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Alkyne Bridged α- Amino Acids by Palladium Mediated Coupling of Alkynes with *N-t*-Boc-4-iodo-phenylalanine Methyl Ester

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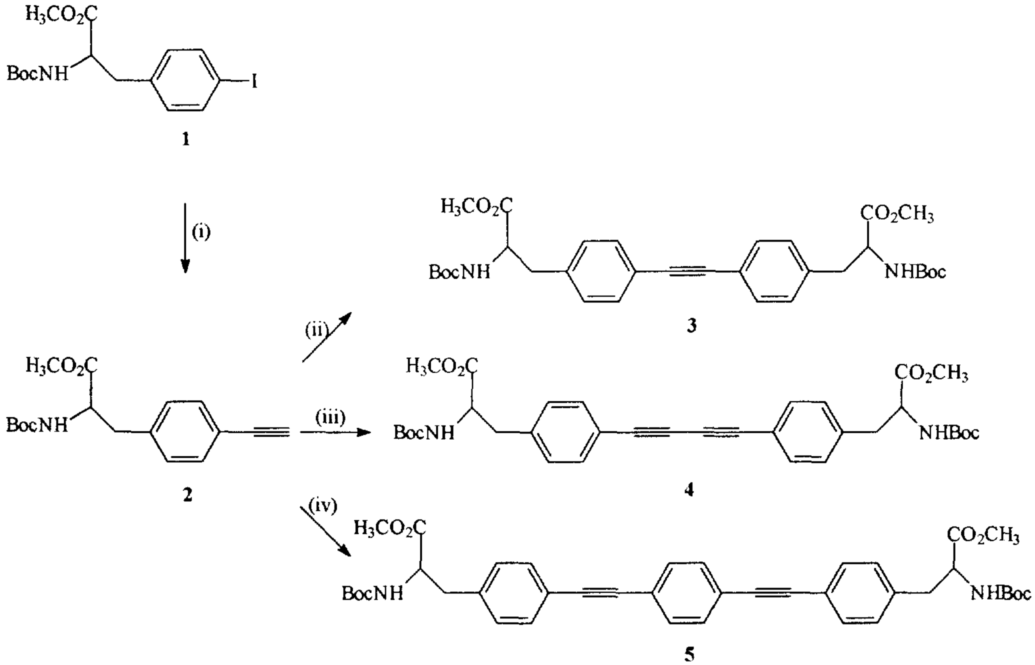
Abstract: The Heck reaction of trimethylsilylacetylene with *N-t*-Boc-4-iodo-L-phenylalanine methyl ester gives *N-t*-Boc-4-ethynyl-L-phenylalanine methyl ester (**2**). Coupling of **2** with different alkynes yields alkyne bridged linear amino acid esters **3**- **5**. Also tripodal and tetrapodal amino acid esters **10** and **11** were prepared by this approach. All compounds have been obtained in enantiomerically pure form. The protecting groups were removed by standard methods to yield the free amino acids as hydrochlorides.

In the course of our studies on metal complexes of α- amino acids and their derivatives[1] we were interested in the preparation of alkyne bridged amino acids which are expected to show nonlinear optical (NLO) activity. Such activity has been observed for acetylenic[2] as well as for coordination compounds.[3] Furthermore metal chelated amino acidates find application in catalysis and asymmetric synthesis.[4]

The synthesis of non-proteinogenic α- amino acids is based either on electrophilic[5] or nucleophilic equivalents.[6] Some methods use the derivatization of serine.[7] Aromatic amino acids and their ring substituted derivatives have been prepared in racemic form[8] by amidoalkylation employing electrophilic glycine equivalents. A promising entry to enantiomerically pure ring substituted phenylalanines has been developed by Schwabacher et al.[9] *N-t*-Boc-4-iodo-L-phenylalanine methyl ester (Boc = *t*-butyloxycarbonyl) was used as starting compound to build, under palladium catalysis, amino acids which are bridged by a heteroatom.[9] The iodo substituent was also replaced by sulfur containing fragments[10] or trimethyltin.[11]

