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Synthesis of linear and cyclic homo-β-peptides based on a binaphthylic β-amino acid with only axial chirality

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Abstract—The terminally protected, linear, homo-β-peptides Boc-[(*R*)-$\beta^{2,2}$-HBin]$_n$-OMe ($n = 2$–6) as well as the cyclic homo-β-peptides c[(*R*)-$\beta^{2,2}$-HBin]$_3$ and c[(*S*)-$\beta^{2,2}$-HBin]$_4$, all derived from the 2′,1′:1,2;1″,2″:3,4-dinaphthcyclohepta-1,3-diene-6-aminomethyl-6-carboxylic acid residue $\beta^{2,2}$-HBin possessing only axial chirality, have been synthesized in solution by the EDC/AtOH coupling method for chain elongation, and by cyclization of pentafluorophenyl esters. A conformational analysis suggested the concomitant occurrence of different intramolecularly H-bonded forms for the linear oligomers in solution.

1. Introduction

The axially chiral 2,2′-substituted-1,1′-binaphthyl derivatives represent a very important family of artificial chiral pool compounds, showing outstanding chiral discrimination properties in a variety of reactions.[1–8] Multibinaphthyl oxygen-, nitrogen- or phosphorous-based dimers, oligomers, and polymers, including polybinaphthyl macrocycles have been also widely used as directors to provide high levels of stereochemical control.[9] In the previous studies, we have designed and synthesized binaphthyl amino acid building blocks in an enantiomerically pure state, 2′,1′:1,2;1″,2″:3,4-dinaphthcyclohepta-1,3-diene-6-amino-6-carboxylic acid (Bin)[10–15] and 2′,1′:1,2;1″,2″:3,4-dinaphthcyclohepta-1,3-diene-6-aminomethyl-6-carboxylic acid ($\beta^{2,2}$-HBin),[16–19] both possessing only axial chirality and also being configurationally highly stable, even at high temperature.[7,9] Owing to their amino acid structure, these building blocks can be easily assembled in new multibinaphthyl peptide architectures by means of well-established techniques of peptide synthesis.

Accordingly, a large set of model linear α-peptides based on (*R*)- and/or (*S*)-Bin in combination with Ala, Gly, or Aib (α-aminoisobutyric acid) residues,[12,15] as well as –[(*S*)-Bin]$_n$– linear homo-peptide series to the pentamer level (Fig. 1),[20] have previously been synthesized and shown to have a conformational preference for β-turns and 3_{10}-helical structures, in the crystal state as well as in solution, induced by the C^{α}-tetrasubstituted α-amino acid residue Bin.[15,20–23] Taking advantage of the fluorescence of the 1,1′-binaphthyl core, the Bin residue has also been used as fluorophore in photophysical studies involving intramolecular energy transfer (fluorescence quenching) and intramolecular spin polarization (CIDEP) effects in designed, rigid peptide-based systems.[21–23]

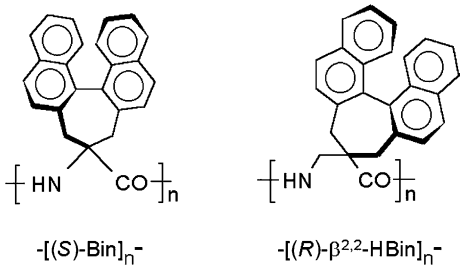

Figure 1. Chemical structures of the axially dissymmetric homo-peptides –[(*S*)-Bin]$_n$– and –[(*R*)-$\beta^{2,2}$-HBin]$_n$–.

In a parallel manner, we envisioned that multibinaphthyl β-peptide architectures based on $\beta^{2,2}$-HBin could be of interest as new chiral fluorophores[24] and potential

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foldamers.[25,26] β-Peptides have attracted considerable attention in the recent years following the pioneering studies of Seebach and Gellman, because of their surprising secondary structural susceptabilities to adopt a variety of stable helical conformations in short linear oligomers (mainly 2.5_{12}, $2.7_{10/12}$ and 3_{14} helices),[27,28] different from those adopted by oligomers of protein α-amino acids and C^{α}-tetrasubstituted α-amino acids (3.6_{13} or α-helix and 3_{10}-helix, respectively).[29] Cyclic tetramers of β^3-amino acids have also been shown to present interesting properties of self-assembly through backbone–backbone hydrogen bonding, resulting in cyclic β^3-peptide nanotubes both in the solid state,[30] and in lipid bilayers to form efficient transmembrane ion channels.[31] Other cyclodi- and cyclotetra-β-peptides have been recently studied.[32–39]

Herein, we report the synthesis of linear, terminally protected homo-β-peptide series –[(*R*)-$\beta^{2,2}$-HBin]$_n$– to the hexamer level ($n = 1$–6) (Fig. 1), and a conformational study by spectroscopic techniques. The corresponding cyclic homo-β-peptides c[(*R*)-$\beta^{2,2}$-HBin]$_3$ and c[(*S*)-$\beta^{2,2}$-HBin]$_4$ have also been synthesized. The $\beta^{2,2}$-HBin residue may be regarded as a di-naphtho-1-aminomethylcycloheptanecarboxylic acid, and its linear homopeptides related to the 1-aminomethylcycloalkane carboxylic acid peptide series –[$\beta^{2,2}$-HAc$_n$c]$_n$– previously investigated by Seebach et al.[40,41]

2. Results and discussion

2.1. Synthesis

The preparation of the N- and C-protected geminally disubstituted β-amino acid building blocks[42] Boc-$\beta^{2,2}$-HBin-OH (Boc, *tert*-butyloxycarbonyl) (*R*)-**1a**, (*S*)-**1a**, and H-$\beta^{2,2}$-HBin-OMe (OMe, methoxy) (*R*)-**1b**, (*S*)-**1b** (Fig. 2), has been previously described.[19] It involves (i) α,α-bis-alkylation of ethyl or methyl cyanoacetate in K_2CO_3/DMF (*N*,*N*-dimethylformamide) with either racemic (*R*,*S*)- or enantiomerically pure (*R*)-2,2′-bis-(bromomethyl)-1,1′-binaphthyl as the alkylating agent, (ii) cobalt(II)-assisted selective reduction of the –C≡N group of the resulting *gem*-cyanoesters upon treatment with sodium borohydride and cobalt(II) chloride, and (iii) resolution of both $\beta^{2,2}$-HBin enantiomers to a pure state, by coupling the N-protected racemic amino acid Bz-(*R*,*S*)-$\beta^{2,2}$-HBin-OH (Bz, benzoyl) with L-phenylalanine cyclohexylamide as the chiral auxiliary, followed by chromatographic separation and hydrolysis of the resulting dipeptides. These building blocks were assembled to form both linear and cyclic homo-β-peptides by solution synthetic procedures.

