Pergamon

Tetrahedron 56 (2000) 1715–1723

TETRAHEDRON

β-Homo-peptides Built from $\beta^{2,2}$-HBip, a Biphenyl-substituted 3-Amino-2,2-dimethylpropanoic Acid

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Received 10 December 1999; accepted 28 January 2000

Abstract—A novel $\beta^{2,2}$-*gem*-disubstituted amino acid, $\beta^{2,2}$-HBip, has been synthesized by α,α-bis-alkylation of alkyl cyanoacetates with 2,2′-bis-(bromomethyl)-1,1′-diphenyl, followed by $NaBH_4/CoCl_2$ reduction of the cyano group. Both its C- and N-protected derivatives have been obtained. A slow interconversion at the NMR time scale is generally observed between the two enantiomers of the conformationally labile $\beta^{2,2}$-HBip residue. The homo-peptides Boc-$(\beta^{2,2}$-HBip$)_n$-OMe have been prepared in solution by the EDC/HOBt coupling method to the hexamer level and a preliminary conformational analysis has been performed by ^{1}H NMR and FT-IR absorption techniques.

Introduction

In search of secondary structure stabilizing peptide mimetics (in particular synthetic foldamers), the field of β-peptides (peptides based on β-amino acids) has recently attracted a considerable interest.[1] Extensive studies of Seebach,[2] Gellman[3] and other groups,[1,4] have shown that β-peptides may adopt a larger variety of stable secondary structures than their α-peptide counterparts. Just in the recent past few years, parallel and antiparallel sheet structures and two new stable helical conformations (3_{14} and 2.5_{12} helices)[1–4] different from those adopted by oligomers of protein aminoacids and $C^{\alpha,\alpha}$-disubstituted glycines (3.6_{13} or α and 3_{10} helices)[5] have been discovered in oligomers of β-amino acids.

In previous studies we have shown that the $C^{\alpha,\alpha}$-disubstituted glycines Bip and Bin (Fig. 1),[6] possessing only an axial chirality, behave as helix inducers in short-chain peptides[7] as well as in the homo-oligomeric series Z-$(Bip)_n$-O*t*Bu.[7b] Furthermore, the Bip and Bin architectures may give rise to *efficient rigid fluorophores* which have been exploited in the design of the first peptide-based system of rigid donor-rigid interchromophore spacer-rigid acceptor,[8] and may also constitute *rigid axially chiral carrier frames* for crown-ether effectors.[9] In this connection, we have been interested in the comparison of the Bip and Bin peptides with their β-analogues. In the present paper we report the synthesis of the terminally protected residue $\beta^{2,2}$-HBip **I** (Fig. 1) and its homo-peptides Boc-$(\beta^{2,2}$-HBip$)_n$-OMe to the hexamer level[10,11] accompanied by a

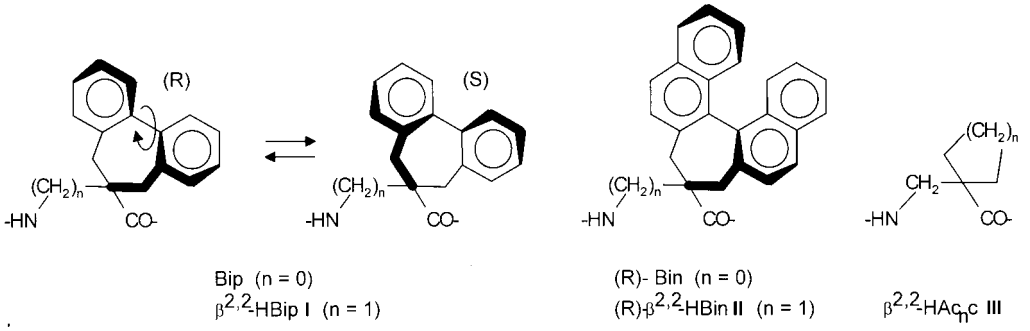

Figure 1. The structures of Bip,[6] $\beta^{2,2}$-HBip **I**, (R)-Bin,[6] (R)-$\beta^{2,2}$-HBin **II** [10] and $\beta^{2,2}$-HAc_nc **III**.[2k,l]

Keywords: β-homo-peptides; $\beta^{2,2}$-HBip; α,α-disubstituted β-amino acids.
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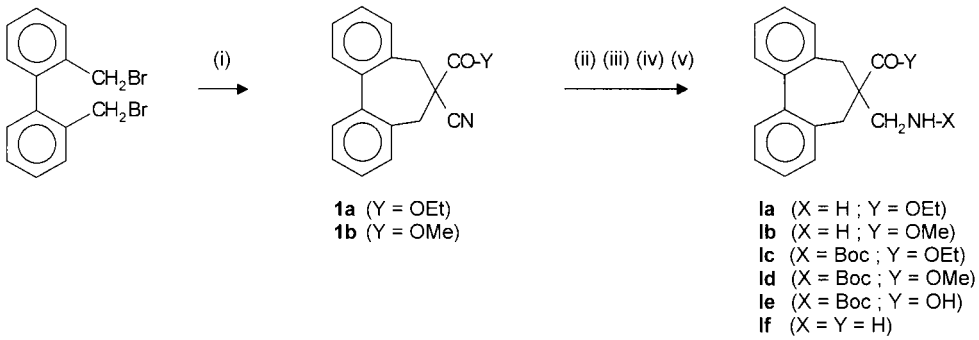

Figure 2. Synthetic scheme for the preparation of the α,α-disubstituted-β-aminoacid derivatives **I**: (i) EtOOC–CH_2–CN or MeOOC–CH_2–CN; DMF; K_2CO_3; (ii) $NaBH_4$; $CoCl_2$; MeOH; (iii) Boc_2O; CH_3CN; (iv) 1N NaOH; MeOH; 80°C (v) TFA/CH_2Cl_2 (1:1).

preliminary analysis of their conformational preferences by ^{1}H NMR and FT-IR absorption techniques. As its Bip analogue,[6b] β^{2,2}-HBip is characterized by an axial chirality, but its enantiomers are rapidly interconverting at rt and cannot be isolated.[12] In contrast, the enantiomers of β^{2,2}-HBin **II** (Fig. 1) are optically stable even at high temperature.[6,10] β^{2,2}-HBip may be regarded as either a 1,1′-biphenyl-substituted 3-amino-2,2-dimethylpropanoic acid (homo-aminoisobutyric acid: β^{2,2}-HAib),[13] or a di-benzo-1-amino-methylcycloheptanecarboxylic acid, related to the 1-amino-methylcycloalkanecarboxylic acid series β^{2,2}-HAc$_n$c **III** (Fig. 1), recently examined by Seebach and coworkers.[2k,l]