In the following we report on the use of *N-t*-Boc-4-iodo-L-phenylalanine methyl ester (**1**) to prepare the *N-t*-Boc-4-ethynyl-L-phenylalanine methyl ester (**2**), the linearly bridged *N*-protected amino acid esters **3**- **5** and the tripodal and tetrapodal amino acid esters **10** and **11**. 4-Ethynyl-L-phenylalanine resembles tyrosine or ethynylglycine, which can alter the metabolism, especially that of microorganisms.[12] Bridged amino acids, when incorporated into peptides or proteins, impose conformational constraint.[13] The bridge may be essential for spacing the pharmacophoric regions in peptides or proteins in their interaction with bioreceptors. Efforts have been made to replace the disulfide bond of cystine by ethylene units.[14]

The Heck reaction[15] of *N-t*-Boc-4-iodo-L-phenylalanine methyl ester (**1**) with trimethylsilylacetylene (TMSE) and the following treatment with tetrabutylammonium fluoride affords the *N-t*-Boc-4-ethynyl-L-phenylalanine methyl ester (**2**). The stereochemical purity of **2** (in form of the free acid **6**) was tested with chiral TLC plates. **2** is a good starting compound to undergo further Heck reaction with **1** to give **3** where two phenylalanines are bridged by one acetylene. **2** may be homocoupled in the presence of oxygen and CuCl by a modified Glaser reaction to yield **4** with a bridge of two acetylenes. The reaction of **2** with 1,4-diiodobenzene yields **5**. Alternatively **5** can be obtained by reaction of **1** with 1,4-diethynylbenzene. The second approach to **5** is preferable because 1,4-diethynylbenzene is conveniently available in large amounts[16] without using TMSE. By this means linearly bridged phenylalanines with a backbone of 12, 14 and 18 carbons are built up as shown in Scheme 1.

