Benzene-Bridged Hexaalkynylphenylalanines and First-Generation Dendrimers Thereof

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Dedicated to Professor Bernt Krebs on the occasion of his 60th birthday

Abstract: The palladium-mediated coupling of *p*-ethynylphenylalanine (*p*-epa) with hexabromobenzene yielded a benzene-bridged hexaalkynyl α-amino acid in high yield. The use of the hexapodal amino acid and of the corresponding tripodal amino acid as backbones for the synthesis of first-generation dendrimers based on poly(trishydroxymethyl) and poly(ornithine) compounds, developed by Newkome et al., Denkewalter et al., and Tam et al., is described.

Keywords: alkynes · α-amino acids · dendrimers · phenylalanine

Introduction

In a previous communication we reported the synthesis of different benzene-bridged 4-ethynylphenylalanines.[1a] These bi-, tri-, and tetrapodal amino acids were synthesized by using the Sonogashira reaction[2] (Heck conditions[3]) between different halogenated benzenes and *p*-ethynylphenylalanine (*p*-epa), a new non-proteinogenic amino acid, which has been shown to be a specific inhibitor of tryptophan-hydroxylase.[4]

The synthesis of unnatural amino acids is based either on electrophilic[5] or nucleophilic[6] equivalents. The derivatization of phenylalanines was developed by Schwabacher et al.,[7] who described a large-scale synthesis of *p*-iodo-L-phenylalanine. *p*-Iodo-L-phenylalanine was used as a starting material to build, under palladium catalysis, amino acids which are bridged by a heteroatom[7] or in which the iodo substituent was replaced by sulfur-containing fragments or trimethyltin.[8] The palladium-mediated coupling of terminal acetylides with iodoarenes was used to synthezise fluorescent marker molecules,[9a] a field in which organometallic chemistry is playing an ever increasing role,[9b-d] and to synthesize markers for peptides, even under biocompatible conditions in water.[9e] Undheim et al.[10a] and Crisp et al.[10b] reported the Pd-catalyzed synthesis of a series of interesting alkyne-bridged bis- and tris-amino acids and oxazolidines. We anticipated our synthesized benzene-bridged alkynyl amino acids would be interesting ligands for multinuclear complexes[1b] and as core molecules for dendritic materials.

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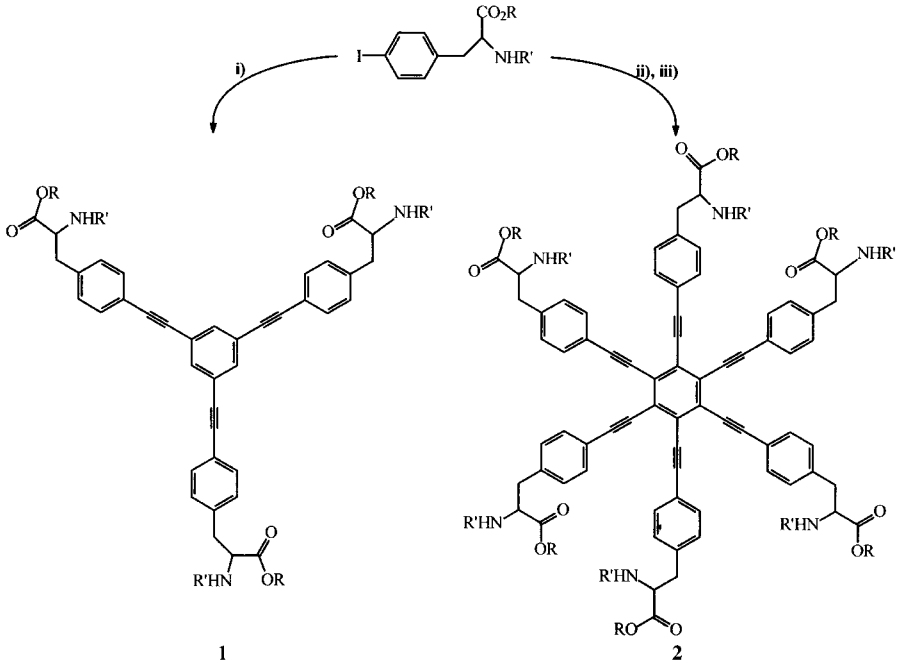
Recently, dendrimers have attracted the attention of many researchers for a variety of reasons.[11] The highly branched architecture and the synthetic control over the chemical composition and the defined number and type of the chain end functionalities have led to dendrimers with potential application in catalysis and as sensors,[12] drug delivery systems,[13] or compounds with interesting electrochemical properties.[14] Although research into the synthesis of novel dendrimers continues rapidly,[15] there is also considerable interest in the functionalization of existing systems either at the core[16] or the end functionalities.[17]