Results and Discussion

Synthesis of β^{2,2}-HBip (I) and its derivatives

As for the previously observed bis-alkylation of benzylidene derivatives of glycine esters,[6] α,α-bis-alkylation of the active methylene of ethyl or methyl cyanoacetate in DMF/K_2CO_3 at 20°C, using 2,2′-bis-(bromomethyl)-1,1′-diphenyl as the alkylating agent, readily furnished the cyanoesters **1a** and **1b** (Fig. 2) in excellent yields (81 and 75%, respectively). The cobalt (II)-assisted selective reduction method of nitriles in the presence of an ester function,[14] was applied to the *gem*-cyanoesters **1a** and **1b** which, upon treatment with sodium borohydride (10 equiv.) and cobalt (II) chloride (2 equiv.) in methanol at rt, gave the amino-esters H-β^{2,2}-HBip-OEt **Ia** (76%) and H-β^{2,2}-HBip-OMe **Ib** (91%), respectively.[15] The N-Boc protected derivatives were synthesized in two steps from the C-protected derivatives **Ia** and **Ib**, which were first treated with di-*tert*-butyl dicarbonate in acetonitrile at rt[6b,16] to give the fully protected compounds Boc-β^{2,2}-HBip-OEt **Ic** (98%) and Boc-β^{2,2}-HBip-OMe **Id** (91%). Saponification of the ester function of **Ic** and **Id**, performed in aqueous 1N NaOH/MeOH at ca. 80°C, a relatively high temperature often required for α,α-disubstituted-amino esters,[2k,6b] afforded the N-Boc protected amino acid Boc-β^{2,2}-HBip-OH **Ie** (92%). Finally, cleavage of the Boc group of **Ie** in TFA/CH_2Cl_2 (1:1) at rt led to the **If** trifluoroacetate (79%).

Synthesis of β^{2,2}-HBip peptides by the EDC/HOBt method

The EDC/HOBt method[17] has been shown previously to be efficient for the coupling of Ala at the C-terminus of α,α-diphenylglycine (Dph),[18] Bip and Bin,[7a] but to proceed with low yield for the coupling of Ala at the N-terminus of Dph.[18] It was chosen by us as a method of choice for coupling at both the α,α-disubstituted COOH function and the relatively unhindered NH_2 function of the β^{2,2}-HBip residue. Indeed, in control experiments, coupling of Boc-β^{2,2}-HBip-OH **Ie** with H-Ala-OMe by the EDC/HOBt method gave Boc-β^{2,2}-HBip-Ala-OMe **Ig** (Fig. 3) in 87% yield, and coupling of N-deprotected **Ig** with Boc-Ala-OH by the same procedure led to Boc-Ala-β^{2,2}-HBip-Ala-OMe **Ih** in 90% overall yield.

Therefore, the EDC/HOBt method in solution was used for the synthesis of the N-Boc protected homo-oligomers of β^{2,2}-HBip (Fig. 4). Coupling of H-β^{2,2}-HBip-OMe **Ib** with Boc-β^{2,2}-HBip-OH **Ie** gave Boc-(β^{2,2}-HBip)$_2$-OMe **2d** (93%), which was N-deprotected in TFA/CH_2Cl_2 (1:1) at rt to give, after neutralization with 5% $NaHCO_3$ and extraction, the N-free dipeptide amino ester H-(β^{2,2}-HBip)$_2$-OMe **2b**. Coupling of **2b** with **Ie** gave the tripeptide Boc-(β^{2,2}-HBip)$_3$-OMe **3d** (78%). Acidic N-deprotection of **3d** gave **3b**, which was coupled with **Ie** to give Boc-(β^{2,2}-HBip)$_4$-OMe **4d** (90%), and acidic N-deprotection of **4d** to **4b**,

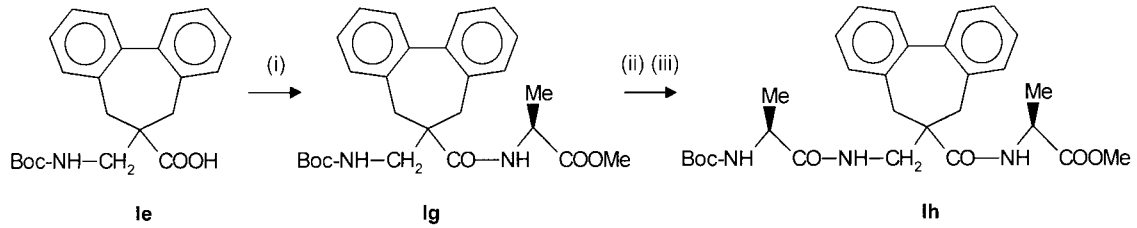

Figure 3. Coupling of protected Ala at the C- and N-terminus of the β^{2,2}-HBip residue: (i) H-Ala-OMe·HCl; Et_3N; EDC; HOBt; (ii) TFA/CH_2Cl_2 (1:1); (iii) Boc-Ala-OH; EDC; HOBt.