For the synthesis of the linear Boc-[(*R*)-$\beta^{2,2}$-HBin]$_n$-OMe ($n = 2$–6) peptides (Fig. 2), stepwise couplings of H-[(*R*)-$\beta^{2,2}$-HBin]$_n$-OMe ($n = 1$–5) amino esters at the sterically demanding α,α-disubstituted –COOH function of Boc-(*R*)-$\beta^{2,2}$-HBin-OH (*R*)-**1a** were performed by the EDC [*N*-ethyl,*N*′-(3-dimethylaminopropyl)-carbodiimide]/AtOH (7-aza-1-hydroxy-1,2,3-benzotriazole)[43] activation method, which is known to be efficient in the coupling at the C-terminus of $C^{\alpha,\alpha}$-disubstituted α-amino acids.[44] Coupling of the monomers (*R*)-**1a** and (*R*)-**1b** gave the N-protected dipeptide ester (*RR*)-**2** in 89% yield. Cleavage of the Boc group of (*RR*)-**2** with TFA (trifluoroacetic acid)/CH_2Cl_2 1:1 yielded H-[(*R*)-$\beta^{2,2}$-HBin]$_2$-OMe, which was coupled with (*R*)-**1a** to afford (*RRR*)-**3** in 92% overall yield. In the same manner, Boc-deprotection of (*RRR*)-**3** followed by coupling of the resulting H-[(*R*)-$\beta^{2,2}$-HBin]$_3$-OMe with (*R*)-**1a**

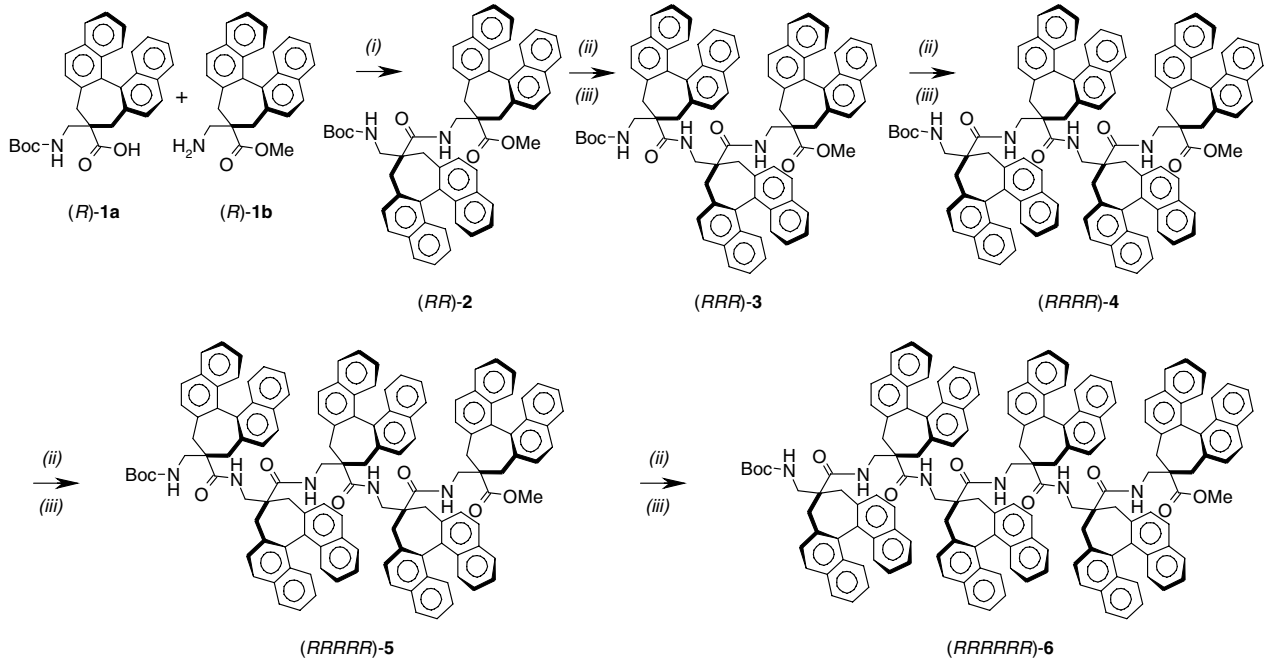

Figure 2. Synthesis of the protected Boc-[(*R*)-$\beta^{2,2}$-HBin]$_n$-OMe ($n = 2$–6) linear homo-β-peptides. (i) EDC; HOAt; CH_2Cl_2/THF (ii) 1. TFA/CH_2Cl_2 1:1; 0 °C to rt. 2. extraction CH_2Cl_2/aq 5% $NaHCO_3$ (iii) (*R*)-**1a**; EDC; HOAt; CH_2Cl_2/THF.