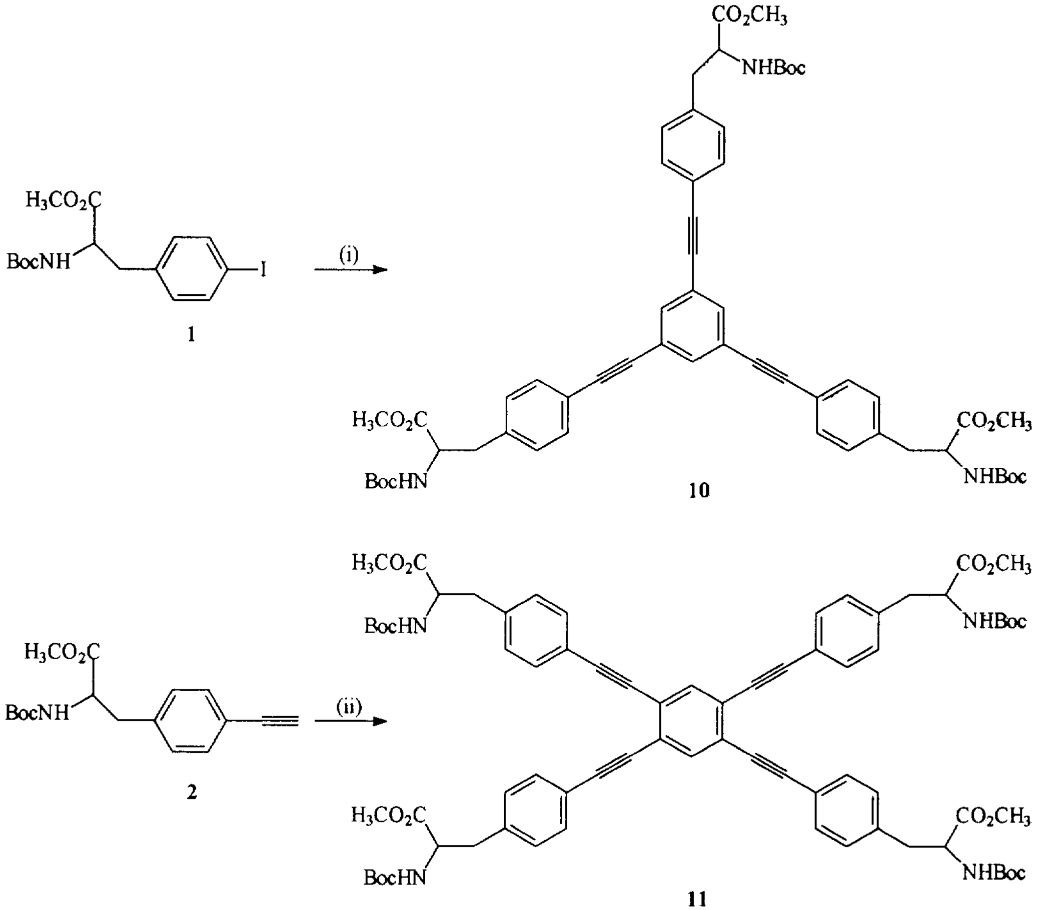


(i) $PdCl_2(PPh_3)_2$, CuI, TMSE, NEt_3, RT
NBu_4F, THF, -78°C
(ii) $PdCl_2(PPh_3)_2$, CuI, **1**, NEt_3, RT
(iii) CuCl, TMEDA, acetone, O_2, 50°C
(iv) $PdCl_2(PPh_3)_2$, CuI, 1,4- $C_6H_4I_2$, NEt_3, RT

Scheme 1.

The corresponding free amino acids **6-9** were obtained by saponification of **2-5** with a LiOH/THF/H_2O mixture followed by removal of the Boc protecting groups using a solution of dry HCl in ethyl acetate from which the amino acids precipitate as hydrochlorides. The saponification of **3-5** could be also be accomplished by acid hydrolysis. In the case of **2** the latter procedure was accompanied by Markownikov directed HCl addition to the triple bond as detected by ^{1}H NMR spectroscopy.

The approach to the bridged phenylalanines can be extended to the tri- and tetrapodal systems **10** and **11** if **1** is submitted to the Heck reaction with 1,3,5-triethynylbenzene or **2** with 1,2,4,5-tetraiodobenzene as the counterpart (see Scheme 2).



(i) $PdCl_2(PPh_3)_2$, CuI, 1,3,5- $(HC{\equiv}C)_3C_6H_3$, NEt_3, RT

(ii)$PdCl_2(PPh_3)_2$, CuI, 1,2,4,5- $C_6H_2I_4$, NEt_3, RT

Scheme 2.

Deprotection can be carried out as described above to yield the free amino acid hydrochlorides **12** and **13**. The highly symmetrical tridentate and tetradentate compounds **10** and **11** could be used as template molecules for the interesting chemistry of amino acid containing macromolecules (peptide bundles).[17] These compounds are models for siderophores[18] or carboanhydrase analogues.[19] The use of **10** and **11** as template molecules and metal complexes of these alkyne bridged α- amino acids will be reported elsewhere.

EXPERIMENTAL

4-Iodo-L-phenylalanine,[9] 1,4-diethynylbenzene,[16] 1,3,5-triethynylbenzene,[16] 1,2,4,5-tetraiodobenzene[20] and $PdCl_2(PPh_3)_2$[21] were prepared as previously described in the literature. Trimethylsilylacetylene was purchased from Fluka.

Melting points are uncorrected. Chromatography was carried out on silica gel (Merck, 70-230 mesh), TLC was performed on chiral TLC plates (Macherey & Nagel) and on silica gel 60 F_{254} plates (Merck) and 0.2% ninhydrin was used for visualization. IR spectra were obtained on a 5ZDX FT- IR and FAB-mass spectra on a Finnigan MAT 90 (m- nitrobenzylalcohol). Specific rotation was measured on a 241 Perkin Elmer polarimeter. ^1H and ^{13}C spectra were recorded on a Jeol GSX-270 and on a Jeol EX-400 instrument using tetramethylsilane as internal standard.