Results and Discussion

The tripodal phenylalanine **1** was synthesized by reaction of 1,3,5-triethynylbenzene with *p*-iodo-L-phenylalanine as previously reported.[1] The synthesis of the hexapodal molecule **2** seemed to be more difficult, because the reaction of hexaiodobenzene with *p*-epa yielded only the 5-substituted benzene as detected by the additional ^{1}H and ^{13}C NMR signals (as well as the corresponding FAB mass spectrometric signal) due to the missing C_6 symmetry. Finally, by employing the reaction conditions used by Vollhardt et al. to synthesize hexaethynylbenzene,[18] and using hexabromobenzene as a source for hexahalogenated benzene, we obtained the expected molecule **2** with C_6 symmetry in high yield (85%) (Scheme 1).

The symmetry of this molecule, which is one of the rare examples of a molecule with six amino acid units,[19] is manifested by the single set of signals in the ^{1}H and ^{13}C NMR spectra (Figure 1). In addition to the typical ^{13}C NMR signals of the methyl ester and *tert*-butyloxycarbonyl groups ($\delta = 172$ and 155), the symmetry is apparent from the five C_6 signals (one for the benzene core and four for the C_6H_4 groups) at

0947-6539/99/0502-0754 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 2



Scheme 1. Synthesis of **1** and **2**. i) 1,3,5-triethynylbenzene, $[PdCl_2(PPh_3)_2]$, CuI; ii) trimethylsilylethyne, $[PdCl_2(PPh_3)_2]$, CuI, $NBu_4F \cdot 3H_2O$; iii) hexabromobenzene, $[PdCl_2(PPh_3)_2]$, CuI, PPh_3. R = Me; R′ = Boc.

$\delta = 121-137$ and the two signals for the acetylide carbon atoms ($\delta = 87$ and 99).

The convergent synthetic route to poly(trishydroxymethyl) dendrimers developed by Newkome et al.[20] and to poly(lysine)-based dendrimers developed by Denkewalter et al. and Tam and Shao[21] has allowed incorporation of diverse core molecules.[11b, 14a, 20, 21] Deprotection of core molecule **1** at the carboxylate terminus yielded the corresponding free triacid which was treated with the amine $H_2NC(CH_2OCH_2CH_2CO_2CH_3)_3$ of the first generation of Newkome's system to yield compound **3** (Scheme 2). The analogous reaction of amino-deprotected **1** with an ornithine system (Boc)Orn(Boc)[(Boc)Orn(Boc)]Orn-OH, analogous to that of Denkewalter et al. and Tam and Shao, yielded the dendritic system **4** (Scheme 2). The hexapodal compound **5** was synthesized by using the strategy for **3** (Scheme 3). Although the reaction of amino-deprotected **2** with the tris(ornithine) seemed to work, the product could not be isolated pure enough to give satisfactory analytical results.

Compounds **3** and **5** were isolated as oils, whereas **4** precipitated as a colorless powder. All substances were characterized by FT-IR, ^1H, and ^{13}C NMR spectroscopy and electrospray mass spectrometry and are in full agreement with the proposed structures. Interestingly, the mass signals found for compounds **3** to **5** always correspond to the $[M+2Na]^{2+}$ ions. The optical rotation of **3** differs significantly from that of **1** ($[\alpha]_D^{20}$ **1**: 65.8; **3**: 21.2), whereas that of **4** ($[\alpha]_D^{20} = 59.8$) is comparable with that of **1**.[22]

In conclusion we have synthesized the hexapodal amino acid **2**, an aesthetic molecule from which new peptidomimetics might be obtained.[23] The formation of first-generation dendrimers with the new backbones **1** and **2** has also been demonstrated. Compound **4** resembles previously described peptide dendrimers which are synthetic peptides.[21b,c]

Experimental Section

General: The synthesis of **2** was carried out in dry solvents under argon. Compounds **3**–**5** were synthesized in solvents of p. a. quality. NMR: Jeol GSX 270, Jeol EX 400; tetramethylsilane as internal standard. IR: 5ZDX FT-IR. Mass spectra: Finnigan MAT 95Q. Melting points are uncorrected. Chromatography was carried out on silica gel (Merck, 70–230 mesh); TLC