afforded (*RRRR*)-**4** in 71% overall yield. In the same manner, (*RRRRR*)-**5** (62%) and (*RRRRRR*)-**6** (43%) were successively obtained. As for the Boc-[(*S*)-$\beta^{2,2}$-HBin]$_n$-OMe ($n = 2$–4) series, similar stepwise couplings of Boc-(*S*)-$\beta^{2,2}$-HBin-OH (*S*)-**1a** and H-[(*S*)-$\beta^{2,2}$-HBin]$_n$-OMe ($n = 1$–3) amino esters successively led to *(SS)*-**2** (95%), (*SSS*)-**3** (76%), and (*SSSS*)-**4** (75%). Altogether, in agreement with previous observations concerning the –[$\beta^{2,2}$-HAib]$_n$–,[40] –[$\beta^{2,2}$-HAc$_n$c]$_n$–,[40,41] and –[$\beta^{2,2}$-HBip]$_n$– series,[45] acylation by standard methods (EDC/HOAt) of the relatively unhindered terminal –NH_2 function of the homo-peptide esters H-[$\beta^{2,2}$-HBin]$_n$-OMe ($n = 2$–5) based on an α,α-dialkylated-β-amino acid appeared to be much easier than in the corresponding homo-peptide esters H-[Bin]$_n$-OMe ($n = 2$–4) based on an α,α-dialkylated-α-amino acid.[20]

For the synthesis of the cyclic homo-β-peptides, the N-protected linear peptides Boc-[(*R*)-$\beta^{2,2}$-HBin]$_3$-OH and Boc-[(*S*)-$\beta^{2,2}$-HBin]$_4$-OH, obtained by saponification of (*RRR*)-**3** and (*SSSS*)-**4**, respectively, were treated with pentafluorophenol in the presence of EDC. The resulting pentafluorophenyl (Pfp) esters Boc-[(*R*)-$\beta^{2,2}$-HBin]$_3$-OPfp and Boc-[(*S*)-$\beta^{2,2}$-HBin]$_4$-OPfp were Boc deprotected in TFA/CH_2Cl_2 1:1, neutralized by addition of DIEA (diisopropylethylamine), and then cyclized in CH_3CN/CH_2Cl_2 at 70 °C to afford c[(*R*)-$\beta^{2,2}$-HBin]$_3$ (57%) and c[(*S*)-$\beta^{2,2}$-HBin]$_4$ (44%) (Fig. 3).

2.2. Conformational analysis

The ^{1}H NMR spectra of the linear peptides Boc-[(*R*)-$\beta^{2,2}$-HBin]$_n$-OMe in the $CDCl_3$ solution present a magnetic non-equivalence of the amide protons for the shorter oligomers ($n = 2$–4). For the pentamer, the amide NH protons appear at 6.73 [1H], 6.53 [2H], 5.79 [1H], 5.31 [1H, NH–Boc] and for the hexamer at 6.89 [1H], 6.72 [1H], 6.62 [2H], 6.02 [1H], 5.34 [1H, NH–Boc], reflecting a probably restricted mobility of the peptide backbone. However, the equivalency of two out of three internal NH protons for the pentapeptide and of two out of four for the hexapeptide, questions the existence of a preferentially populated secondary structure. No attempts were performed for the evaluation of the amide NH chemical shift dependence upon the addition of increasing amounts of DMSO to the $CDCl_3$ solution,[46] or of the line broadening dependence upon addition of increasing the amounts of TEMPO,[47] because of the partly overlapping broad signals recorded for Boc-[(*R*)-$\beta^{2,2}$-HBin]$_6$-OMe, the most interesting compound according to the FT-IR absorption results (vide infra). Both ^{1}H NMR spectra of the cyclic β-peptides c[(*R*)-$\beta^{2,2}$-HBin]$_3$ and c[(*S*)-$\beta^{2,2}$-HBin]$_4$ (the latter spectrum is shown in Fig. 4) in $CDCl_3$ solution present a magnetic equivalence for the amide NH, the N–CH_2 (N–CH, NCH′), and the Ar–CH_2 (ArCH, ArCH′, ArC′H, and ArC′H′) protons, which demonstrates that these two compounds adopt a predominant conformation possessing a three-fold and a four-fold symmetry, respectively.

The electronic absorption spectrum of the naphthalene chromophores of the $\beta^{2,2}$-HBin residue above 300 nm consists of a relatively weak, but complex band centered at 307 nm in CH_2Cl_2 solution, assigned to the ^1L_b transition by Platt[48] and corresponding to a polarization in the direction of the naphthyl long axis.[49] The total molar absorbance values increase regularly as the β-peptide main chain is progressively enhanced (Fig. 5A). The fluorescence spectra of the same solutions (excitation at 307 nm) exhibit a maximum at ca. 360 nm (Fig. 5B). The total molar intensities steadily increase from monomer to hexamer.

