *J* 6.3, 2 x CH_3); δ_C (75 MHz; DMSO-d_6; Me_4Si) 170.8, 156.1, 144.0, 141.0, 140.7, 128.0, 127.7, 127.1, 127.0, 126.8, 125.4, 121.4, 120.1, 64.7, 65.7, 60.4, 54.9, 30.4, 46.7, 19.3 and 18.4.

***N*-Z-L-Ala-L-Phenylglycinol (3h)**. (0.280 g, 82% yield). White microcrystals; mp 131.0─133.0 °C (from ethyl acetate/hexanes). $[\alpha]_D^{24}$ -29.0 (*c* 1.0 in MeOH). (Found: C, 66.51; H, 6.31; N, 7.99). Calc. for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18). δ_H (300 MHz; $CDCl_3$; Me_4Si); 7.16-7.33 (10 H, m, Ar*H*), 6.97 (1 H, br s, N*H*), 5.40 (1 H, d, *J* 7.2,

N*H*), 5.08 (2 H, s, CH_2), 4.95-5.03 (1 H, m, C*H*), 4.29 (1 H, t, *J* 6.6, C*H*), 3.77-3.82 (2 H, m, CH_2), 2.70 (1 H, br s, O*H*) and 1.37 (3 H, d, J 6.9, CH_3); δ_C (75 MHz, $CDCl_3$; Me_4Si) 172.7, 156.2, 138.9, 136.2, 129.0, 128.8, 128.5, 128.3, 128.0, 126.8, 67.3, 66.4, 55.9, 53.4, 51.0 and 18.0.

***N*-Cbz-L-Phe-L-Phenylglycinol (3i)**. (0.192 g, 46%). White solid; mp 131─133 ºC (from hexanes); $[\alpha]_D^{24}$ -83.0 (*c* 1.0 in MeOH). (Found: Found: C, 71.49; H, 6.52; N, 6.50. Calc. for $C_{25}H_{26}N_2O_4$: C, 71.75; H, 6.26; N, 6.69). δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.25-7.30 (14 H, m, Ar*H*), 7.10 (1 H, d, *J* 6.3, N*H*), 6.66 (1 H, br s, Ar*H*), 5.61 (1 H, d, *J* 2.3, N*H*), 4.92-5.07 (3 H, m, CH_2Ar and C*H*), 4.47 (1 H, m, C*H*), 3.59-3.70 (2 H, m, CH_2OH), 2.96-3.07 (2 H, m, CHCH_2Ar) and 2.79 (1 H, br s, O*H*); δ_C (75 MHz; $CDCl_3$; Me_4Si) 171.2, 170.1, 156.2, 143.5, 138.7, 136.6, 129.4, 128.9, 128.7, 128.4, 128.2, 127.9, 127.3, 126.8, 67.3, 65.9, 56.7, 55.9 and 39.0.

***N*-Cbz-L-Phe-L-Luecinol (3j)**. (0.179 g, 45%). White solid; mp 99.0─101.0 ºC (from hexanes); $[\alpha]_D^{24}$ -10.0 (*c* 1.0 in MeOH). (Found: C, 69.01; H, 7.99; N, 7.07. Calc. for $C_{23}H_{30}N_2O_4$: C, 69.32; H, 7.59; N, 7.03%). δ_H (300 MHz; $CDCl_3$, Me_4Si) 7.24-7.34 (10 H, m, Ar*H*), 5.71 (1 H, d, *J* 8.1, N*H*), 5.47 (1 H, br s, N*H*), 5.05-5.09 (2 H, br s, OCH_2Ar), 4.36 (1 H, d, *J* 6.9, C*H*), 3.94 (1 H, br s, C*H*CH_2OH), 3.42-3.45 (1 H, m, CHCH_2OH), 3.30-3.35 (1 H, m, CHCH_2Ar), 3.12-3.18 (1 H, m, CHCH_2Ar), 2.95-3.03 (1 H, m, CHCH_2OH), 2.00 (1 H, br s, O*H*), 1.45-1.47 (1 H, m, CH_3C*H*CH_3), 1.22-1.24 (2 H, m, CH_2) and 0.85 (6 H, d, *J* 6.3, 2 x CH_3); δ_C (75 M; $CDCl_3$; Me_4Si) 171.1, 156.2, 136.7, 136.2, 129.5, 129.0, 128.8, 128.5, 128.3, 127.4, 67.4, 65.5, 56.9, 50.1, 24.8, 23.1, 22.3, 40.0 and 39.0.