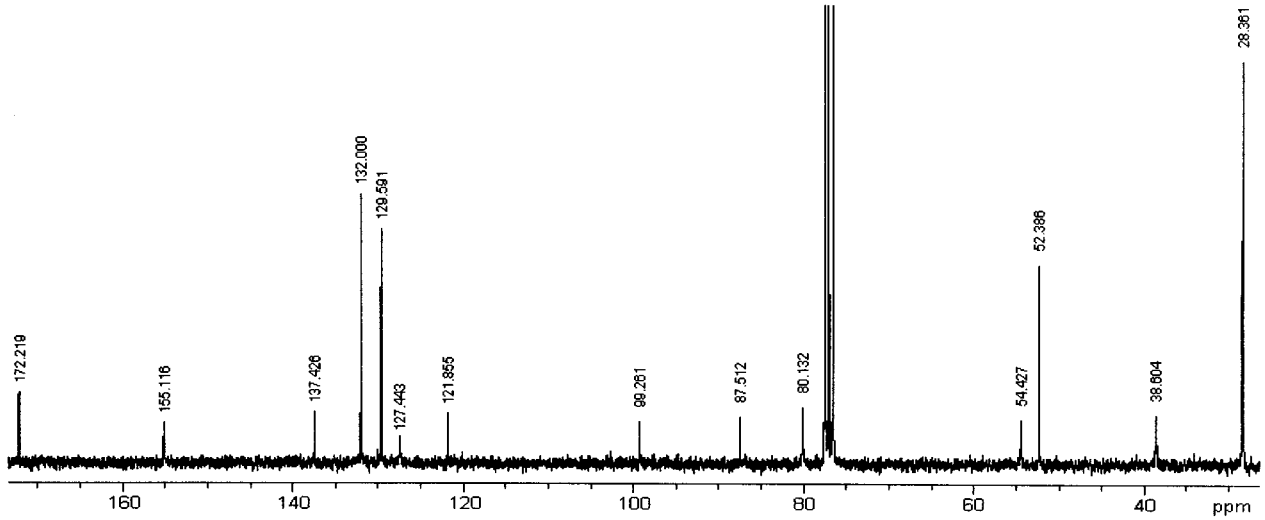
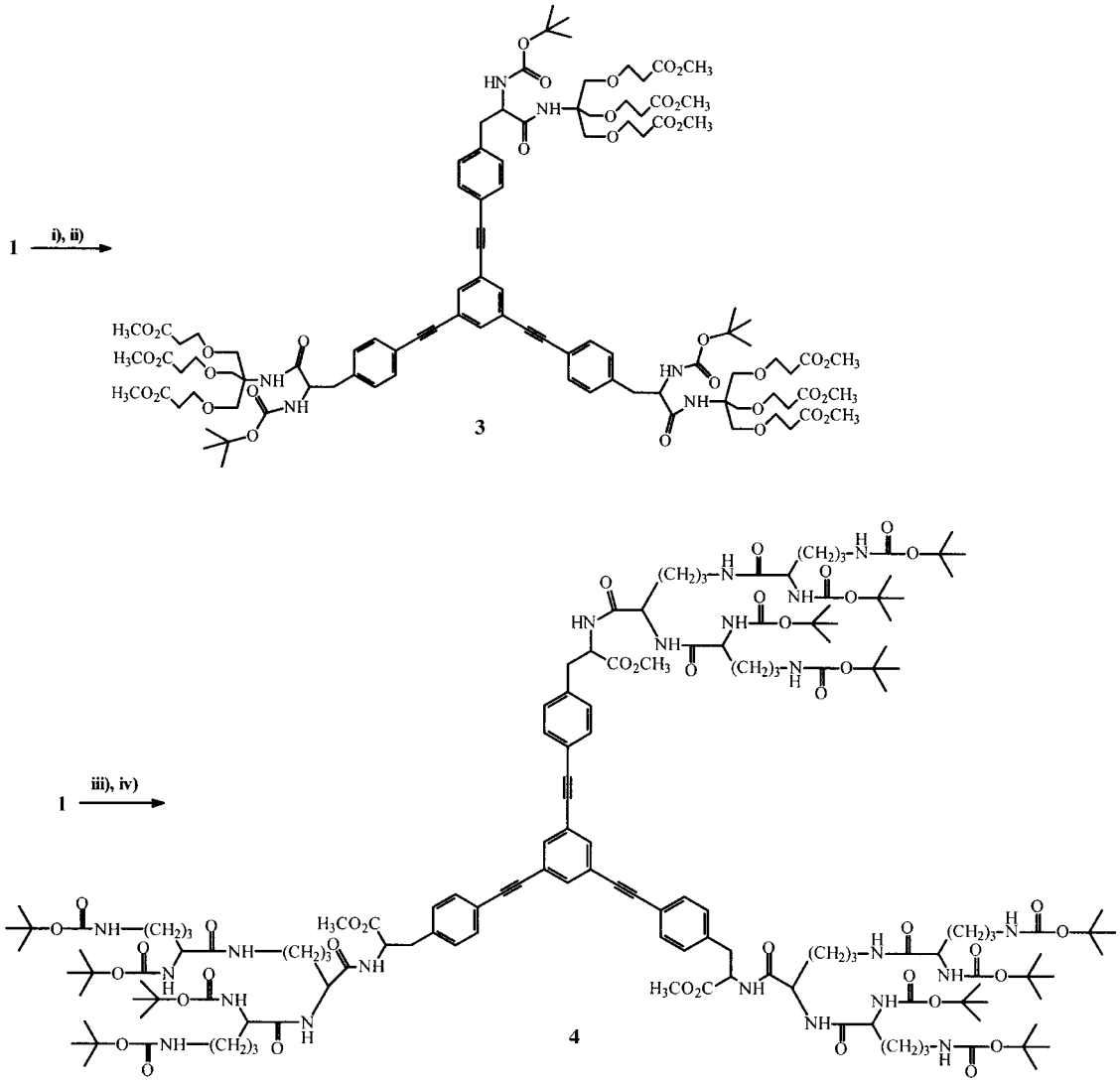