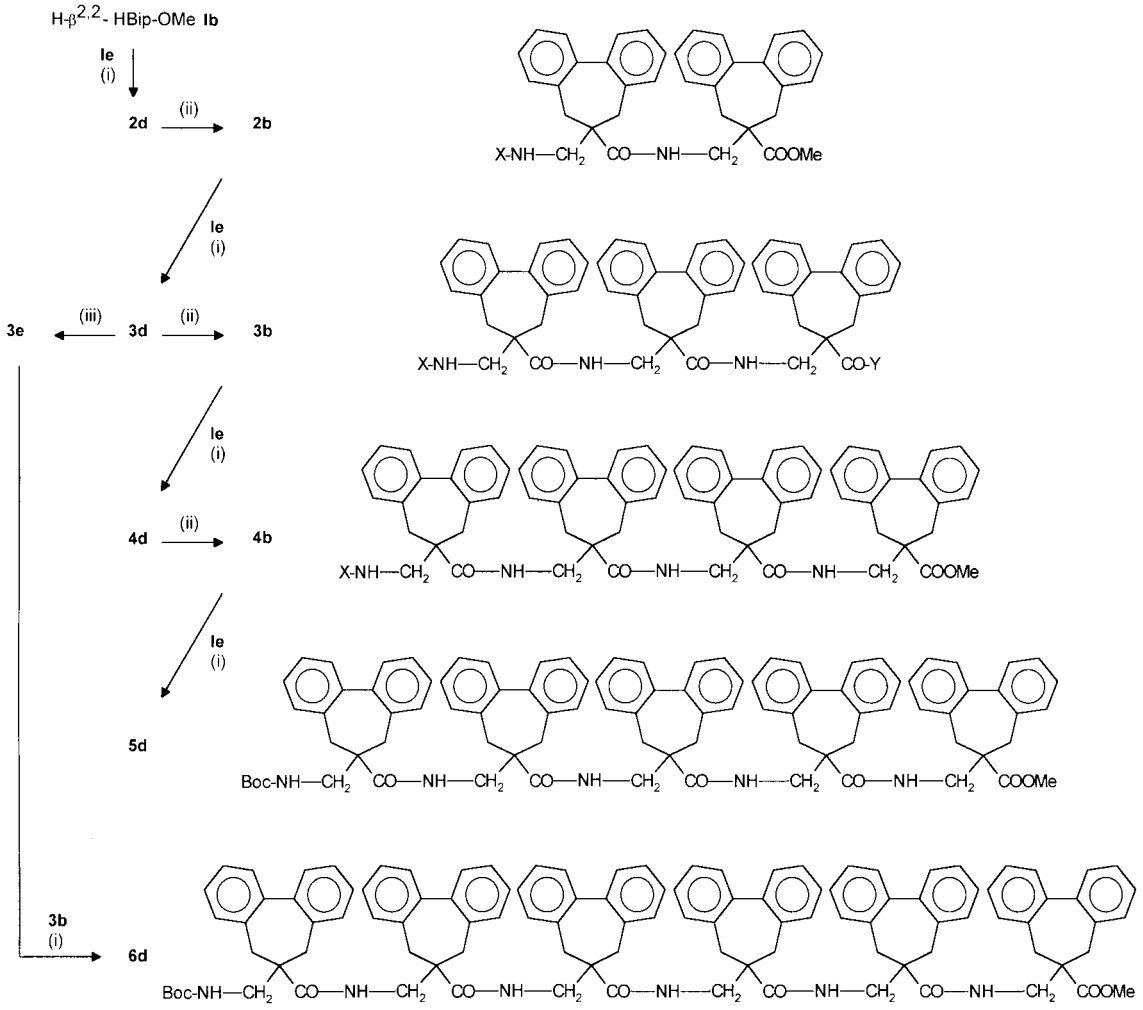

Figure 4. Synthesis of the homo-oligomers X-($\beta^{2,2}$-HBip)$_n$-Y (n = 2–6). **b**: X=H; Y=OMe, **d**: X=Boc; Y=OMe, **e**: X=Boc; Y=OH. (i) EDC; HOBt; (ii) TFA/CH_2Cl_2 (1:1); (iii) 1 M NaOH/MeOH; reflux.

followed by coupling with **Ie**, gave Boc-($\beta^{2,2}$-HBip)$_5$-OMe **5d** (80%). Finally, 3+3 fragment condensation of **3b** with Boc-($\beta^{2,2}$-HBip)$_3$-OH **3e**, resulting from C-deprotection of **3d**, gave Boc-($\beta^{2,2}$-HBip)$_6$-OMe **6d** (50%).

^{1}H NMR analysis of $\beta^{2,2}$-HBip and its homo-peptides

Because of the conformational lability of the $\beta^{2,2}$-HBip residue, broadened signals are generally observed in the ^{1}H NMR spectra of the X-$\beta^{2,2}$-HBip-Y derivatives at rt, indicating a slow interconversion on the NMR time scale between the two conformers resulting from rotation about the 1-1′ bond of the biphenyl moiety (**I** in Fig. 1). As an example, for Boc-$\beta^{2,2}$-HBip-OEt **Ic** (Fig. 5a) the benzylic protons H_a^{β}–H_e^{β} and $H_a^{\beta'}$–$H_e^{\beta'}$ show at 333 K a single pair of doublets in fast-exchange conditions. This spectral pattern reflects the equivalence of the two benzylic carbon atoms C^{β} and $C^{\beta'}$ in a quasi-planar average structure of the biphenyl moiety, presumably similar to the planar transition state of interconversion. At 263 K two distinct pairs of doublets are observed, in agreement with a non planar common structure of the two enantiomeric conformers (*R*)- and (*S*)-Boc-$\beta^{2,2}$-HBip-OEt in slow exchange on the NMR time scale. The patterns of the CH_2NH(Boc) and COOCH_2CH$_3$ protons are also temperature dependent. From the coalescence temperatures T_C and the corresponding chemical shift differences $\Delta\nu$, the calculated[19] rotational energy barrier is ca. 14 kcal mol^{-1}, as expected.[6b,12]

For the Boc-($\beta^{2,2}$-HBip)$_n$-OMe series, the axial chirality of each $\beta^{2,2}$-HBip residue results in the presence of diastereoisomeric conformers in slow exchange, generating very complex NMR spectra. However, in the case of the homodimer Boc-($\beta^{2,2}$-HBip)$_2$-OMe **2d** (Fig. 5b), split signals for both NH protons and Boc $(CH_3)_3C$ protons of the two expected diastereoisomers (*RR*,*SS*) and (*RS*,*SR*) are clearly observed at 238 K, in a ratio slightly different than 1:1, while signals for a single 'achiral' structure are seen at ≥296 K.

FT-IR absorption analysis of the Boc-($\beta^{2,2}$-HBip)$_n$-OMe homo-peptides

The FT-IR absorption spectra of the Boc-($\beta^{2,2}$-HBip)$_n$-OMe homo-peptide series **2d**–**6d** in $CDCl_3$ solution show the presence of two strong bands at about 3450 cm^{-1} (free NH groups) and at 3413–3398 cm^{-1} (weakly H-bonded NH groups) and a weaker band at 3376–3334 cm^{-1}

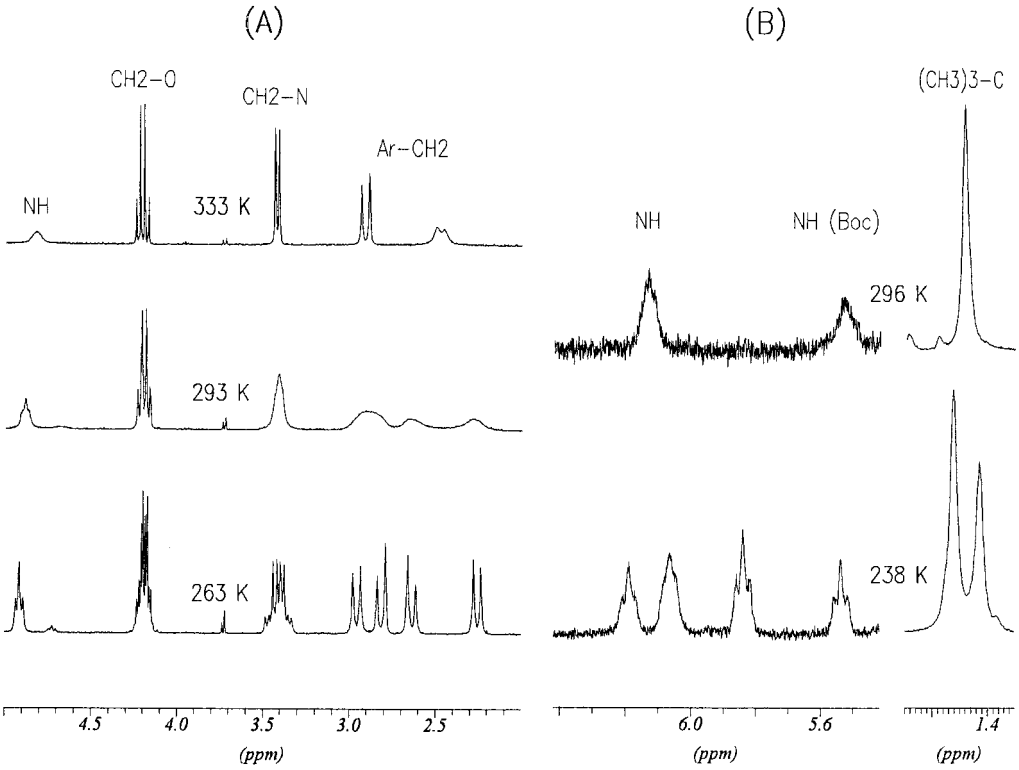

Figure 5. Temperature-dependent ^{1}H NMR spectra (300 MHz) of: (a) Boc-$\beta^{2,2}$-HBip-OEt **Ic**; and (b) Boc-($\beta^{2,2}$-HBip)$_2$-OMe **2d** in $CDCl_3$ solution.