***N*-Fmoc-L-Glu(OtBu)-L-Phenylalaninol (3k).** (0.447 g, 80%). White microcrystals; mp 128.0─130.0 ºC (ethyl acetate/Hexanes); $[\alpha]_D^{24}$ - 41.0 (*c* 1.0 in MeOH). Found: C, 70.62; H, 6.51; N, 4.95. Calc. for $C_{33}H_{38}N_2O_6$: C, 70.95; H, 6.86; N, 5.01); δ_H (300 MHz; DMSO-d_6; Me_4Si) 7.91 (2 H, d, *J* 7.5 , Ar*H*), 7.72-7.78 (2 H, m, Ar*H*), 7.69 (1 H, d, *J* 8.4, N*H*), 7.43 (3 H, t, *J* 7.5, Ar*H*), 7.34 (2 H, t, *J* 7.5, Ar*H*), 7.20-7.26 (4 H, m, Ar*H*), 7.15 (1 H, d, *J* 4.8, N*H*), 4.81 (1 H, t, *J* 5.4, C*H*), 4.20-4.33 (3 H, m, CH_2, C*H*), 3.85-4.00 (2 H, m, CH_2), 3.29-3.32 (2 H, m, CH_2), 2.83(1 H, dd, *J* 5.7, 13.5, C*H* of CH_2), 2.65 (1 H, dd, *J* 8.1, 13.5, C*H* of CH_2), 2.15 (2 H, t, *J* 7.2, CH_2), 1.62-1.85 (2 H, m, C*H*, O*H*), 1.40 (9 H, s, 3x CH_3); δ_C (75 MHz, DMSO-d_6; Me_4Si) 171.6, 170.7, 155.7, 143.9, 143.7, 140.7, 140.7, 138.9, 129.1, 128.9, 128.0, 127.6, 127.2, 127.0, 125.8, 125.2, 121.3, 120.1, 120.0, 79.6, 65.6, 62.2, 54.0, 52.3, 46.6, 36.4, 31.3, 27.7 and 27.5.

***N*-Fmoc-L-Asp(OtBu)-L-Phenylglycinol (3l)**. (0.408 g, 77%). White microcrystals; mp 164.0─166.0 ºC (from ethyl acetate/Hexanes); $[\alpha]_D^{24}$ -14.0 (*c* 1.0 in MeOH). HRMS, $[M+Na]^+$: Found. 553.2306, Theoretical for $C_{31}H_{34}N_2O_6Na^+$: 553.2309; δ_H (300 MHz; DMSO-d_6; Me_4Si) 8.24 (1 H, d, *J* 7.8, N*H*), 7.90 (2 H, d, *J* 7.5, Ar*H*), 7.68-7.716 (3 H, m, Ar*H*, N*H*), 7.42 (3 H, t, *J* 7.2, Ar*H*), 7.20-7.36 (6 H, m, Ar*H*), 4.93 (1 H, brs, C*H*), 4.78-4.83 (1 H, m, C*H*), 4.40-4.50 (1 H, m, C*H*), 4.20-4.30 (3 H, m, CH_2 & C*H* of CH_2), 3.55 (2 H, brs, CH_2), 2.70 (1 H, dd, *J* 4.5, 16.2, C*H* of CH_2), 2.43-2.47 (1 H, m, O*H*), 1.38 (s, 9H, 3x CH_3); δ_C (75 MHz, DMSO-d_6; Me_4Si) 170.2, 169.4, 155.8, 143.9, 143.7, 140.9, 140.7, 128.9, 128.0, 127.7, 127.3, 127.1, 127.0, 126.9, 126.7, 125.3, 121.4, 120.1, 120.0, 80.1, 65.8, 64.6, 55.1, 51.5, 46.6, 37.7 and 27.7.