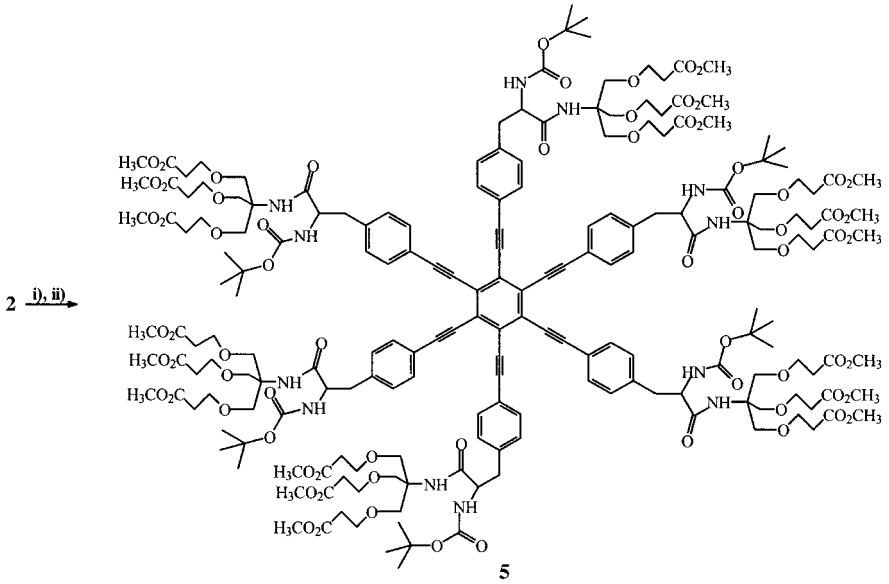