N-[(1,1-Dimethylethoxy)carbonyl]-4-ethynyl-L-phenylalanine methyl ester (2): Trimethylsilylacetylene (166 µl, 1.2 mmol) was added to a stirred suspension of *N-t*-Boc-4-iodo-L-phenylalanine methyl ester (405 mg, 1.0 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol) and CuI (4 mg, 0.02 mmol) in triethylamine (10 ml) under argon. The mixture was stirred at ambient temperature for 12 h and then diluted with water. The aqueous solution was extracted with ether (2 x 30 ml), the organic layer was washed with water (3 x 50 ml), dried ($MgSO_4$) and evaporated. Two eq. of tetrabutylammonium fluoride x 3 H_2O were added to the solution of the residue in dry THF (20 ml) under argon at -78 °C. The mixture was stirred at -78 °C for 2 h. The cooling bath was removed, water (10 ml) was added and THF was evaporated from the mixture at reduced pressure. The aqueous solution was extracted with ether (3 x 25 ml), the organic layer washed with saturated NaCl solution (3 x 30 ml), dried ($MgSO_4$) and evaporated. The crude product was purified by chromatography on silica gel using petrol ether/ ethyl acetate 4/ 1; yield 200 mg (66 %). m.p.: 106°C. Anal. Found: C, 67.25; H, 6.86; N, 4.51. Calc. for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62 %. $[\alpha]_D$ 56.8° (c 1.01, $CHCl_3$). R_f 0.81 (petrol ether/ ethyl acetate 3:2). IR (KBr): ν 3382, 2976, 2109, 1735, 1706, 1503. ^1H NMR ($CDCl_3$): δ 1.38, 3.00 (dd, *J* 7.4 Hz and *J* 13.9 Hz, 1H, CH'H), 3.04, 3.09 (dd, *J* 6.0 Hz and *J* 13.9 Hz, 1H, CHH'), 3.67, 4.55 (pq, *J* 8.2 Hz, 1H, CH), 4.97 (d, *J* 7.8 Hz, 1H, NH), 7.06 (d, *J* 8.1 Hz, 2H, C_6H_4), 7.38 (d, *J* 8.1 Hz, 2H, C_6H_4). ^{13}C NMR ($CDCl_3$): δ 28.18, 38.19, 52. 23, 54.19, 77.29, 80.01, 83.36, 120.85, 129.35, 132.31, 137.07, 155.07, 172.17. MS(FAB): 327 (M^+ Na).

4,4'-(1,2-Ethynediyl)bis[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanine] dimethyl ester (3): *N-t*-Boc-4-ethynyl-L-phenylalanine methyl ester (**2**) (303 mg, 1.0 mmol) was added to a stirred suspension of *N-t*-Boc-4-iodo-L-phenylalanine methyl ester (405 mg, 1.0 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol) and CuI (4 mg, 0.02 mmol) in triethylamine (15 ml) under argon. The mixture was stirred at ambient temperature for 12 h and then diluted with water. The aqueous solution was extracted with ether (2 x 30 ml), the organic layer washed with water (3 x 50 ml), dried ($MgSO_4$) and evaporated. The crude product was purified by chromatography on silica gel using petrol ether/ ethyl acetate 2/ 1; yield 412 mg (71 %); m.p.: 146°C. Anal. Found: C, 66.17; H, 6.90; N, 5.11 . Calc. for $C_{32}H_{40}N_2O_8$: C, 66.19; H, 6.94; N, 4.82 %. $[\alpha]_D$ 72.5° (c 1.01, $CHCl_3$). R_f 0.59 (petrol ether/ ethylacetate 3:2). IR (KBr): ν 3362, 2919, 1753, 1736, 1715, 1693, 1521. ^{1}H NMR ($CDCl_3$): δ 1.40, 3.03 (dd, *J* 6.1 Hz and *J* 9.2 Hz, 2H, CH'H), 3.12 (dd, *J* 5.5 Hz and *J* 9.2 Hz, 2H, CHH'), 3.69, 4.57 (pq, *J* 6.1 Hz, 2H, CH), 4.97 (d, *J* 7.6 Hz, 2H, NH), 7.10 (d, *J* 8.0 Hz, 4H, C_6H_4), 7.42 (d, *J* 8.0 Hz, 4H, C_6H_4). ^{13}C NMR ($CDCl_3$): δ 28.16, 38.13, 52. 20, 54.28, 80.01, 89.25, 122.01, 129.41, 131.79, 136.50, 155.15, 172.30. MS(FAB): 603 (M^+ Na), 580 (M^+).