***N*-Fmoc-L-Lys(Boc)-L-Leucinol (3m).** (0.482 g, 85%). White microcrystals; mp 112.0─114.0 ºC (from ethyl acetate/Hexanes); $[\alpha]_D^{24}$ -30.0 (*c* 1.0 in MeOH). Found: C,

67.58; H, 8.46; N, 7.28. Calc. for $C_{32}H_{45}N_3O_6$: C, 67.70; H, 7.99; N, 7.40); δ_H (300 MHz; DMSO-d_6; Me_4Si) 7.90 (2 H, d, *J* 7.5, Ar*H*), 7.73 (2 H, d, *J* 69, Ar*H*), 7.40-7.50 (4 H, m, Ar*H,* 2x N*H*), 7.33 (2 H, t, *J* 7.2, Ar*H*), 6.78 (1 H, brs, N*H*), 4.64 (1 H, brs, C*H*), 4.25 (3 H, brs, CH_2, C*H*), 3.90-4.00 (1 H, m, C*H*), 3.79 (1 H, brs, C*H* of CH_2), 3.30 (1 H, brs, C*H*), 3.21 (1 H, brs, C*H* of CH_2), 2.89 (2 H, d, *J* 5.1, CH_2), 1.50-1.65 (3 H, m, CH_2, O*H*), 1.37 (9 H, s, 3x CH_3), 1.20-1.40 (6 H, m, 3x CH_2), 0.84 (3 H, d, *J* 6.6, CH_3), 0.81 (3 H, d, *J* 6.6, CH_3); δ_C (75 MHz, DMSO-d_6; Me_4Si) 171.4, 155.8, 155.5, 143.9, 143.7, 140.7, 127.6, 127.2, 127.0, 125.3, 120.1, 77.3, 65.5, 63.7, 54.7, 48.6, 46.7, 31.8, 29.2, 28.2, 24.0, 23.3, 22.8 and 21.8.

***N*-Fmoc-L-Trp-L-Phenylalaninol (3n).** (0.464 g, 83%). White microcrystals; mp 146.0─148.0 ºC (from ethyl acetate/Hexanes); $[\alpha]_D^{24}$ -31.0 (*c* 1.0 in MeOH). Found: C, 75.01; H, 6.09; N, 7.45. Calc. for $C_{35}H_{33}N_3O_4$: C, 75.11; H, 5.94; N, 7.51); δ_H (300 MHz; DMSO-d_6; Me_4Si) 10.83 (1 H, s, N*H*), 7.83-7.90 (2 H, m, Ar*H*), 7.62-7.69 (3 H, m, Ar*H,* N*H*), 7.66 (3 H, t, *J* 9.6, Ar*H*), 7.49 (1 H, d, *J* 8.7, N*H*), 7.40 (2 H, t, *J* 9, Ar*H*), 7.20-7.35 (6 H, m, Ar*H*), 7.13-7.16 (2 H, m, Ar*H*), 7.07 (1 H, t, *J* 7.2 , Ar*H*), 6.98 (1 H, t, *J* 6.9, Ar*H*), 4.82 (1 H, br s, C*H*), 4.21-4.27 (1 H, m, C*H*), 4.13-4.17 (2 H, m, CH_2), 3.90-3.95 (1 H, m, C*H* of CH_2), 3.25-3.32 (2 H, m, CH_2), 3.04 (1 H, dd, *J* 3.9, 14.4 , C*H* of CH_2), 2.83-2.95 (2 H, m, CH_2), 2.63-2,70 (1 H, m, O*H*); δ_C (75 MHz, DMSO-d_6; Me_4Si) 171.4, 155.6, 143.8, 143.7, 140.6, 139.0, 136.0, 129.1, 128.0, 127.6, 127.3, 127.0, 125.8, 125.3, 125.2, 123.6, 120.8, 120.0, 118.5, 118.1, 111.2, 110.3, 65.6, 62.2, 55.6, 52.4, 46.6, 36.4 and 28.0.