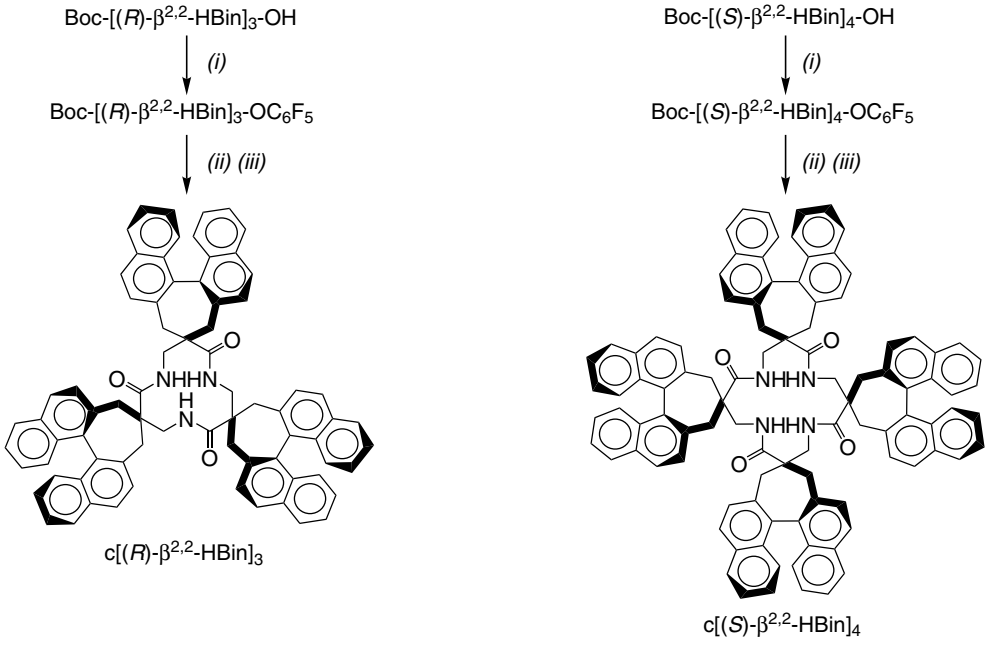

Figure 3. Synthesis of the cyclic homo-β-peptides c[(*R*)-$\beta^{2,2}$-HBin]$_3$ and c[(*S*)-$\beta^{2,2}$-HBin]$_4$. (i) C_6F_5OH; EDC; CH_2Cl_2; rt (ii) TFA/CH_2Cl_2 1:1; 0 °C to rt (iii) DIEA; CH_3CN/CH_2Cl_2; 70 °C.

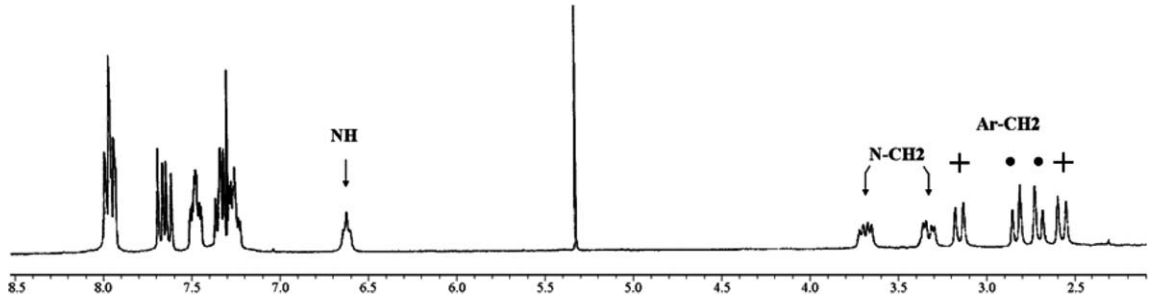

Figure 4. ^{1}H NMR spectrum (300 MHz; $CDCl_3$) of c[(*S*)-$\beta^{2,2}$-HBin]$_4$ showing the equivalence of the amide NH, the N–CH_2 and the Ar–CH_2 protons of the four $\beta^{2,2}$-HBin residues.

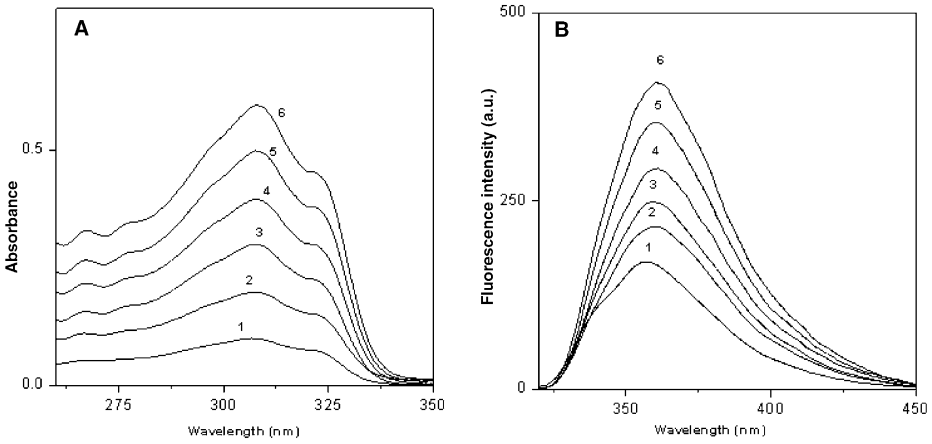

Figure 5. UV absorption spectra in the 260–350 nm region of Boc-(*S*)-$\beta^{2,2}$-HBin-OMe ($n = 1$) and the linear β-peptides Boc-[(*R*)-$\beta^{2,2}$-HBin]$_n$-OMe ($n = 2$–6) (**A**), and fluorescence spectra ($\lambda_{exc} = 307$ nm) in the 320–450 region of the same peptides (**B**). All measurements were performed at 0.01 mM peptide concentration in CH_2Cl_2 solution.

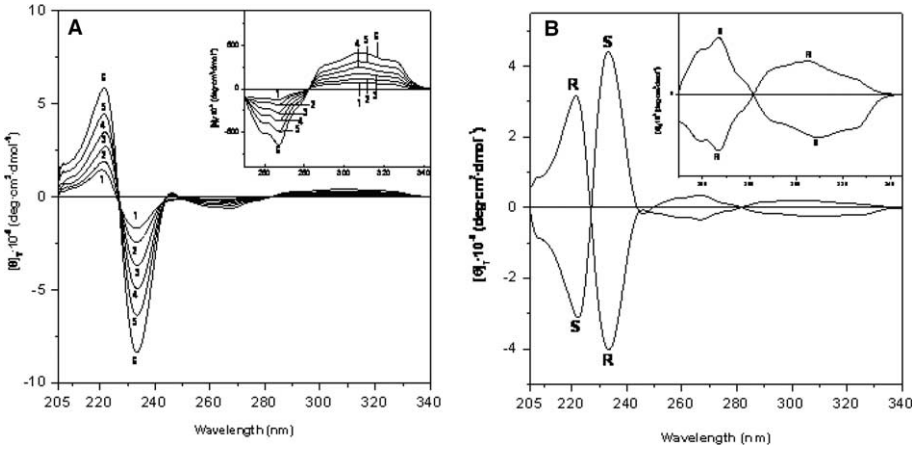

Figure 6. CD spectra in the 205–340 nm region of Boc-(*R*)-$\beta^{2,2}$-HBin-OH ($n = 1$) and the linear β-peptides Boc-[(*R*)-$\beta^{2,2}$-HBin]$_n$-OMe ($n = 2$–6) (**A**) and the cyclic β-peptides c[(*R*)-$\beta^{2,2}$-HBin]$_3$ and c[(*S*)-$\beta^{2,2}$-HBin]$_4$ (**B**), in CH_2Cl_2 solution (peptide concentration: 0.5 mM).