4,4'(1,3-Butadiyne-1,4-diyl)bis[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanine] dimethyl ester (4): TMEDA (0.9 ml, 0.008 mmol) was added to a stirred solution of *N-t*-Boc-4-ethynyl-L-phenylalanine methyl ester (**2**) (303 mg, 1.0 mmol) and CuCl (6 mg, 0.07 mmol) in acetone (10 ml). The green mixture was stirred at 50 °C under a flow of O_2. After the mixture had turned deep brown the solvent was evaporated. The crude product was purified by chromatography on silica gel using petrol ether/ ethyl acetate 2/ 1; yield 472 mg (78 %); m.p.: 131°C. Anal. Found: C, 67.64; H, 6.57; N, 4.32. Calc. for $C_{34}H_{40}N_2O_8$: C, 67.53; H, 6.67; N, 4.63 %. $[\alpha]_D$ 68.5° (c 1.01, $CHCl_3$). R_f 0.55 (petrol ether/ ethyl acetate 3:2). IR (KBr): ν 3369, 2978, 1745, 1716, 1694, 1506. ^{1}H NMR ($CDCl_3$): δ 1.34, 2.96 (dd, *J* 6.3 Hz and *J* 15.6 Hz, 2H, CH'H), 3.07 (dd, *J* 5.8 Hz and *J* 15.6 Hz, 2H, CHH'), 3.64, 4.52 (pq, *J* 5.9 Hz, 2H, CH), 4.97 (d, *J* 8.3 Hz, 2H, NH), 7.03 (d, *J* 8.2 Hz, 4H, C_6H_4), 7.37 (d, *J* 8.2 Hz, 4H, C_6H_4). ^{13}C NMR ($CDCl_3$): δ 28.11, 38.27, 52. 21, 54.12, 73.99, 79.99, 81.31, 120.45, 129.51, 132.64, 137.71, 155.08, 172.16. MS(FAB): 627 (M^+ Na), 604 (M^+).

4,4'-(1,4-Phenylenedi-2,1-ethynediyl)bis[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanine] dimethyl ester (5): 1,4-Diethynylbenzene (126 mg, 1.0 mmol) was added to a stirred suspension of *N-t*-Boc-4-iodo-L-phenylalanine methyl ester (818 mg, 2.02 mmol), $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol) and CuI (8 mg, 0.04 mmol) in triethylamine (20 ml) under argon. The mixture was stirred at ambient temperature for 12 h and then diluted with water. The aqueous solution was extracted with ether (2 x 50 ml), the organic layer washed with water (3 x 100 ml), dried ($MgSO_4$) and evaporated. The crude product was purified by chromatography on silica gel using petrol ether/ ethyl acetate 2/ 1; yield 490 mg (72 %); m.p.: 157 °C. Anal. Found: C, 70.53; H, 6.54; N, 3.79. Calc. for $C_{40}H_{44}N_2O_8$: C, 70.57; H, 6.52; N, 4.11 %. $[\alpha]_D$ 65.7° (c 1.01, $CHCl_3$). R_f 0.57 (petrol ether/ ethyl acetate 3:2). IR (KBr): ν 3373, 2980, 1745, 1724, 1712, 1520. ^{1}H NMR ($CDCl_3$): δ 1.40, 3.03 (dd, *J* 6.1 Hz and *J* 14.1 Hz, 2H, CH'H), 3.12 (dd, *J* 5.9 Hz and *J* 14.1 Hz, 2H, CHH'), 3.69, 4.57 (pq, *J* 7.9 Hz, 2H, CH), 4.98 (d, *J* 8.3 Hz, 2H, NH), 7.10 (d, *J* 8.2 Hz, 4H, C_6H_4), 7.43 (d, *J* 8.2 Hz, 4H, C_6H_4), 7.47. ^{13}C NMR ($CDCl_3$): δ 28.17, 38.21, 52.23, 54.20, 80.03, 89.26, 90.99, 121.77, 123.11, 129.47, 131.59, 131.83, 136.75, 155.11, 172.29. MS(FAB): 680 (M^+).