***N*-Fmoc-L-His(Trt)-L-*t*-Leucinol (3o).** (0.431 g, 60%). White microcrystals; mp 128.0─130.0 ºC (Diethyl ether/Hexanes); $[\alpha]_D^{24}$ -21.0 (*c* 1.0 in MeOH). HRMS,

$[M+Na]^+$: Found. 741.3425 , Theoretical for $C_{46}H_{46}N_4O_4.Na^+$: 741.3411; δ_H (300 MHz; DMSO-d_6; Me_4Si) 7.89 (2 H, d, *J* 7.8 , Ar*H*),7.66 (2 H, t, *J* 7.8, Ar*H*), 7.20-7.49 (16 H, m, Ar*H*, N*H*), 7.04-7.06 (6 H, m, Ar*H*), 6.75 (1 H, s, N*H*), 4.71 (1 H, brs, C*H*), 4.29-4.36 (1 H, m, C*H*), 4.14-4.22 (3 H, m, CH_2, C*H*), 3.50-3.64 (2 H, m, CH_2), 2.91 (1 H, dd, *J* 4.2, 14.7, C*H* of CH_2), 2.79 (1 H, dd, *J* 3.0, 15.0, C*H* of CH_2), 1.25 (1 H, brs, O*H*), 0.84 (9 H, s, 3x CH_3); δ_C (75 MHz, DMSO-d_6; Me_4Si) 171.2, 155.6, 143.7, 142.2, 140.6, 137.5, 137.1, 129.2, 128.1, 127.9, 127.6, 127.0, 125.2, 120.0, 119.0, 74.4, 65.7, 60.7, 58.7, 54.7, 46.6, 33.6, 31.0 and 26.8.

***N*-Fmoc-L-Cys(Trt)-L-Leucinol (3p).** (0.479 g, 70 %). White microcrystals; mp 128.0─130.0 ºC (Diethyl ether/Hexanes); $[\alpha]_D^{24}$ -20.0 (*c* 1.0 in MeOH). HRMS, $[M+Na]^+$: Found. 707.2933, Theoretical for $C_{43}H_{44}N_2O_4S.Na^+$, 707.2914; δ_H (300 MHz; $CDCl_3$; Me_4Si 0.72- 7.60 (2 H, t, *J* 5.4, Ar*H*), 7.41 (2 H, d, *J* 6.6, Ar*H*), 7.20-7.32 (8H, m, Ar*H*), 7.00-7.18 (11 H, m, Ar*H*), 5.67 (1 H, d, *J* 5.7, N*H*), 4.95 (1 H, d, *J* 4.2, N*H*), 4.23 (2 H, d, *J* 6, CH_2), 4.00-4.05 (1H, m, C*H*), 3.79 (1H, br s, C*H*), 3.61 (1 H, d, *J* 4.8, C*H*), 3.49 (1 H, d, *J* 9.3, C*H* of CH_2), 3.25-3.30 (1 H, m, C*H* of CH_2), 2.40-2.60 (2 H, m, CH_2), 1.36-1.48 (1 H, m, O*H*), 1.36-1.48 (1 H, m, C*H*), 1.12-1.18 (2 H, m, CH_2), (6 H, d, *J* 6, 2x CH_3); δ_C (75 MHz, DMSO-d6; Me_4Si) 170.6, 156.3, 144.5, 143.8, 143.8, 141.5, 129.7, 128.4, 128.0, 127.3, 127.2, 125.2, 125.2, 120.2, 67.6, 67.3, 65.6, 54.5, 50.5, 47.3, 40.0, 33.9, 25.0, 23.2 and 22.3.

Preparation of *N*-Fmoc-α-dipeptides 4a, 4b; General Procedure

N-Protected(α-aminoacyl)benzotriazoles **1** (0.5 mmol) were added at room temperature to a solution of unprotected α-amino acid (0.5 mmol) in a solution of MeCN (7 mL) and H_2O (3 mL) in the presence of Et_3N (0.5 mmol). The reaction mixture was then stirred at

20 ^{0}C until **1** was completely consumed. Then 6 M HCl aq. (1 mL) was added, and the solution was concentrated under reduced pressure. The residue was extracted with EtOAc, washed with 6 M HCl aq., NaCl aq., and the organic layer was dried over $MgSO_4$. Evaporation of the solvent followed by recrystallization from DCM / hexanes afforded desired dipeptides **4a, 4b**.