The far-UV CD spectra of Boc-(*R*)-$\beta^{2,2}$-HBin-OH and Boc-[(*R*)-$\beta^{2,2}$-HBin]$_n$-OMe ($n = 2$–6) (Fig. 6A) as well as those of c[(*R*)-$\beta^{2,2}$-HBin]$_3$ and c[(*S*)-$\beta^{2,2}$-HBin]$_4$ in CH_2Cl_2 solution (Fig. 6B) show extremely intense Cotton effects, dominated by the contribution of the binaphthyl chromophore ($^{1}B_b$ transition). In particular, the observed negative band at a longer wavelength (~232 nm) and positive band at a shorter wavelength (~218 nm) are typical of a binaphthyl moiety with an (*R*)-absolute configuration. In fact, quasi-symmetric CD spectra were observed for the (*RRR*)- and (*SSSS*)-cyclic peptides. Also, the similarity between the CD spectra of the linear and cyclic trimers highlights the predominance of the monomer chirospectroscopic contributions. In conclusion, because of such overwhelming contribution of the binaphthyl over the amide

chromophore, no clear-cut information can be extracted on the preferred secondary structure of these peptides.

The FT-IR absorption spectra in the N–H stretching (amide A) region for the linear β-homopeptides Boc-[(*R*)-$\beta^{2,2}$-HBin]$_n$-OMe ($n = 1$–6) in $CDCl_3$ solution (Fig. 7) are dominated by a strong band at 3450 cm^{-1} (free, solvated NH groups).[50] This is the only band occurring in the spectrum of the amino acid derivative **1**. The spectra of the higher oligomers show multiple, additional contributions at lower wavenumbers, assigned to H-bonded NH groups. As the spectra are virtually concentration independent over the 1.0–0.1 mM concentration range (data not shown), these latter bands must be ascribed to intramolecularly H-bonded forms. Most of the bands related to the H-bonded NH vibrators are broad. They can be grouped as follows: (i) a band at about 3410 cm^{-1}, present in all spectra from dimer (as a shoulder) to a hexamer; (ii) a band at 3375 cm^{-1}, well developed in the tripeptide while weaker in the higher oligomers; and (iii) a broad band centered at about 3330 cm^{-1}, arising as a weak and broad contribution at the tripeptide level and becoming progressively more intense for the penta- and the hexamer.

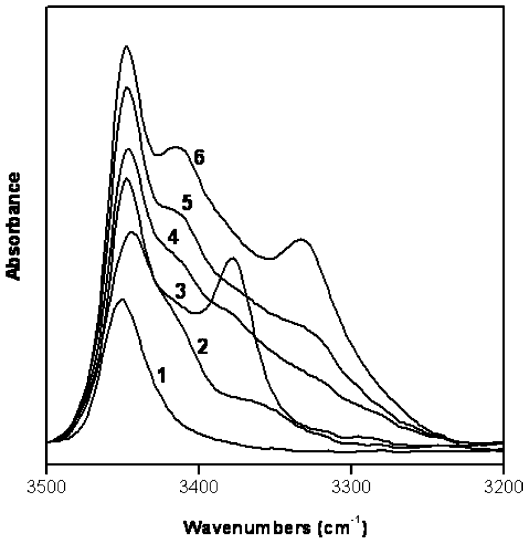

Figure 7. FT-IR absorption spectra in the N–H stretching region of the Boc-($\beta^{2,2}$-HBin)$_n$-OMe ($n = 1$–6) peptide series in $CDCl_3$ solution (peptide concentration: 1 mM).

The crystal structure of the homo-tripeptide Boc-($\beta^{2,2}$-HAc$_6$c)$_3$-OMe, reported by Seebach et al.,[40] is characterized by the occurrence of two intramolecularly H-bonded forms, namely a C_6 form (N_i-H$\cdots$O=C_i) at the level of the N-terminal residue, and a C_{10} form (N_i-H$\cdots$O=C_{i+1}) encompassing residues 2 (i) and 3 ($i + 1$), in which the H-bond acceptor is the C-terminal ester carbonyl oxygen. Geometrical considerations suggest that the H-bond of the C_6 form must be weaker compared to that of the C_{10} form. Therefore, the N–H stretching mode of the C_6 form was expected to be seen at higher wavenumbers than that of the C_{10} form. On these bases, in the spectrum of homo-tripeptide **3**, we tentatively assigned the two bands at 3410 and 3375 cm^{-1} to a C_6 and a C_{10} form, respectively. The assignment of the 3330 cm^{-1} band to a single, specific, intramolecularly H-bonded form is more problematic. In principle, it can be related either to a C_{10} form, analogous to that discussed above but internal to the peptide sequence (the different nature of the H-bond acceptor, peptide versus ester carbonyl oxygen, may account for the lower wavenumber of its maximum), or to C_{12}/C_{14} H-bonded forms. Unfortunately, no reference data are available in the literature about the H-bonded N–H stretching frequencies of helical β-peptides. In any case, the general trend of the relative intensities of H-bonded versus free NH bands as a function of main-chain length is not compatible with the full development of an intramolecularly H-bonded helix. The present set of spectra parallels to some extent that reported for the corresponding Boc-($\beta^{2,2}$-HBip)$_n$-OMe series.[45]

3. Conclusion

A new series of enantiopure, fluorophoric, axially chiral, multibinaphthyl linear and cyclic β-peptide architectures, utilizing the (*R*)- or (*S*)-enantiomer of the $\beta^{2,2}$-HBin residue as the building block, have been shown to be easily accessible by peptide synthesis in solution. However, all compounds were obtained as amorphous solids for which 3D-structural information could not be obtained by single-crystal X-ray diffraction analysis. A conformational analysis of the linear homo-β-peptides Boc-[(*R*)-$\beta^{2,2}$-HBin]$_n$-OMe ($n = 2$–6) in solution suggested the concomitant occurrence of different intramolecularly H-bonded forms. Other multi-binaphthyl β-peptide architectures based on $\beta^{2,3}$-HBin (rather than $\beta^{2,2}$-HBin) as potential fluorophoric foldamers are currently being explored in our groups.