Figure 1. ^{13}C NMR spectrum of **2** in $CDCl_3$.



Scheme 2. Synthesis of **3** and **4** from **1**. i) $LiOH \cdot H_2O$, THF/H_2O; ii) EDC, HOBT, $H_2NC(CH_2OCH_2CH_2CO_2CH_3)_3$; iii) TFA/CH_2Cl_2; iv) EDC, HOBT, Orn_3CO_2H.



Scheme 3. Synthesis of **5** from **2**. i) $LiOH \cdot H_2O$, THF/H_2O; ii) EDC, HOBT, $H_2NC(CH_2OCH_2CH_2CO_2CH_3)_3$.

was performed on silica gel 60 F_{254} plates (Merck) and 0.2% ninhydrin was used for visualization. Elemental analyses were performed by the University of Munich Microanalytical Laboratory. *N-tert*-Boc-4-ethynyl-L-phenylalanine methyl ester,[1] 4,4′,4″-(1,3,5-benzene-triyltri-2,1-ethynediyl)tris[*N*-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanine] trimethyl ester (**1**),[1] $[PdCl_2(PPh_3)_2]$,[24] tris(2-methoxycarbonylethoxymethylaminomethane,[20] and (Boc)Orn(Boc)[(Boc)Orn(Boc)]Orn-OH[21b,c] were prepared according to literature procedures. Hexabromobenzene, CuI (Aldrich) and HOBT, EDC (Fluka) were commercial available compounds.

4,4′,4″,4‴,4⁗,4⁗′-(1,2,3,4,5,6-Benzenehexaylhexa-2,1-ethynediyl)hexakis-[*N*-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanine]hexamethyl ester (**2**): *N-tert*-Boc-4-ethynyl-L-phenylalanine methyl ester (1.820 g, 6.00 mmol) was added to a stirred suspension of hexa-

0947-6539/99/0502-0756 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 2

bromobenzene (331 mg, 0.60 mmol), $[PdCl_2(PPh_3)_2]$ (30 mg, 0.04 mmol), CuI (30 mg, 0.16 mmol), and triphenylphosphane (75 mg, 0.29 mmol) in triethylamine (30 mL) under argon. The mixture was stirred at 95 °C for 48 h, the solvent was evaporated and the resulting precipitate was extracted with tetrahydrofuran (2 × 10 mL). The solvent was evaporated and the crude product was purified by chromatography on silica gel using petroleum ether/ethyl acetate 3/2. Yield 962 mg (85 %) as a yellow solid; m.p. 176 °C; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta =$ 1.40 (s, 54 H, CH_3), 3.05 (dd, $J =$ 13.8 Hz, $J =$ 6.8 Hz, 6 H, CH′H), 3.14 (dd, $J =$ 13.8 Hz, $J =$ 6.4 Hz, 6 H, CHH′), 3.71 (s, 18 H, CH_3), 4.59 (pq, $J =$ 7.0 Hz, 6 H, CH), 5.03 (d, $J =$ 7.3 Hz, 6 H, NH), 7.15 (d, $J =$ 8.2 Hz, 12 H, C_6H_4), 7.53 (d, $J =$ 8.2 Hz, 12 H, C_6H_4); ^{13}C NMR (67.9 MHz, $CDCl_3$): $\delta =$ 28.26 ($C(CH_3)_3$), 38.51 (CH_2), 52.29 (CH_3), 54.33 (CH), 80.03 ($C(CH_3)_3$), 87.41, 99.17 (C≡C), 121.76, 127.36, 129.50, 131.90, 137.33 (42C, C_6H_4, C_6), 155.02 (CON), 172.12 (CO_2); IR (KBr): $\tilde{\nu} = 3368\ cm^{-1}$ (NH), 2204 (C≡C), 1746, 1715 (CO_2); $C_{108}H_{120}N_6O_{24}$ (1886.2); calcd. C 68.77, H 6.41, N 4.46; found C 68.65, H 6.49, N 4.21.

Deprotection of the carboxylate terminus of compound 1 and 2: LiOH · H_2O (20 mg, 0.45 mmol) was added to a solution of **1** (98 mg, 0.10 mmol) or **2** (94 mg, 0.05 mmol) in a mixture of THF/H_2O (3/1) at room temperature. The mixtures were stirred overnight and the pH was adjusted to ≈2.5 by addition of 0.5 M $NaHSO_4$. The aqueous solutions were extracted with ethyl acetate, the organic layer was dried over $MgSO_4$, and evaporated to yield powders of the free acids. Yield for **1**: 87 mg (93 %); yield for **2**: 83 mg (92 %). The crude free acids of **1** and **2** were not further characterized and were used without further purification for the synthesis of **3** and **5**.

Deprotection of the amine terminus of compound 1: Trifluoroacetic acid (10 mL) was added slowly to a solution of **1** (98 mg, 0.01 mmol) in dichloromethane (10 mL). After the mixture had been stirred for 30 min, the volatiles were evaporated, and the residue was washed with diethyl ether (4 × 5 mL) and dried. Yield: 98 mg (95 %). The crude triflate salt of **1** was not characterized and was used without further purification for the synthesis of **4**.