(strongly H-bonded NH groups) (Fig. 6).[20] The relative intensity of the two latter bands increases with increasing peptide main-chain length. No concentration effect is observed.

These results might suggest the concomitant occurrence of intramolecularly H-bonded forms of different ring size in these homo-oligomers. Although it has been emphasized that homo-peptides consisting of $\beta^{2,2}$-amino acids do not fit into the presently known helical secondary structures of β-peptides, Seebach et al.[2k] have recently shown that the crystal structure of the parent homo-tripeptide Boc-($\beta^{2,2}$-$HAc_6c)_3$-OMe is characterized by a new turn-motif for β-peptides, consisting of a ten-membered ring system formed by an intramolecular H-bond between the C-terminal carbonyl group and the amide NH of the second

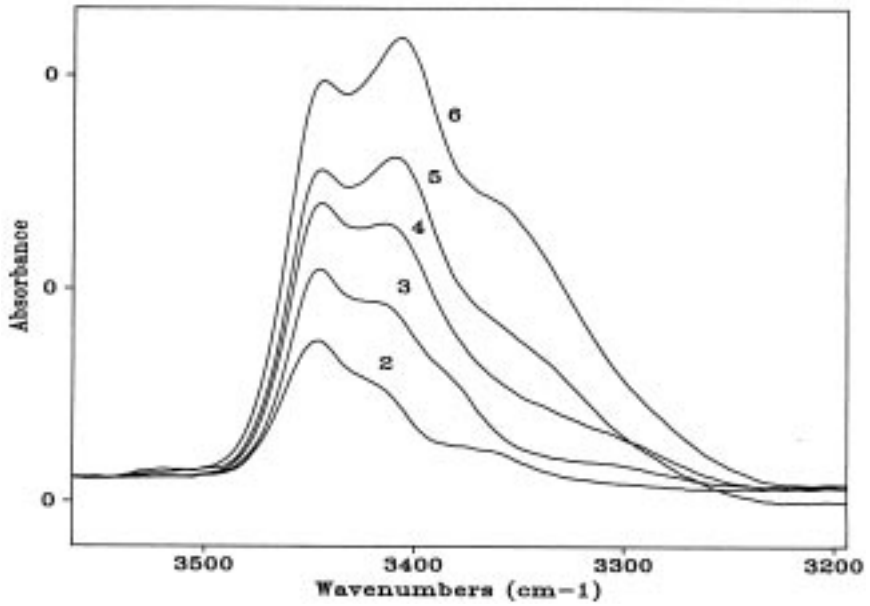

Figure 6. FT-IR absorption spectra in the N–H stretching region of the Boc-($\beta^{2,2}$-HBip)$_n$-OMe (n = 2–6) peptide series in $CDCl_3$ solution (peptide concentration: 1 mM).

amino acid. These authors also suggested 'the possible occurrence of string-of-pearls-type structure for the higher oligomers, stabilized by intramolecular H-bonds in the successive ten-membered H-bonded rings'. Unfortunately, in the present study deeper structural information on the homo-peptides Boc-($\beta^{2,2}$-HBip)$_n$-OMe **2d**–**6d** could be obtained neither from the ^{1}H NMR analysis, because of a too high complexity of the spectra (vide supra), nor from an X-ray analysis, because of the lack of crystallinity of these series of compounds.[21] Effort is being made to identify the conformation by higher field NMR and more sophisticated methods. Moreover, higher crystallinity and simpler ^{1}H NMR spectra are expected for homo-peptides built from the corresponding axially chiral and conformationally rigid $\beta^{2,2}$-HBin residue,[11] which hopefully will allow us a better understanding of their folding patterns.

Experimental

Abbreviations

$\beta^{2,2}$-HBip, 2′,1′:1,2;1″,2″:3,4-dibenzcyclohepta-1,3-diene-6-aminomethyl-6-carboxylic acid; Boc, *tert*-butyloxycarbonyl; EDC, 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide; TFA, trifluoroacetic acid; HOBt, 1-hydroxybenzotriazole; THF, tetrahydrofurane; DMF, *N*,*N*,-dimethylformamide; TLC, thin-layer chromatography.

General

2,2′-Bis(bromomethyl)-1,1′-biphenyl was purchased from Aldrich. Melting points were determined with a temperature raise of 3°C min^{-1} and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, the solvent $CDCl_3$ or CD_3OD being used as internal standard (δ=7.27 or 3.31 ppm for ^{1}H and 77.00 or 49.00 ppm for ^{13}C). Splitting patterns are abbreviated as follows: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet. The optical rotations were measured with an accuracy of 0.3%, in a 1 dm thermostated cell. Analytical TLC and preparative column chromatography were performed on Kieselgel F 254 and on Kieselgel 60 (0.040–0.063 mm) (Merck), respectively, with the following eluent systems: CH_2Cl_2 (I); 1% MeOH-99% CH_2Cl_2 (II); 2.5% MeOH-97.5% CH_2Cl_2 (III); 5% MeOH-95% CH_2Cl_2 (IV); 10% MeOH-90% CH_2Cl_2 (V). UV light (254 nm) allowed visualization of the spots after TLC runs for all compounds.

2′,1′:1,2;1″,2″:3,4-Dibenzcyclohepta-1,3-diene-6-cyano-6-carboxylic acid ethyl ester (1a). A mixture of 2,2′-bis(bromomethyl)-1,1′-biphenyl (5.56 g; 16.3 mmol), ethyl cyanoacetate (2.1 mL; 19.6 mmol) and anhydrous potassium carbonate (5.4 g; 39 mmol) in DMF (17 mL) was magnetically stirred at rt for 16 h. The reaction mixture was then poured in a separatory funnel and extracted with diethyl ether (200 mL). The organic layer was washed with water (5 × 50 mL), dried ($MgSO_4$), filtered and evaporated in vacuo. The resulting yellow oil was chromatographed on a 4 × 20 cm column of silica gel with eluent (I) to give 3.83 g (81%) of pure **1a** as an oil. R_f=0.6 (I). ^{1}H NMR ($CDCl_3$): 7.45–7.37 [m, 8H, ArH], 4.33 [q, *J*=7 Hz, 2H, OCH_2], 3.40–2.80 [m, 4H, $ArCH_2^{\beta}$], 1.38 [t, *J*=7 Hz, 3H, CH_3]. ^{13}C NMR ($CDCl_3$): 167.5 (CO), 140.4, 132.8, 130.0, 128.5, 128.4, 128.0 (C^{Ar}), 119.4 (CN), 62.9 (OCH_2), 52.9 (C^{α}), 38.5 ($ArCH_2^{\beta}$], 14.0 (CH_3). Anal. for $C_{19}H_{17}NO_2$: calcd C 78.33, H 5.88, N 4.81; found C 77.98, H 5.92, N 4.75.