Alternatively the Heck reaction can be carried out using the above procedure with *N-t*-Boc-4-ethynyl-L-phenylalanine methyl ester (**2**) (660 mg, 2.02 mmol) and 1,4-diiodobenzene (328 mg, 1.00 mmol).

4,4',4''-(1,3,5-Benzenetriyltri-2,1-ethynediyl)tris[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanine] trimethyl ester (10): 1,3,5-Triethynylbenzene (150 mg, 1.0 mmol) was added to a stirred suspension of *N-t*-Boc-4-iodo-L-phenylalanine methyl ester (1228 mg, 3.03 mmol), $PdCl_2(PPh_3)_2$ (21 mg, 0.03 mmol) and CuI (11 mg, 0.06 mmol) in triethylamine (25 ml) under argon. The mixture was stirred at ambient temperature for 24 h and then diluted with water. The aqueous solution was extracted with ether (2 x 50 ml), the organic layer washed with water (3 x 100 ml), dried ($MgSO_4$) and evaporated. The crude product was purified by chromatography on silica gel using petrol ether/ ethyl acetate 3/ 2; yield 540 mg (55 %); m.p.: 108°C. Anal. Found: C, 69.41; H, 6.74; N, 3.82 %. Calc. for $C_{57}H_{63}N_3O_{12}$: C, 69.71; H, 6.47; N, 4.28 %. $[\alpha]_D$ 65.8° (c 1.00, $CHCl_3$). R_f 0.35 (petrol ether/ ethyl acetate 3:2). IR (KBr): ν 3369, 2977, 2214, 1747, 1716, 1510. ^{1}H NMR ($CDCl_3$): δ 1.40, 3.03 (dd, *J* 6.3 Hz and *J* 14.0 Hz, 3H, CH'H), 3.13 (dd, *J* 5.8 Hz and *J* 14.0 Hz, 3H, CHH'), 3.70, 4.58 (pq, *J* 6.4 Hz, 3H, CH), 4.99 (d, *J* 8.4 Hz, 3H, NH), 7.11 (d, *J* 8.4 Hz, 6H, C_6H_4), 7.44 (d, *J* 8.4 Hz, 6H, C_6H_4), 7.60. ^{13}C NMR ($CDCl_3$): δ 28.22, 38.30, 52.30, 54.25, 80.11, 87.99, 90.31, 121.58, 124.12, 129.55, 131.96, 134.14, 137.04, 155.16, 172.32. MS(FAB): 982 (M^+).

4,4',4'',4'''-(1,2,4,5-Benzenetetrayltetra-2,1-ethynediyl)tetrakis[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanine] tetramethyl ester (11): *N-t*-Boc-4-ethynyl-L-phenylalanine methyl ester (**2**) (1226 mg, 4.04 mmol) was added to a stirred suspension of 1,2,4,5- tetraiodobenzene (582 mg, 1.0 mmol), $PdCl_2(PPh_3)_2$ (28 mg, 0.04 mmol) and CuI (30 mg, 0.16 mmol) in triethylamine (30 ml) under argon. The mixture was stirred at ambient temperature for 24 h and then diluted with water. The aqueous solution was extracted with ether (2 x 75 ml), the organic layer washed with water (3 x 100 ml), dried ($MgSO_4$) and evaporated. The crude product was purified by chromatography on silica gel using petrol ether/ ethyl acetate 1/ 1; yield 462 mg (36 %); m.p.: 137°C. Anal. Found: C, 68.80; H, 6.53; N, 3.97. Calc. for $C_{74}H_{82}N_4O_{16}$: C, 69.24; H, 6.44; N, 4.36 %. $[\alpha]_D$ 59.2° (c 1.00, $CHCl_3$). R_f 0.25 (petrol ether/ ethyl acetate 3:2). IR (KBr): ν 3363, 2978, 2205, 1745, 1715, 1517. ^{1}H NMR ($CDCl_3$): δ 1.34, 2.98 (dd, *J* 6.1 Hz and *J* 13.9 Hz, 4H, CH'H), 3.07 (dd, *J* 6.0 Hz and *J* 13.9