1,3,5-C_6H_3{C≡$CC_6H_4CH_2CH[NHCO_2C(CH_3)_3][CONHC(CH_2OCH_2CH_2CO_2CH_3)_3]$}$_3$ (**3**): A solution of tris(2-methoxycarbonylethoxymethyl)aminomethane (97 mg, 0.25 mmol) in tetrahydrofuran (5 mL) and *N*-ethylmorpholine (32.3 μL, 0.25 mmol) was added to a solution of the tri acid of **1** (48 mg, 0.05 mmol) in tetrahydrofuran (5 mL). The solution was cooled to 0 °C and 1-hydroxybenzotriazole (HOBT) (41 mg, 0.30 mmol) and 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (EDC) (58 mg, 0.30 mmol) were added. After the mixture had been stirred for 24 h, concentration of the solution gave a colorless oil from which the product was isolated by flash chromatography on silica gel (30 cm) using dichloromethane/methanol 30/1. Yield 93 mg (92 %) as a colorless oil; $[\alpha]_D = 21.2$ ($c = 0.7$, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta =$ 1.39 (s, 27 H, CH_3), 2.54 (t, $J =$ 6.1 Hz, 18 H, CH_2), 2.98 (dd, $J =$ 13.7 Hz, $J =$ 6.3 Hz, 3 H, CH′H), 3.05 (dd, $J =$ 13.7 Hz, $J =$ 6.6 Hz, 3 H, CHH′), 3.59- 3.64 (m, 18 H, CH_2), 3.64- 3.67 (m, 18 H, CH_2), 3.68 (s, 27 H, CH_3), 4.33 (pq, $J =$ 6.8 Hz, 3 H, CH), 5.26 (d, $J =$ 6.7 Hz, 3 H, NH), 6.18 (s, 3 H, NH), 7.29 (d, $J =$ 8.3 Hz, 6 H, C_6H_4), 7.44 (d, $J =$ 8.3 Hz, 6 H, C_6H_4), 7.61 (s, 3 H, C_6H_3); ^{13}C NMR (67.9 MHz, $CDCl_3$): $\delta =$ 28.36 ($C(CH_3)_3$), 34.75 (CH_2), 39.31 (CH_2), 51.79 (CH_3), 55.89, 59.84 (CH, C), 66.79 (CH_2), 69.09 (CH_2), 79.74 ($C(CH_3)_3$), 87.81 (C≡C), 90.50 (C≡C), 121.13, 124.14, 129.86, 131.71, 133.99, 138.24 (C_6H_3, C_6H_4), 155.26 (CON), 170.80, 172.13 (CO_2); IR (CH_2Cl_2): $\tilde{\nu} = 3415\ cm^{-1}$ (NH), 2213 (C≡C), 1740, 1720 (CO_2); ESI-MS m/z: 1034.8 ($[M + 2Na]^{2+}$) (calcd mass: $C_{102}H_{138}N_6O_{36}$ 2024.2).

1,2,3,4,5,6-C_6{C≡$CC_6H_4CH_2CH[NHCO_2C(CH_3)_3][CONHC(CH_2OCH_2CH_2CO_2CH_3)_3]$}$_6$ (**5**): A solution of tris(2-methoxycarbonylethoxymethyl)-aminomethane (51 mg, 0.13 mmol) in tetrahydrofuran (5 mL) and *N*-ethylmorpholine (16.9 μL, 0.13 mmol) was added to a solution of the hexa acid of **2** (30 mg, 0.017 mmol) in tetrahydrofuran (5 mL). The solution was cooled to 0 °C and HOBT (18 mg, 0.13 mmol) and EDC (25 mg, 0.13 mmol) were added. After the mixture had been stirred for 24 h, concentration of the solution gave a brown oil from which the product was isolated by flash chromatography on silica gel (30 cm) using dichloromethane/methanol 30/1. Yield 93 mg (50 %) as a brown oil; $[\alpha]_D = 21.2$ ($c =$ 0.5, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta =$ 1.37 (s, 54 H, CH_3), 2.53 (t, $J =$ 6.1 Hz, 36 H, CH_2), 2.87 – 3.00 (m, 6 H, CH′H), 3.16 (dd, $J =$ 14.1 Hz, $J =$ 6.0 Hz, 6 H, CHH′), 3.52- 3.70 (m, 126 H, CH_2, CH_2, CH_3), 4.29- 4.41 (m, 6 H, CH), 5.32 (d, $J =$ 7.5 Hz, 6 H, NH), 6.33 (s, 6 H, NH), 7.33 (d, $J =$ 7.7 Hz, 12 H, C_6H_4), 7.57 (d, $J =$ 7.7 Hz, 12 H, C_6H_4); ^{13}C NMR (67.9 MHz, $CDCl_3$): $\delta =$ 28.32 ($C(CH_3)_3$), 34.75 (CH_2), 39.14 (CH_2), 51.76 (CH_3), 55.94, 59.83 (CH, C), 66.81 (CH_2), 69.09 (CH_2), 79.72 ($C(CH_3)_3$), 87.29 (C≡C), 99.38 (C≡C), 121.37, 127.37, 129.92, 131.79, 138.95 (C_6, C_6H_4), 155.33 (CON), 170.06, 172.14 (CO_2); IR (CH_2Cl_2): $\tilde{\nu} = 3410\ cm^{-1}$ (NH), 2212 (C≡C), 1738 (CO_2); ESI-MS m/z: 2008.3 ($[M + 2Na]^{2+}$) (calcd mass: $C_{198}H_{270}N_{12}O_{72}$ 3970.3).