2′,1′:1,2;1″,2″:3,4-Dibenzcyclohepta-1,3-diene-6-cyano-6-carboxylic acid methyl ester (1b). Obtained in the same way as **1a** from 2,2′-bis(bromomethyl)-1,1′-biphenyl (13.6 g; 40 mmol), methyl cyanoacetate (3.9 mL; 44 mmol) and anhydrous potassium carbonate (12.2 g; 88 mmol) in DMF (40 mL). Yield 8.27 g (75%) after column chromatography (SiO_2; eluent I), as an amorphous solid. Mp=112°C. R_f=0.5 (I). ^{1}H NMR ($CDCl_3$): 7.51–7.40 [m, 8H, ArH], 3.89 [s, 3H, OCH_3], 3,40–2,80 [m, 4H, $ArCH_2^{\beta}$]. ^{13}C NMR ($CDCl_3$): 167.8 (CO), 140.2, 132.6, 129.9, 128.4, 128.2, 127.9 (C^{Ar}), 119.1 (CN), 53.5 (OCH_3), 52.7 (C^{α}), 38.3 ($ArCH_2^{\beta}$]. Anal. for $C_{18}H_{15}NO_2$: calcd C 77.96, H 5.45, N 5.05; found C 77.91, H 5.52, N 5.15.

2′,1′:1,2;1″,2″:3,4-Dibenzcyclohepta-1,3-diene-6-aminomethyl-6-carboxylic acid ethyl ester, H-$\beta^{2,2}$-HBip-OEt (Ia). To a solution of cyanoester **1a** (1.89 g; 6.49 mmol) and cobaltous chloride hexahydrate (3.1 g; 13 mmol) in 99% MeOH (80 mL), stirred at rt, was added $NaBH_4$ (2.45 g; 65 mmol) by portions, resulting in evolution of hydrogen gas and formation of a black precipitate. When addition was completed, stirring was continued for 30 min at rt. Then, 0.5 M HCl (1.2 L) was poured in the reaction mixture in order to dissolve the black precipitate. After evaporation of MeOH the aqueous layer was made alkaline by addition of conc. NH_4OH and then extracted with diethyl ether (4×200 mL). The combined extracts were washed with brine, dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was chromatographed on a 2.5×24.5 cm^2 column of silica gel with eluent (III) to give 1.45 g (76%) of an amorphous solid. Mp=91°C. R_f=0.1 (III). ^{1}H NMR ($CDCl_3$): 7.41–7.29 [m, 8H, ArH], 4,25 [q, *J*=7 Hz, 2H, OCH_2], 3.4–1.8 [broad m, 6H, $ArCH_2^{\beta}$ and NCH_2^{β}], 1.33 [t, *J*=7 Hz, 3H, CH_3] 1.30 (broad s, 2H, NH_2). ^{13}C NMR ($CDCl_3$): 175.4 (CO), 140.7, 136.4, 129.7, 128.1, 127.4, 127.2 (C^{Ar}), 60.7 (OCH_2), 60.1 (C^{α}), 47.9 (NCH_2^{β}), 37.7, 36.1 ($ArCH_2^{\beta}$), 14.3 (CH_3). Anal. for $C_{19}H_{21}NO_2$: calcd C 77.25, H 7.17, N 4.74; found C 76.79, H 7.22, N 4.55.

2′,1′:1,2;1″,2″:3,4-Dibenzcyclohepta-1,3-diene-6-aminomethyl-6-carboxylic acid methyl ester, H-$\beta^{2,2}$-HBip-OMe (Ib). Prepared in the same way as **Ia** from **1b** (8.27 g; 29.8 mmol), cobaltous chloride hexahydrate (14.2 g; 59.7 mmol) and $NaBH_4$ (11 g; 300 mmol) in 99% MeOH (350 mL). Yield 4.12 g (91%) after column chromatography (SiO_2; eluent IV), as an amorphous solid. Mp=48°C. R_f=0.6 (V). ^{1}H NMR ($CDCl_3$): 7.32–7.23 [m, 8H, ArH], 3.75 [s, 3H, OCH_3], 3,4–1.8 [broad m, 6H, $ArCH_2^{\beta}$ and NCH_2^{β}], 1.55 (broad s, 2H, NH_2). ^{13}C NMR ($CDCl_3$): 175.8 (CO), 140.6, 136.3, 129.6, 128.1, 127.4, 127.2 (C^{Ar}), 60.1 (C^{α}), 51.9 (OCH_3), 47.9 (NCH_2^{β}), 37.8, 36.3 ($ArCH_2^{\beta}$). Anal. for $C_{18}H_{19}NO_2 \cdot 0.15H_2O$: calcd C 76.11, H 6.85, N 4.93; found C 76.16, H 6.81, N 4.93.

2′,1′:1,2;1″,2″:3,4-Dibenzcyclohepta-1,3-diene-6-*N*-*tert*-butyloxycarbonylaminomethyl-6-carboxylic acid ethyl

ester, Boc-β^{2,2}-HBip-OEt (Ic). To a solution of the β-amino ester **Ia** (1.37 g; 4.66 mmol) in acetonitrile (50 mL) was added di-*tert*-butyl dicarbonate (2.03 g; 9.32 mmol). The solution was stirred at rt overnight and evaporated in vacuo. The oily residue was directly chromatographed on a 2.5×22.5 cm^2 column of silica gel with eluent (III) to give 1.80 g (98%) of pure **Ic** as an oil. R_f=0.8 (III). ^{1}H NMR ($CDCl_3$): 7.42–7.29 [m, 8H, ArH], 4.91 [broad m, 1H, NHBoc], 4.19 [q, *J*=7 Hz, 2H, OCH_2], 3.41 [broad m, 2H, NCH_2^{β}], 3.09–2.12 [broad m, 4H, $ArCH_2^{\beta}$], 1.48 [s, 9H, CH_3 (Boc)], 1.28 [t, *J*=7 Hz, 3H, CH_3]. ^{13}C NMR ($CDCl_3$): 174.9 (CO), 155.8 (CO Boc), 146.7, 140.6, 135.9, 129.9, 128.0, 127.3 (C^{Ar}), 79.3 (O–C Boc), 61.0 (OCH_2), 58.4 (C^{α}), 45.5 (NCH_2^{β}], 37.9, 36.1 ($ArCH_2^{\beta}$), 27.3 (CH_3 Boc), 14.2 (CH_3). Anal. for $C_{24}H_{29}NO_4\cdot 0.3H_2O$: calcd C 71.90, H 7.44, N 3.49; found C 71.81, H 7.68, N 3.27.

2′,1′:1,2;1″,2″:3,4-Dibenzcyclohepta-1,3-diene-6-*N*-*tert*-butyloxycarbonylaminomethyl-6-carboxylic acid methyl ester, Boc-β^{2,2}-HBip-OMe (Id). Prepared in the same way as **Ic** from the β-aminoester **Ib** (2.53 g; 9 mmol) and di-*tert*-butyl dicarbonate (3.92 g; 18 mmol) in acetonitrile (100 mL). Yield 3.12 g (91%) after column chromatography (SiO_2; eluent II), as an oil. R_f=0.6 (III). ^{1}H NMR ($CDCl_3$): 7.32–7.21 [m, 8H, ArH], 4.99 [broad m, 1H, NHBoc], 3.63 [s, 3H, OCH_3], 3.32 [broad m, 2H, NCH_2^{β}], 2.99–1.98 [broad m, 4H, $ArCH_2^{\beta}$], 1.39 [s, 9H, CH_3 (Boc)]. ^{13}C NMR ($CDCl_3$): 175.1 (CO), 155.6 (CO Boc), 140.4, 135.9, 129.4, 127.9, 127.3, 127.2 (C^{Ar}), 79.0 (O–C Boc), 58.4 (C^{α}), 51.9 (OCH_3), 45.4 (NCH_2^{β}], 37.6, 35.9 ($ArCH_2^{\beta}$), 28.1 (CH_3 Boc). Anal. for $C_{23}H_{27}NO_4\cdot H_2O$: calcd C 69.15, H 7.31, N 3.50; found C 69.96, H 7.08, N 3.53.