4. Experimental

4.1. General experimental

Melting points were determined with an increase in temperature of 3 °C/min and are uncorrected. NMR spectra were recorded at 300 MHz or 200 MHz for ^{1}H, and at 77 MHz or 50 MHz for ^{13}C, on Bruker AC300 or AC200 spectrometers, the solvent $CDCl_3$ being used as internal standard ($\delta = 7.27$ ppm for ^{1}H and 77.0 ppm for ^{13}C). Splitting patterns are abbreviated as follows: (s) singlet, (d) doublet, (t) triplet, (q) quartet, and (m) multiplet. Mass spectra (electrospray mode) were recorded by Mr. Vincent Steinmetz (SIRCOB), on a Hewlett–Packard HP5989MS spectrometer. Elemental analyses were performed by the C.N.R.S. Service of Microanalyses in Gif-sur-Yvette (France). The optical rotations were measured with an accuracy of 0.3%, in a 1 dm thermostatted cell. Analytical thin-layer chromatography (TLC), preparative TLC and column chromatography were performed on silica gel F_{254} (Merck), silica gel G-25 (1 mm) (Macherey-Nagel) and silica gel 60 (0.040–0.063 mm) (Merck), respectively, with the following eluent systems: 1% MeOH–99% CH_2Cl_2 (I); 5% MeOH–95% CH_2Cl_2 (II); 1% EtOAc–99% CH_2Cl_2

(III); 2% EtOAc–98% CH_2Cl_2 (IV); 3% EtOAc–97% CH_2Cl_2 (V); 4% EtOAc–96% CH_2Cl_2 (VI); 5% EtOAc–95% CH_2Cl_2 (VII). UV light (254 nm) allowed visualization of the spots after TLC runs for all compounds, even at low concentration.

4.2. Boc deprotection: general procedure A1

The *N*-Boc-protected peptide was dissolved in CH_2Cl_2 and cooled to 0 °C. An equal volume of TFA was added and the solution magnetically stirred at 0 °C for 15 min and then at rt for 2.5 h. The solution was evaporated in vacuo at 25 °C and the residue repeatedly co-evaporated in vacuo with CH_2Cl_2 at 40 °C, to yield a crude product which was used in the next step without further purification.

4.3. Boc deprotection: general procedure A2

The crude product, obtained according to the general procedure A1, was dissolved in either CH_2Cl_2 or EtOAc [for compounds (*RR*)-**2** and (*SS*)-**2**], the solution washed with 5% $NaHCO_3$ and then with H_2O, dried over $MgSO_4$, filtered, and evaporated in vacuo at 40 °C, to yield a crude product, which was used in the next step without further purification.

4.4. Saponification: general procedure B

To a solution of the fully protected peptide in MeOH was added a large excess of 1 M NaOH. The resulting milky suspension slowly clarified upon stirring at 75 °C. After 24 h, the mixture was ice-cooled and acidified to pH 2 by the addition of a large excess of 0.5 M HCl, after which it was extracted with CH_2Cl_2 (three portions). The organic phase was washed with H_2O (two portions), dried over $MgSO_4$, filtered, and evaporated in vacuo at 40 °C, to yield a crude product which was used in the next step without further purification.

4.5. Peptide coupling with EDC: general procedure C

To a solution of the *N*-Boc-protected amino acid (1 equiv), the peptide ester, obtained by N-deprotection according to the general procedure A2 (ca. 0.9 equiv), and HOAt (2 equiv) in THF/CH_2Cl_2 was added EDC (1.5 equiv). The solution was magnetically stirred at rt for 2–3 days, and concentrated in vacuo. The residue was dissolved in CH_2Cl_2, the solution was successively extracted with 0.5 M HCl (two portions), H_2O, 5% $NaHCO_3$ (two portions), and H_2O (two portions), then dried over $MgSO_4$, filtered, and evaporated in vacuo at 40 °C, to yield a crude product which was purified by chromatography.

4.6. Esterification with pentafluorophenol: general procedure D

CH_2Cl_2 solution of the *N*-Boc-protected peptide, obtained by saponification according to the general procedure B, and pentafluorophenol (2 equiv), was cooled to 0 °C and EDC (1.5 equiv) then added. The solution was magnetically stirred at 0 °C for 15 min and then at rt overnight. The reaction mixture was diluted with CH_2Cl_2 and the solution was successively extracted with 0.5 N HCl (two portions) and H_2O (four portions), then dried over $MgSO_4$, filtered, and evaporated in vacuo at 40 °C, to yield a crude product, which was used in the next step without further purification.

4.7. Cyclization: general procedure E

To a magnetically stirred solution of DIEA (2 equiv) in CH_3CN maintained at 70 °C under an argon atmosphere was added dropwise, over 3 h, a CH_3CN/CH_2Cl_2 solution of the peptide pentafluorophenylester TFA salt, obtained by N-deprotection of the corresponding Boc-peptide pentafluorophenylester according to the general procedure A1. The solution was then stirred at rt for 24 h and evaporated in vacuo. The residue was taken up in CH_2Cl_2 and the solution successively extracted with 0.5 M HCl (two portions), H_2O, 5% $NaHCO_3$ (two portions), and H_2O (two portions), then dried over $MgSO_4$, filtered, and evaporated in vacuo at 40 °C, to yield a crude product which was purified by chromatography.