Hz, 4H, CHH'), 3.64, 4.52 (pq, *J* 7.1 Hz, 4H, CH), 5.01 (d, *J* 8.4 Hz, 4H, NH), 7.07 (d, *J* 8.0 Hz, 8H, C_6H_4), 7.42 (d, *J* 8.0 Hz, 8H, C_6H_4), 7.65. ^{13}C NMR ($CDCl_3$): δ 28.19, 38.32, 52.20, 54.22, 79.94, 87.57, 95.15, 121.50, 125.12, 129.39, 131.74, 134.83, 137.03, 154.95, 172.06. MS(FAB): 1306 (M^+Na), 1283 (M^+).

General Procedure for deprotection of the compounds 2- 5 and 10- 11

LiOH x H_2O (1.5 eq. for 1 eq. ester) was added to a solution of the amino acids in a mixture of THF/ H_2O (3/ 1) at ambient temperature. The reaction was monitored by TLC ($CHCl_3$/ MeOH/ H_2O 80/ 20/ 2) until no starting compound was detected (2- 12h). The pH was adjusted to ~2.5 by the addition of 0.5M $NaHSO_4$. The aqueous solution was extracted with ethyl acetate, the organic layer dried ($MgSO_4$) and evaporated to yield foams of the free acids.

A solution of dry HCl in ethyl acetate (~ 2.5 M; 5 ml for 2 mmol Boc) was added to the free acids at ambient temperature. The mixtures were stirred for 2-4 h. During that period the hydrochlorides of the free amino acids precipitated. The solvent was concentrated to a third of its volume, pentane was added, the products were isolated and dried *in vacuo*.

4-Ethynyl-L-phenylalanine hydrochloride (6): Anal. Found: C, 58.24; H, 5.44; N, 6.06. Calc. for $C_{11}H_{12}NO_2Cl$: C, 58.55; H, 5.36; N, 6.21 %. IR (KBr): ν 3438, 2979, 2108, 1741, 1603, 1485, 1211. ^{1}H NMR (CD_3OD): δ 3.16 (dd, *J* 7.7 Hz and *J* 14.7 Hz, 1H, CH'H), 3.31 (dd, *J* 5.4 Hz and *J* 14.7 Hz, 1H, CHH'), 3.51, 4.25 (dd, *J* 7.7 Hz and *J* 5.4 Hz, 1H, CH), 7.29 (d, *J* 8.5 Hz, 2H, C_6H_4), 7.47 (d, *J* 8.5 Hz, 2H, C_6H_4).

4,4'-(1,2-Ethynediyl)bis[L-phenylalanine] dihydrochloride (7): Anal. Found: C, 55.46; H, 5.50; N, 6.25. Calc. for $C_{20}H_{22}N_2O_4Cl_2$x ½ H_20: C, 55.31; H, 5.34; N, 6.45 %. IR (KBr): ν 3429, 2970, 1740, 1596, 1495, 1210. ^{1}H NMR (CD_3OD): δ 3.17 (dd, *J* 7.8 Hz and *J* 14.5 Hz, 2H, CH'H), 3.33 (dd, *J* 5.6 Hz and *J* 14.5 Hz, 2H, CHH'), 4.28 (dd, *J* 5.6 Hz and *J* 7.8 Hz, 2H, CH), 7.33 (d, *J* 8.4 Hz, 4H, C_6H_4), 7.52 (d, *J* 8.4 Hz, 4H, C_6H_4).