***N*-Fmoc-L-Phe-L-Ala-OH (4a)**. (1.2 g**,** 85%). White microcrystals; mp 208.0─210.0 °C (from ethyl acetate/hexanes) (Lit.[12b] 208.7─210.6 °C). $[\alpha]_D^{24}$ -32.0 (*c* 1.0 in MeOH). δ_H (300 MHz, DMSO-d_6; Me_4Si) 8.39 (1 H, d, *J* 7.2, N*H*), 7.87 (2 H, d, *J* 7.5, Ar*H*), 7.62-7.66 (3 H, m, 2 x Ar*H*, N*H*), 7.35-7.43 (4 H, m, Ar*H*), 7.17-7.32 (5 H, m, Ar*H*), 4.29-4.34 (2 H, m, CH_2), 4.12-4.17 (3 H, m, C*H* and CH_2), 3.03-3.08 (1 H, m, C*H*), 2.78 (1 H, t, *J* 12.6, C*H*) and 1.32 (3 H, d, *J* 7.1, CH_3); δ_C (75 MHz, DMSO-d_6; Me_4Si) 171.1, 171.6, 155.9, 143.8, 143.7, 140.7, 138.3, 129.3, 128.1, 127.7, 127.1, 126.3, 125.4, 125.3, 120.1, 65.7, 56.0, 47.6, 46.6, 37.5 and 17.2.

***N*-Fmoc-Gly-L-Leu-OH (4b).** (0.4 g**,** yield: 78%). White microcrystals. mp 133.0─134.0 °C (from ethyl acetate/hexanes) (lit.[14] 133.0─135.0 °C). $[\alpha]_D^{24}$ -29.0 (*c* 1.0 in MeOH). δ_H (300 MHz, $CDCl_3$/DMSO-d_6; Me_4Si); 7.75 (2 H, d, *J* 7.2, Ar*H*), 7.57-7.66 (3 H, m, Ar*H*, N*H*), 7.30-7.42 (4 H, m, Ar*H*), 6.93 (1 H, br s, N*H*), 4.50 (1 H, br s, C*H*), 4.34 (1 H, d, *J* 6.3, C*H*), 4.23 (1 H, d, *J* 5.7, C*H*), 3.86 (2 H, s, CH_2), 1.62-1.67 (3 H, m, C*H,* CH_2), 1.16-1.20 (1 H, m, C*H*), 0.91 (6 H, d, *J* 4.2, 2 x CH_3); δ_c (75 MHz, $CDCl_3$/ DMSO-d_6; Me_4Si) 173.7, 168.5, 143.1, 140.3, 127.0, 126.4, 124.5, 119.2, 65.8, 49.9, 46.3, 43.4, 40.34, 23.9, 22.2, 21.1.

Preparation of *N*-Fmoc-dipeptidoylbenzotriazoles 5a, 5b; General Procedure.

To a solution of BtH (5.23 mmol) in CH_2Cl_2 (20 mL) was added $SOCl_2$ (1.57 mmol). After stirring for 30 min at room temperature, the reaction mixture was cooled to -15°C, and Fmoc-protected dipeptide (**4a or 4b**) (1.31 mmol) was added in one portion. The reaction mixture was stirred at -15°C for a further 3 hours. The white precipitate was filtered off and the filtrate was concentrated to dryness under reduced pressure, residue was dissolved in CH_2Cl_2 (60 mL) and the solution was washed with sat. Na_2CO_3 (5 mL, 3 times), brine (5 mL, 2 times) and dried over anhydrous $MgSO_4$. Evaporation of solvent and recrystalization from CH_2Cl_2/hexanes gave *N*-Fmoc-dipeptidoylbenzotriazoles **5a, 5b**.