4.8. Boc-[(*R*)-$\beta^{2,2}$-HBin]$_2$-OMe (*RR*)-2

The N-protected amino acid Boc-(*R*)-$\beta^{2,2}$-HBin-OH (*R*)-**1a**[19] (0.169 g; 0.362 mmol) was coupled with the amino ester H-(*R*)-$\beta^{2,2}$-HBin-OMe (*R*)-**1b**[19] (0.126 g; 0.330 mmol) in THF (1 mL) and CH_2Cl_2 (2 mL), according to the general procedure C. The crude product was purified by preparative TLC on silica gel with eluant (I) to afford 0.244 g (89%) of pure (*RR*)-**2** as a solid. Mp = 225 °C. $R_f = 0.7$ (II). ^{1}H NMR ($CDCl_3$): δ 8.05–7.22 [m, 24H, ArH], 6.02 [m (t-like), 1H, NH], 5.32 [m (t-like), 1H, NH–Boc], 3.38 [m, 4H, N–CH_2], 3.32 [s, 3H, OCH_3], 3.12 and 2.39 [d, $J = 13.4$, 1H and d, $J = 13.4$, 1H, Ar–CH_2], 3.06 and 2.25 [d, $J = 13.4$, 1H and d, $J = 13.1$, 1H, Ar–CH_2], 2.82 and 2.68 [d, $J = 13.1$, 1H and d, $J = 13.1$, 1H, Ar–CH_2], 2.77 and 2.68 [d, $J = 13.4$, 1H and d, $J = 13.4$, 1H, Ar–CH_2], 1.44 [s, 9H, CH_3 Boc]. ^{13}C NMR ($CDCl_3$): δ 175.5, 175.2 (C=O), 156.4 (C=O Boc), 135.5, 135.2, 134.7, 134.4, 134.3, 134.1, 134.0, 133.2, 133.1, 133.0, 132.0, 131.9, 131.8 (CAr), 128.7, 128.54, 128.50, 128.4, 128.3, 128.2, 128.1, 127.9, 127.4, 127.36, 127.32, 127.2, 126.1, 126.0, 125.97, 125.9, 125.5, 125.4, 125.3 (CHAr), 79.4 (C–O Boc), 59.5, 58.9 (Cα), 52.3 (OCH_3), 45.9, 44.4 (N–CH_2), 39.0, 38.9, 37.3, 36.6 (Ar–CH_2), 28.6 (CH_3 Boc). $[\alpha]^{25}_{589} = -132$; $[\alpha]^{25}_{578} = -137$; $[\alpha]^{25}_{546} = -152$; $[\alpha]^{25}_{436} = -164$; $[\alpha]^{25}_{365} = +602$ (*c* 0.16; CH_2Cl_2). ESI$^+$ MS *m/z*: 853.5 $(M+Na)^+$, 831.5 $(M+H)^+$, 731.4 $(M+H-Boc)^+$. Anal. Calcd for $C_{56}H_{50}N_2O_5 \cdot 0.5H_2O$ (839.984): C, 80.07; H, 6.12; N, 3.33. Found: C, 79.91; H, 6.13; N, 3.16.

4.9. Boc-[(*S*)-$\beta^{2,2}$-HBin]$_2$-OMe (*SS*)-2

Prepared in the same way as (*RR*)-**2** by coupling (*S*)-**1a**[19] (0.241 g; 0.516 mmol) with (*S*)-**1b**[19] (0.174 g; 0.457 mmol) in THF (1 mL) and CH_2Cl_2 (2 mL). The crude

product was purified by column chromatography on silica gel with eluent (IV) to afford 0.361 g (95%) of pure (*SS*)-**2** as a solid. Mp = 216 °C. ^{1}H NMR and ^{13}C NMR ($CDCl_3$): see (*RR*)-**2**. $[\alpha]^{25}_{589} = +158$; $[\alpha]^{25}_{578} = +155$; $[\alpha]^{25}_{546} = +161$; $[\alpha]^{25}_{436} = +154$; $[\alpha]^{25}_{365} = -554$ (*c* 0.11, CH_2Cl_2). ESI$^+$ MS *m*/*z*: 853.6 $(M+Na)^+$. Anal. Calcd for $C_{56}H_{50}N_2O_5{\cdot}0.5H_2O$ (839.984): C, 80.07; H, 6.12; N, 3.33. Found: C, 80.02; H, 6.15; N, 3.46.