1,3,5-C_6H_3{C≡$CC_6H_4CH_2CH[NHCO(Orn)_3][CO_2CH_3]$}$_3$ (**4**): (Boc)Orn-(Boc)[(Boc)Orn(Boc)]Orn-OH (91 mg, 0.12 mmol) and *N*-ethylmorpholine (26.6 μL, 0.21 mmol) was added to a solution of the trifluoroacetate salt of **1** (31 mg, 0.03 mmol) in tetrahydrofuran (10 mL). The solution was cooled to 0 °C and HOBT (20 mg, 0.15 mmol) and EDC (29 mg, 0.15 mmol) were added. After the mixture had been stirred for 24 h, concentration of the solution gave a colorless solid from which the product was isolated by flash chromatography on silica gel (30 cm) using dichloromethane/ethyl acetate/methanol 2/2/1. Yield 85 mg (97 %) as a colorless solid; m.p. 185 °C (decomp); $[\alpha]_D = 59.8$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$ + CD_3OD): $\delta =$ 1.34 (s, 108 H, CH_3), 1.36 – 1.75 (m, 36 H, CH_2), 2.86 – 3.11 (m, 24 H, CH_2), 3.61 (s, 9 H, CH_3), 3.85 – 4.04 (m, 6 H, CH), 4.30 – 4.41 (m, 3 H, CH), 4.65 (pq, $J =$ 6.9 Hz, 3 H, CH), 7.08 (d, $J =$ 8.5 Hz, 6 H, C_6H_4), 7.36 (d, $J =$ 8.5 Hz, 6 H, C_6H_4), 7.53 (s, 3 H, C_6H_3), 7.64 (d, $J =$ 8.8 Hz, 3 H, NH); ^{13}C NMR (67.9 MHz, $CDCl_3$ + CD_3OD): $\delta =$ 25.17, 25.80, 26.01 (CH_2), 28.21, 28.32 ($C(CH_3)_3$), 29.00, 29.65, 29.86 (CH_2), 37.68, 38.15, 38.29, 39.68 (CH_2), 52.35, 53.47, 53.57, 54.02 (CH, CH_3), 79.22, 80.04 ($C(CH_3)_3$), 87.88 (C≡C), 90.30 (C≡C), 121.42, 124.02, 129.30, 131.83, 133.92, 136.95 (C_6H_3, C_6H_4), 156.08, 156.66 (CON), 171.83, 172.17, 172.96, 173.28 (CON, CO_2); IR (KBr): $\tilde{\nu} = 3330\ cm^{-1}$ (H_2O), 2215 (C≡C), 1740, 1692 (CO_2); ESI-MS m/z: 1478.1 ($[M + 2Na]^{2+}$) (calcd mass 2908.6); $C_{147}H_{225}N_{21}O_{39} \cdot CH_2Cl_2$ (2993.5); calcd. C 59.38, H 7.64, N 9.83; found C 59.02, H 7.78, N 9.88.

Acknowledgements

Financial support by the Deutsche Forschungsgemeinschaft, Fonds der Chemischen Industrie and Wacker Chemie, München, is gratefully acknowledged. We thank Professor W. Steglich and Dr. W. Spahl for MS spectra.

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Received: July 1, 1998
Revised version: September 7, 1998 [F 1246]

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