***N*-Fmoc-L-Phe-L-Ala-Bt (5a).** (0.448 g, 80%). White microcrystals, mp 155─156°C (from ethyl aceate/methylene chloride). (Lit.[12b] 155─157°C). $[\alpha]_D^{24}$ -49.5 (*c* 1.0 in MeOH). δ_H (300 MHz, DMSO-d_6; Me_4Si) 9.03 (1 H, d, *J* 5.4, N*H*), 8.29 (1 H, d, *J* 8.4, Ar*H*), 8.24 (1 H, d, *J* 8.1, Ar*H*), 7.80-7.89 (4 H, m, Ar*H*), 7.60-7.70 (3 H, m, Ar*H* and N*H*), 7.35-7.40 (4H, m, Ar*H*), 7.17-7.32 (5 H, m, Ar*H*), 5.64 (1 H, t, *J* 6.6, C*H*), 4.36-4.41 (1 H, m, C*H*), 4.13-4.17 (3 H, m, C*H* and CH_2) 3.06-3.09 (1 H, m, C*H*), 2.79 (1 H, t, *J* 12.3, C*H*) and 1.59 (3 H, d, *J* 7.2, CH_3); δ_C (75 MHz, DMSO-d_6; Me_4Si) 172.1, 171.8, 155.8, 145.3, 143.6, 140.5, 138.0, 131.0, 130.6, 129.2, 127.5, 126.9, 126.7, 126.2, 125.3, 125.2, 120.1, 120.0, 113.9, 65.5, 55.6, 48.6, 46.4, 37.2 and16.5.

***N*-Fmoc-Gly-L-Leu-Bt (5b).** (0.419 g, yield: 82%) White microcrystals; mp. 165─167°C (from ethyl acetate/methylene chloride). $[\alpha]_D^{24}$ -50.0 (*c* 1.0 in MeOH). (Found: C, 67.77; H, 5.63; N, 13.64. Calc. for $C_{29}H_{29}N_5O_4$: C, 68.09; H, 5.71; N, 13.69). δ_H (300 MHz, $CDCl_3$; Me_4Si), 8.19-8.21 (1 H , m, Ar*H*), 8.12 (1 H, d, *J* 8.4, Ar*H*), 7.75

(2 H, d, *J* 7.2, Ar*H*), 7.50-7.65 (4 H, m, Ar*H*), 7.28-7.42 (5 H, m, Ar*H*, N*H*), 6.79 (1 H, br s, N*H*), 6.01-6.08 (1 H, m, N*H*)), 5.53 (1 H, br s, C*H*), 4.43-4.45 (2 H, m, CH_2), 4.24 (1 H, t, *J* 6.6, C*H*), 3.98-4.02 (2 H, m, CH_2), 1.74-1.92 (2 H, m, CH_2), 1.06 (3 H, d, *J* 6.0, CH_3), 0.93 (3 H, d, *J* 6.3, CH_3); δ_c (75 MHz, $CDCl_3$; Me_4Si) 171.9, 169.5, 156.9, 146.1, 143.8, 141.4, 131.2, 130.9, 127.9, 127.3, 126.7, 125.2, 120.5, 120.2, 114.5, 67.6, 51.9, 47.2, 41.8, 31.2, 25.5, 23.3, and 21.5.

Preparation of Preparation of Tripeptide alcohols 6a-c; General Procedure

To a solution of *N*-Fmoc-dipeptidoylbenzotriazole **5** (0.29 mmol) in THF (5mL) aminoalcohol **2** (0.29 mmol) was added at 0 ^{0}C. The reaction mixture was stirred at 0 ^{0}C for 4 h followed by 3 hours at room temperature. Hexane (5 mL) was added and the separated solid was washed with ether (2x10 mL) and dried to give the corresponding tripeptide alcohol **6**.

***N*-Fmoc-L-Phe-L-Ala-L-Phenylalaninol (6a)**. (0.11 g, 69%); White microcrystals: mp. 185.0─186.0 °C (from tetrahydrofuran/hexanes). $[\alpha]_D^{24}$ -67.0 (*c* 1.0 in MeOH). (Found: C, 71.29; H, 6.25; N, 6.83. Calc. for $C_{36}H_{37}N_3O_5H_2O$: C, 70.92; H, 6.12; N, 6.89). δ_H (300 MHz, DMSO-d_6; Me_4Si) 8.12 (1 H, d, *J* 7.2, N*H*), 7.87 (2 H, d, *J* 7.5, Ar*H*), 7.73 (1 H, d, *J* 8.1, N*H*), 7.61-7.66 (2 H, m, Ar*H*), 7.41(2 H, t, *J* 8.1, Ar*H*), 7.15-7.34 (13 H, m, Ar*H, N*H), 4.81 (1 H, bs, C*H*), 4.25-4.29 (2 H, m, CH_2), 4.13-4.17 (4 H, m, 2 x CH_2), 3.82-3.89 (1 H, m, C*H*), 2.62-3.01 (5 H, m, CH_2, 2 x C*H*, O*H*) and 1.18 (3 H, d, *J* 6.9, CH_3); δ_C (75 MHz, DMSO-d_6; Me_4Si) 171.8, 171.2, 155.9, 143.8, 140.7, 138.3, 129.3, 129.2, 128.2, 128.1, 127.7, 127.2, 126.3, 126.0, 125.3, 120.2, 65.7, 62.1, 56.1, 52.4, 48.41, 46.6, 37.5, 36.4 and 18.6.