2′,1′:1,2;1″,2″:3,4-Dibenzcyclohepta-1,3-diene-6-*N*-*tert*-butyloxycarbonylaminomethyl-6-carboxylic acid, Boc-β^{2,2}-HBip-OH (Ie). A suspension of the ester **Ic** (0.277 g; 0.70 mmol) in MeOH (20 mL) and 1 N NaOH (10 mL) was stirred at 80°C for 2 h. The resulting clear solution was allowed to cool at rt, acidified by addition of an excess of 0.5 M HCl and extracted with diethyl ether. The organic solution was washed twice with water, dried ($MgSO_4$), filtered and evaporated in vacuo, to give 0.234 g (92%) of pure **Ie** as an amorphous solid. The same procedure, applied to **Id** (3.12 g; 8.19 mmol) in MeOH (165 mL) and 1 M NaOH (85 mL), gave 2.72 g (91%) of **Ie**. Mp=108°C. R_f=0.3 (IV). ^{1}H NMR ($CDCl_3$): 7.44–7.32 [m, 8H, ArH], 6.39 [broad s, 1H, OH], 5.03 [broad m, 1H, NHBoc], 3.49 [broad m, 2H, NCH_2^{β}], 3.1–2.2 [broad m, 4H, $ArCH_2^{\beta}$], 1.45 [s, 9H, CH_3 (Boc)]. ^{13}C NMR ($CDCl_3$): 180.4 (CO), 155.9 (CO Boc), 140.6, 135.7, 130.1, 128.2, 127.4 (C^{Ar}), 81.3 (O–C Boc), 58.4 (C^{α}), 45.5 (NCH_2^{β}], 37.7, 36.0 ($ArCH_2^{\beta}$), 28.3 (CH_3 Boc). Anal. for $C_{22}H_{25}NO_4\cdot 0.5H_2O$: calcd C 70.19, H 6.96, N 3.72; found C 69.73, H 6.61, N 3.37.

2′,1′:1,2;1″,2″:3,4-Dibenzcyclohepta-1,3-diene-6-aminomethyl-6-carboxylic acid, H-β^{2,2}-HBip-OH (If). The N-Boc protected compound **Ie** (0.60 g; 1.63 mmol) was solubilized in CH_2Cl_2 (10 mL) and TFA (10 mL) was added. The solution was stirred at rt for 2 h and evaporated in vacuo. Addition of CH_2Cl_2 to the residue, followed by evaporation in vacuo was repeated several times. The resulting solid was triturated in diethyl ether, decanted and dried in vacuo to yield 0.49 g (79%) of **If** trifluoroacetate as an amorphous solid. Mp=193°C. ^{1}H NMR (CD_3OD): 7.43–7.31 [m, 8H, ArH], 3.16 [broad m, 2H, NH_2], 2.98 [d, *J*=13.8 Hz, 2H, NCH_2^{β}], 2.9–2.0 [m, 4H, $ArCH_2^{\beta}$], ^{13}C NMR (CD_3OD): 176.9 (CO), 142.0, 136.2, 1, 131.2, 129.5, 129.1, 128.9 (C^{Ar}), 56.7 (C^{α}), 45.4 (NCH_2^{β}], 39.2, 38.1 ($ArCH_2^{\beta}$). Anal. for $C_{19}H_{18}NF_3O_4\cdot 0.5H_2O$: calcd C 58.45, H 4.90, N 3.58; found C 58.45 H 4.90, N 3.58.

Boc-β^{2,2}-HBip-Ala-OMe (Ig). To a solution of **Ie** (0.400 g; 1.10 mmol), H-Ala-OMe (0.306 g; 2.20 mmol), triethylamine (0.306 mL; 2.20 mmol) and HOBt (0.298 g; 2.20 mmol) in CH_2Cl_2 (8 mL)/THF (8 mL) was added a solution of EDC (0.253 g; 1.32 mmol) in CH_2Cl_2 (4 mL). The reaction mixture was stirred at rt for 16 h and the solvents evaporated in vacuo. The residue was solubilized in EtOAc (100 mL) and 0.5 M HCl (20 mL). The organic phase was successively extracted with 0.5 M HCl (20 mL), H_2O (2×20 mL), 5% $NaHCO_3$ (2×20 mL) and H_2O (2×20 mL), then dried ($MgSO_4$), filtered and evaporated in vacuo. The residue was chromatographed on a (3×33 cm) column of silica gel with eluent (III) to give 0.494 g (87%) of pure **Ig** as an amorphous solid. Mp=146°C. R_f=0.6 (III); 0.8 (IV). ^{1}H NMR ($CDCl_3$): 7.42–7.30 [m, 8H, ArH], 6.14 [broad m, 1H, NH (Ala)], 5.39 [broad m, 1H, NHBoc], 4.53 [m, 1H, H^{α} (Ala)], 3.76 [s, 3H, OCH_3], 3.40 [broad m, 2H, NCH_2^{β}], 3,1–2.1 [broad m, 4H, $ArCH_2^{\beta}$], 1.45 [s, 9H, CH_3 (Boc)], 1.37 [d, *J*=7.2 Hz, 3H, CH_3 (Ala)]. ^{13}C NMR ($CDCl_3$): 175.2, 173.4 (CO Ala and β^{2,2}-HBip), 156.3 (CO Boc), 140.6, 136.1, 134.8, 130.3, 128.4, 127.7 (C^{Ar}), 79.2 (O–C Boc), 58.1 (C^{α} β^{2,2}-HBip], 52.5 (OCH_3), 48.4 (C^{α} Ala), 45.5 (NCH_2^{β}], 38.2, 36.4 ($ArCH_2^{\beta}$], 28.4 (CH_3 Boc), 17.7 (CH_3 Ala). Anal. for $C_{26}H_{32}N_2O_5\cdot H_2O$: calcd C 66.36, H 7.28, N 5.95; found C 66.52, H 7.28, N 5.95.