4,4'-(1,3-Butadiyne-1,4-diyl)bis[L-phenylalanine] dihydrochloride (8): Anal. Found: C, 57.74; H, 5.36; N, 5.90. Calc. for $C_{22}H_{22}N_2O_4Cl_2$x ½ H_20: C, 57.65; H, 5.06; N, 6.11 %. IR (KBr): ν 3436, 2964, 1742, 1590, 1505, 1211. ^{1}H NMR (CD_3OD): δ 3.18 (dd, *J* 7.7 Hz and *J* 14.6 Hz, 2H, CH'H), 3.33 (dd, *J* 5.7 Hz and *J* 14.6 Hz, 2H, CHH'), 4.27 (dd, *J* 5.7 Hz and *J* 7.7 Hz, 2H, CH), 7.34 (d, *J* 8.2 Hz, 4H, C_6H_4), 7.54 (d, *J* 8.2 Hz, 4H, C_6H_4).

4,4'-(1,4-Phenylenedi-2,1-ethynediyl)bis[L-phenylalanine] dihydrochloride (9): Anal. Found: C, 62.31; H, 5.40; N, 5.12. Calc. for $C_{28}H_{26}N_2O_4Cl_2$x ½ H_20: C, 62.92; H, 5.09; N, 5.24 %. IR (KBr): ν 3430, 2911, 1741, 1597, 1520, 1210. ^{1}H NMR (CD_3OD): δ 3.18 (dd, *J* 7.5 Hz and *J* 14.5 Hz, 2H, CH'H), 3.34 (dd, *J* 5.6 Hz and

J 14.5 Hz, 2H, CHH'), 4.29 (dd, *J* 5.6 Hz and *J* 7.5 Hz, 2H, CH), 7.34 (d, *J* 8.4 Hz, 4H, C_6H_4), 7.52, 7.54 (d, *J* 8.4 Hz, 4H, C_6H_4).

4,4',4''-(1,3,5-Benzenetriyltri-2,1-ethynediyl)tris[L-phenylalanine] trihydrochloride (12): Anal. Found: C, 59.82; H, 5.46; N, 4.62. Calc. for $C_{39}H_{36}N_3O_6Cl_3$x 2 H_20: C, 59.66; H, 5.14; N, 4.59 %. IR (KBr): ν 3433, 2931, 2214, 1739, 1582, 1509, 1221. ^{1}H NMR (CD_3OD): δ 3.19 (dd, *J* 7.5 Hz and *J* 14.5 Hz, 3H, CH'H), 3.35 (dd, *J* 5.6 Hz and *J* 14.5 Hz, 3H, CHH'), 4.28 (dd, *J* 5.6 Hz and *J* 7.5 Hz, 3H, CH), 7.36 (d, *J* 8.3 Hz, 6H, C_6H_4), 7.58 (d, *J* 8.3 Hz, 6H, C_6H_4), 7.64.

4,4',4'',4'''-(1,2,4,5-Benzenetetrayltetra-2,1-ethynediyl)tetrakis[L-phenylalanine] tetrahydrochloride (13): Anal. Found C,58.26; H, 5.25; N, 5.10. Calc. for $C_{50}H_{46}N_4O_8Cl_4$x 3 H_20: C, 58.48; H, 5.10; N, 5.45 %. IR (KBr): ν 3424, 2930, 2205, 1737, 1599, 1516, 1221. ^{1}H NMR (CD_3OD): δ 3.22 (dd, *J* 7.7 Hz and *J* 13.9 Hz, 4H, CH'H), 3.35 (dd, *J* 5.5 Hz and *J* 13.9 Hz, 4H, CHH'), 4.29 (dd, *J* 5.5 Hz and *J* 7.7 Hz, 4H, CH), 7.39 (d, *J* 8.1 Hz, 8H, C_6H_4), 7.59 (d, *J* 8.1 Hz, 8H, C_6H_4), 7.77.

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