***N*-Fmoc-L-Phe-L-Ala-L-Phenylgylcinol (6b).** (0.1 g, yield: 65%); White microcrystals, mp. 211.0─213.0 °C (from tetrahydrofuran/hexanes). $[\alpha]_D^{24}$ -12.0 (*c* 1.0 in MeOH). (Found: C, 71.41; H, 6.07; N, 7.20. Calc. for $C_{35}H_{35}N_3O_5 \cdot ½H_2O$: C, 71.65; H, 6.18; N, 7.16) δ_H (300 MHz, DMSO-d_6; Me_4Si) 8.21-8.25 (2 H, m, 2 x N*H*), 7.86 (2 H, d, *J* 7.5, CH_2), 7.60-7.67 (3 H, m, Ar*H,* N*H*), 7.40 (2 H, t, *J* 7.5, Ar*H*), 7.16-7.31 (12 H, m, Ar*H*), 4.82-4.92 (2 H, m, CH_2), 4.38-4.43 (1 H, m, C*H*), 4.24-4.29 (1 H, m, C*H*), 4.09-4.16 (3 H, m, O*H,* CH_2), 3.54-3.59 (2 H, m, CH_2), 2.95 (1 H, d, *J* 10.8, C*H*), 2.75 (1 H, t, *J* 12.3, C*H*), 1.27 (3 H , d, *J* 6.9, CH_3); δ_c (75 MHz, DMSO-d_6; Me_4Si) 171.6, 171.2, 155.7, 143.6, 140.8, 140.5, 138.1, 129.1, 127.9, 127.5, 127.0, 126.8, 126.7, 126.1, 125.1, 120.0, 65.5, 64.6, 55.9, 54.7, 48.2, 46.4, 37.3 and 18.3.

***N*-Fmoc-Gly-L-Leu-L-Phenylalaninol (6c).** (0.12 g, yield: 69%); White microcrystals mp. 176.0─178.0.0 °C (from tetrahydrofuran/hexanes). $[\alpha]_D^{24}$ -40.0 (*c* 1.0 in MeOH). (Found: C, 70.30; H, 6.85; N, 7.72, Calc. For $C_{32}H_{37}N_3O_5$: C, 70.70; H, 7.23; N, 7.73). δ_H (300 MHz, DMSO-d_6; Me_4Si) 7.89 (3 H, d, *J* 7.5, Ar*H*, N*H*), 7.71 (3 H, d, *J* 6.9, Ar*H*), 7.56-7.60 (1 H , m, N*H*), 7.42 (2 H, t, *J* 7.2, Ar*H*), 7.33 (2 H, t, *J* 7.2, Ar*H*), 7.15-7.25 (5 H, m, Ar*H*), 4.75 (1 H, t, *J* 5.4, C*H*), 4.26-4.28 (4 H, m, 2 x CH_2), 3.85-3.87 (1 H, m, C*H*), 3.65 (1 H, d, *J* 5.7, C*H*), 3.27-3.39 (2 H, m, CH_2), 2.81-2.88 (1 H, m, C*H*), 2.59-2.66 (1 H, m, C*H*), 1.49-1.52 (1 H, m, C*H*), 1.33-1.38 (2 H, m, CH_2), 1.09 (1 H, t, *J* 7.2, C*H*), 0.82 (6 H, t, *J* 7.5, 2 x CH_3). δ_c (75 MHz, DMSO-d_6; Me_4Si) 172.5, 169.9, 157.2, 143.8, 141.4, 138.0, 129.4, 128.6, 128.0, 127.3, 126.6, 125.2, 120.2, 67.5, 63.5, 53.1, 52.6, 47.2, 44.6, 41.0, 36.9, 24.9, 22.9 and 22.2.