Boc-Ala-β^{2,2}-HBip-Ala-OMe (Ih). To a cold (0°C) solution of **Ig** (0.470 g; 1.04 mmol) in CH_2Cl_2 (7 mL) was added TFA (7 mL). The solution was stirred at rt for 2 h and evaporated in vacuo. The residue was solubilized in EtOAc (100 mL) and 5% $NaHCO_3$ (10 mL). The organic phase was extracted with 5% $NaHCO_3$ (2×10 mL), dried ($MgSO_4$), filtered and evaporated in vacuo to give crude H-β^{2,2}-HBip-Ala-OMe (0.367 g; quantitative yield) which was directly used in the next step. A solution of this compound with Boc-Ala-OH (0.236 g; 1.25 mmol) and HOBt (0.281 g; 2.08 mmol) in CH_2Cl_2 (8 mL)/THF (8 mL), was cooled to ca. −10°C (ice–salt bath) and a solution of EDC (0.239 g; 1.25 mmol) in CH_2Cl_2 (4 mL) was added. The reaction mixture was stirred from −10°C to rt for 20 h. Extraction as for **Ig** followed by column chromatography on silica gel first with eluent (III), then with eluent (IV), led to 0.490 g (90%) of pure **Ih** as an amorphous solid. Mp=62°C. R_f=0.4 (IV). ^{1}H NMR ($CDCl_3$): 8.02 [m (d-like), 1H, NH (Ala2)], 7.70 [broad m, 1H, NH β^{2,2}-HBip], 7.42–7.26 [m, 8H, ArH], 5.13 [d, *J*=6 Hz, 1H, NHBoc (Ala1)], 4.47 [m, 1H, H^{α} (Ala2)], 4.05 [m, 3H, H^{α} (Ala1) and NCH_2^{β}], 3.80 [s, 3H, OCH_3], 3.32, 2.90, 2.69, 2.45 [4×d, *J*≅13 Hz, 4×1H, $ArCH_2^{\beta}$], 1.45–1.39 [m, 6H, CH_3 (Ala1, Ala2)], 1.33 [s, 9H, CH_3 (Boc)]. ^{13}C NMR ($CDCl_3$): 176.5, 175.7, 174.2 (CO Ala1, Ala2, β^{2,2}-HBip), 156.2 (CO Boc), 141.1, 140.7, 136.8, 135.6, 131.3, 130.6, 128.2, 127.7, 127.5, 127.2 (C^{Ar}), 80.4 (O–C Boc), 59.7 (C^{α} β^{2,2}-HBip),

53.0 (OCH_3), 51.6, 49.7 (C^{α} Ala1, Ala2), 43.8 (NCH_2^{β}), 36.7, 34.0 ($ArCH_2^{\beta}$), 28.4 (CH_3 Boc), 17.2, 15.9 (CH_3 Ala1, Ala2). Anal. for $C_{29}H_{37}N_3O_6 \cdot 0.7\ H_2O$: calcd C 64.95, H 7.22, N 7.84; found C 64.87, H 7.01, N 8.41.

Boc-β^{2,2}-HBip-β^{2,2}-HBip-OMe (2d). To a solution of Boc-β^{2,2}-HBip-OH **Ie** (1.31 g; 3.57 mmol), H-β^{2,2}-HBip-OMe **Ib** (1.00 g; 3.56 mmol) and HOBt (0.48 g; 3.56 mmol) in CH_2Cl_2 (40 mL)/THF (40 mL), was added a solution of EDC (0.68 g; 3.56 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at rt for 20 h. Extraction as for **Ig**, followed by column chromatography on silica gel with eluent (III), led to 2.09 g (93%) of pure **2d** as an amorphous solid. Mp=128°C. R_f=0.7 (III). ^{1}H NMR ($CDCl_3$): 7.5–7.2 [m, 16H, ArH], 6.11 [broad m, 1H, NH], 5.45 [broad m, 1H, NHBoc], 3.9–3.1 [broad m, 4H, NCH_2^{β}], 3.61 [s, 3H, OCH_3], 3.1–2.1 [broad m, 8H, $ArCH_2^{\beta}$], 1.44 [s, 9H, CH_3 (Boc)]. ^{13}C NMR ($CDCl_3$): 175.4, 175.3 (CO), 156.3 (CO Boc), 140.6, 135.2 (broad), 130.0 (broad), 128.5, 128.2, 128.1, 127.9, 127.8, 127.6, 127.5 (C^{Ar}), 79.2 (O–C Boc), 58.5, 58.0 (C^{α}), 52.3 (OCH_3), 45.7, 44.5 (NCH_2^{β}), 37.8–36.4 (broad) ($ArCH_2^{\beta}$), 28.4 (CH_3 Boc). ESI$^+$ MS *m/z* (relative intensity): 653 (100) $(M+Na)^+$; 631 (7) $(M+H)^+$. Anal. for $C_{40}H_{42}N_2O_5 \cdot H_2O$: calcd C 74.03, H 6.83, N 4.32; found C 74.27, H 6.92, N 4.48.

Boc-β^{2,2}-HBip-β^{2,2}-HBip-β^{2,2}-HBip-OMe (3d). The dipeptide **2d** (0.238 g; 0.38 mmol) was N-deprotected in CH_2Cl_2 (1.5 mL)/TFA (1.5 mL) as for **Ig** (see **Ih**). To a solution of the resulting crude H-β^{2,2}-HBip-β^{2,2}-HBip-OMe **2b** (0.200 g; quantitative yield), Boc-β^{2,2}-HBip-OH **Ie** (0.139 g; 0.38 mmol) and HOBt (0.051 g; 0.38 mmol) in CH_2Cl_2 (4 mL)/THF (4 mL) was added a solution of EDC (0.073 g; 0.38 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at rt for 18 h. Extraction as for **Ig**, followed by column chromatography on silica gel with eluent (III), led to 0.252 g (76%) of pure **3d** as an amorphous solid. In a duplicate experiment, coupling of crude **2b** (0.782 g; 1.47 mmol) with **Ie** (0.541 g; 1.47 mmol) under the same experimental conditions gave 1.005 g (78%) of pure **3d**. Mp=170°C. R_f=0.85 (IV). ^{1}H NMR ($CDCl_3$): 7.5–7.2 [m, 24H, ArH], 6.78 [broad m, 1H, NH], 6.14 [broad m, 1H, NH], 5.28 [broad m, 1H, NHBoc], 3.7–3.1 [broad m, 6H, NCH_2^{β}], 3.54 [s, 3H, OCH_3], 3.1–2.0 [broad m, 12H, $ArCH_2^{\beta}$], 1.41 [s, 9H, CH_3 (Boc)]. ^{13}C NMR ($CDCl_3$): 175.5, 175.3, 175.0 (CO), 156.2 (CO Boc), 140.6, 135.6 (broad), 130.0 (broad), 128.5, 128.2, 127.9, 127.8, 127.7, 127.5 (C^{Ar}), 79.3 (O–C Boc), 58.3, 58.0, 57.9 (C^{α}), 52.3 (OCH_3), 46.2, 44.4 (NCH_2^{β}), 37.7 (broad) ($ArCH_2^{\beta}$), 28.4 (CH_3 Boc). ESI$^+$ MS *m/z* (relative intensity): 902 (100) $(M+Na)^+$; 880 (19) $(M+H)^+$. Anal. for $C_{57}H_{57}N_3O_6 \cdot H_2O$: calcd C 76.23, H 6.62, N 4.68; found C 75.74, H 6.11, N 4.58.

Boc-β^{2,2}-HBip-β^{2,2}-HBip-β^{2,2}-HBip-β^{2,2}-HBip-OMe (4d). The tripeptide **3d** (0.120 g; 0.14 mmol) was N-deprotected in CH_2Cl_2 (1 mL)/TFA (1 mL) as for **Ig** (see **Ih**). To a solution of the resulting crude H-β^{2,2}-HBip-β^{2,2}-HBip-β^{2,2}-HBip-OMe **3b** (0.106 g; quantitative yield), Boc-β^{2,2}-HBip-OH **Ie** (0.050 g; 0.14 mmol) and HOBt (0.020 g; 0.14 mmol) in CH_2Cl_2 (1.5 mL)/THF (1.5 mL) was added a solution of EDC (0.028 g; 0.14 mmol) in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred at rt for 18 h. Extraction as for **Ig**, followed by column chromatography on silica gel with eluent (II), led to 0.121 g (79%) of pure **4d** as an amorphous solid. In a duplicate experiment, coupling of crude **3b** resulting from N-deprotection of **3d** (0.204 g; 0.23 mmol) with **Ie** (0.086 g; 0.23 mmol) under the same experimental conditions gave 0.238 g (90%) of pure **4d**. Mp=173°C. R_f=0.2 (II). ^{1}H NMR ($CDCl_3$): 7.5–7.0 [m, 32H, ArH], 6.78 [broad m, 1H, NH], 6.66 [broad m, 1H, NH], 6.18 [broad m, 1H, NH], 5.47 [broad m, 1H, NHBoc], 3.8–3.1 [broad m, 8H, NCH_2^{β}], 3.52 [s, 3H, OCH_3], 3.1–2.0 [broad m, 16H, $ArCH_2^{\beta}$], 1.41 [s, 9H, CH_3 (Boc)]. ^{13}C NMR ($CDCl_3$): 175.4, 175.3, 175.2, 175.1 (CO), 156.3 (CO Boc), 140.6, 135.6 (broad), 130.0 (broad), 128.6, 128.3, 127.9, 127.8, 127.7, 127.6, 127.5 (C^{Ar}), 79.2 (O–C Boc), 58.3, 58.0, 57.7 (C^{α}), 52.3 (OCH_3), 46.1, 44.9, 44.6, 44.5 (NCH_2^{β}), 37.8 (broad) ($ArCH_2^{\beta}$), 28.4 (CH_3 Boc). ESI$^+$ MS *m/z* (relative intensity): 1152 (100) $(M+Na)^+$; 1130 (7) $(M+H)^+$. Anal. for $C_{74}H_{72}N_4O_7 \cdot 1.5\ H_2O$: calcd C 76.85, H 6.54, N 4.84; found C 76.42, H 6.66, N 4.82.

Boc-β^{2,2}-HBip-β^{2,2}-HBip-β^{2,2}-HBip-β^{2,2}-HBip-β^{2,2}-HBip-OMe (5d). The tetrapeptide **4d** (0.079 g; 0.07 mmol) was N-deprotected in CH_2Cl_2 (1 mL)/TFA (1 mL) as for **Ig** (see **Ih**). To a solution of the resulting crude H-β^{2,2}-HBip-β^{2,2}-HBip-β^{2,2}-HBip-β^{2,2}-HBip-OMe 4b, Boc-β^{2,2}-HBip-OH **Ie** (0.026 g; 0.07 mmol) and HOBt (0.010 g; 0.07 mmol) in CH_2Cl_2 (1 mL)/THF (1 mL) was added a solution of EDC (0.014 g; 0.07 mmol) in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred at rt for 3 days. Extraction as for **3d**, followed by column chromatography on silica gel with eluent (III), led to 0.078 g (80%) of pure **5d** as an amorphous solid. Mp=163°C. ^{1}H NMR ($CDCl_3$): 7.5–7.0 [m, 40H, ArH], 7.0–6.5 [broad m, ≈3H, NH], 6.16 [broad m, 1H, NH], 5.35 [broad m, 1H, NHBoc], 3.8–3.1 [broad m, 10H, NCH_2^{β}], 3.51 [s, 3H, OCH_3], 3.1–2.0 [broad m, 20H, $ArCH_2^{\beta}$], 1.38 [s, 9H, CH_3 (Boc)]. ^{13}C NMR ($CDCl_3$): 175.4, 175.2, 175.1, 174.9 (CO), 156.2 (CO Boc), 140.6, 135.2 (broad), 130.0 (broad), 128.5, 128.3, 128.2, 128.1, 127.6, 127.5, 127.3 (C^{Ar}), 79.2 (O–C Boc), 58.2, 58.0, 57.9, 57.8, 57.5 (C^{α}), 52.3 (OCH_3), 46.2, 45.0, 44.9, 44.8, 44.4 (NCH_2^{β}), 37.8 (broad) ($ArCH_2^{\beta}$), 28.4 (CH_3 Boc). ESI$^+$ MS *m/z* (relative intensity): 1400 (100) $(M+Na)^+$; 1378 (35) $(M+H)^+$. Anal. for $C_{91}H_{87}N_5O_8 \cdot 5H_2O$: calcd C 74.41, H 6.65, N 4.77; found C 74.52, H 6.26, N 4.79.

Boc-β^{2,2}-HBip-β^{2,2}-HBip-β^{2,2}-HBip-β^{2,2}-HBip-β^{2,2}-HBip-β^{2,2}-HBip-OMe (6d). A solution of tripeptide **3d** (0.120 g; 0.14 mmol) in MeOH (4 mL) and 1 M NaOH (2 mL) was stirred at ca. 80°C for 4 h, then cooled to rt, acidified by addition of a large excess of 0.5 M HCl and extracted with CH_2Cl_2 (3×50 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated in vacuo. The resulting crude Boc-β^{2,2}-HBip-β^{2,2}-HBip-β^{2,2}-HBip-OH **3e** was coupled as above (see **4d**), with crude H-β^{2,2}-HBip-β^{2,2}-HBip-β^{2,2}-HBip-OMe **3b**, obtained by N-deprotection of **3d** (0.120 g; 0.14 mmol) in the presence of HOBt (0.019 g; 0.14 mmol) and EDC (0.027 g; 0.14 mmol) in CH_2Cl_2 (2.5 mL)/THF (1.5 mL) at rt for 18 h. Extraction as for **Ig**, followed by column chromatography on silica gel with eluent (II) and preparative TLC, led to 0.110 g (50%) of pure **6d** as an amorphous solid. Mp=163°C. ^{1}H NMR ($CDCl_3$): 7.5–7.0 [m, 48H, ArH], 7.0–6.5 [broad m, ≈4H, NH], 6.13 [broad m, 1H, NH], 5.44 [broad m, 1H, NHBoc],

3.8–3.1 [broad m, 12H, NCH_2^{β}], 3.51 [s, 3H, OCH_3], 3.1–2.0 [broad m, 24H, $ArCH_2^{\beta}$], 1.38 [s, 9H, CH_3 (Boc)]. ^{13}C NMR ($CDCl_3$): 175.4 (broad), 175.1 (broad), 175.0 (broad) (CO), 156.2 (CO Boc), 140.6, 135.8 (broad), 130.1 (broad), 128.5, 128.3, 128.2, 127.7, 127.6 (C^{Ar}), 79.1 (O–C Boc), 58.3, 58.0, 57.7, 57.5 (C^{α}), 52.3 (OCH_3), 46.1, 45.0 (broad), 44.5 (NCH_2^{β}), 37.9 (broad) ($ArCH_2^{\beta}$), 28.4 (CH_3 Boc). ESI^+ MS *m/z* (relative intensity): 1650 (100) $(M+Na)^+$; 1628 (13) $(M+H)^+$. Anal. for $C_{108}H_{102}N_6O_9 \cdot 6H_2O$: calcd C 74.71, H 6.62, N 4.84; found C 74.62, H 6.03, N 4.74.

Acknowledgements

We thank the students Nicolas Couasnon and Fabrice Bintein for their contribution to the synthesis.

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