4.10. Boc-[(*R*)-β^{2,2}-HBin]$_3$-OMe (*RRR*)-3

The dipeptide (*RR*)-**2** (0.233 g; 0.280 mmol) was N-deprotected in TFA/CH_2Cl_2 1:1 (7 mL) according to the general procedure A2. The obtained crude H-[(*R*)-β^{2,2}-HBin]$_2$-OMe was coupled with (*R*)-**1a**[19] (0.143 g; 0.306 mmol) in THF (1 mL) and CH_2Cl_2 (2 mL), according to the general procedure C. The crude product was purified by column chromatography on silica gel with eluants (III)–(VII) to afford 0.304 g (92%) of pure (*RRR*)-**3** as a solid. Mp = 299 °C. $R_f = 0.5$ (VII). ^{1}H NMR ($CDCl_3$): δ 8.10–7.09 [m, 36H, ArH], 6.81 [m (t-like), 1H, NH], 6.18 [m (t-like), 1H, NH], 5.19 [m (t-like), 1H, NH–Boc], 3.72 and 3.26 [dd, $J = 13.1$; 7.7, 1H, and dd (masked), 1H, N–CH_2], 3.52 and 3.26 [dd, $J = 13.5$; 7.3, 1H, and dd (masked), 1H, N–CH_2], 3.34 and 2.24 [d, $J = 13.5$, 1H, and d, $J = 13.1$, 1H, Ar–CH_2], 3.22 [s, 3H, OCH_3], 3.16 and 2.29 [d (masked), 1H, and d, $J = 13.1$, 1H, Ar–CH_2], 3.06 and 2.66 [dd, $J = 13.4$; 5.9, 1H, and dd (masked), 1H, N–CH_2], 2.87 and 2.69 [d, $J = 13.6$, 1H, and d, $J = 13.1$, 1H, Ar–CH_2], 2.85 and 1.97 [d, $J = 13.0$, 1H, and d, $J = 13.3$, 1H, Ar–CH_2], 2.79 and 2.58 [d, $J = 13.3$, 1H, and d, $J = 13.4$, 1H, Ar–CH_2], 2.75 and 2.50 [d, $J = 12.6$, 1H, and d, $J = 12.5$, 1H, Ar–CH_2], 1.41 [s, 9H, CH_3 Boc]. ^{13}C NMR ($CDCl_3$): δ 175.6, 175.2, 174.8 (C=O), 156.4 (C=O Boc), 135.5, 135.3, 135.1, 134.7, 134.55, 134.5, 134.4, 134.3, 134.2, 134.0, 133.3, 133.1, 133.0, 132.9, 131.9, 131.8 (CAr), 129.1, 128.7, 128.5, 128.4, 128.2, 128.1, 128.0, 127.7, 127.4, 127.2, 126.1, 126.0, 125.5, 125.3, 125.2 (CHAr), 79.8 (C–O Boc), 59.5, 59.4, 58.9 (Cα), 52.2 (OCH_3), 46.2, 44.4, 43.7 (N–CH_2), 39.3, 38.7, 36.5, 36.0 (Ar–CH_2), 28.6 (CH_3 Boc). $[\alpha]^{25}_{589} = -18$; $[\alpha]^{25}_{578} = -26$; $[\alpha]^{25}_{546} = -25$; $[\alpha]^{25}_{436} = +47$; $[\alpha]^{25}_{365} = +994$ (*c* 0.13; CH_2Cl_2). ESI$^+$ MS *m*/*z*: 1202.7 $(M+Na)^+$ 1180.7 $(M+H)^+$, 1080.6 $(M+H-Boc)^+$. Anal. Calcd for $C_{81}H_{69}N_3O_6{\cdot}H_2O$ (1198.402): C, 81.17; H, 5.97; N, 3.50. Found: C, 81.45; H, 6.03; N, 3.52.

4.11. Boc-[(*S*)-β^{2,2}-HBin]$_3$-OMe (*SSS*)-3

Prepared in the same way as (*RRR*)-**3** by coupling (*S*)-**1a**[19] (0.205 g; 0.439 mmol) with crude H-[(*S*)-β^{2,2}-HBin]$_2$-OMe, obtained by N-deprotection of (*SS*)-**2** (0.295 g; 0.404 mmol), in THF (1 mL) and CH_2Cl_2 (2 mL). The crude product was purified by column chromatography on silica gel with eluant (IV) to afford 0.365 g (76%) of pure (*SSS*)-**3** as a solid. Mp > 300 °C. ^{1}H NMR and ^{13}C NMR ($CDCl_3$): see (*RRR*)-**3**. $[\alpha]^{25}_{589} = +60$; $[\alpha]^{25}_{578} = +54$; $[\alpha]^{25}_{546} = +55$; $[\alpha]^{25}_{436} = -55$; $[\alpha]^{25}_{365} = -1083$ (*c* 0.10; CH_2Cl_2). ESI$^+$ MS *m*/*z*: 1203.1 $(M+Na)^+$. Anal. Calcd for $C_{81}H_{69}N_3O_6{\cdot}0.5H_2O$ (1189.394): C, 81.79; H, 5.93; N, 3.53. Found: C, 81.55; H, 5.93; N, 3.57.

4.12. Boc-[(*R*)-β^{2,2}-HBin]$_4$-OMe (*RRRR*)-4

The tripeptide (*RRR*)-**3** (0.102 g; 0.086 mmol) was N-deprotected in TFA/CH_2Cl_2 1:1 (2 mL) according to the general procedure A2. The crude H-[(*R*)-β^{2,2}-HBin]$_3$-OMe obtained (0.100 g) was coupled with (*R*)-**1a**[19] (0.044 g; 0.094 mmol) in THF (0.5 mL) and CH_2Cl_2 (1 mL), according to the general procedure C. The crude product was purified by preparative TLC on silica gel with eluant (IV) to afford 0.094 g (71%) of pure (*RRRR*)-**4** as a solid. Mp = 285 °C. $R_f = 0.6$ (VI). ^{1}H NMR ($CDCl_3$): δ 8.02–7.06 [m, 48H, ArH], 6.56 [m (t-like), 1H, NH], 6.49 [m (t-like), 1H, NH], 5.89 [m (t-like), 1H, NH], 5.31 [m (t-like), 1H, NH–Boc], 3.04 [s, 3H, OCH_3], 3.46–1.89. [m, 24H, Ar–CH_2 and N–CH_2], 1.38 [s, 9H, CH_3 Boc]. ^{13}C NMR ($CDCl_3$): δ 175.0, 174.9, 174.6, 174.5 (C=O), 156.4 (C=O Boc), 135.5, 135.1, 134.9, 134.7, 134.4, 134.2, 134.13, 134.1, 134.0, 133.9, 133.8, 133.0, 132.93, 132.9, 132.8, 132.7, 131.7, 131.6, 131.58, 131.5 (CAr), 128.6, 128.3, 128.2, 128.1, 127.85, 127.8, 127.7, 127.6, 127.2, 127.1, 127.0, 126.9, 125.9, 125.7, 125.2, 125.1, 125.0 (CHAr), 79.3 (C–O Boc), 59.2, 59.0, 58.7, 58.6 (Cα), 51.7 (OCH_3), 46.0, 44.9, 43.8, 43.1 (N–CH_2), 39.2, 38.8, 38.5, 36.9, 36.5, 36.2, 35.5 (Ar–CH_2), 28.4 (CH_3 Boc). $[\alpha]^{25}_{589} = -22$; $[\alpha]^{25}_{578} = -26$; $[\alpha]^{25}_{546} = -25$; $[\alpha]^{25}_{436} = +52$; $[\alpha]^{25}_{365} = +995$ (*c* 0.12, CH_2Cl_2). MALDI MS *m*/*z*: 1567.4 $(M+K)^+$, 1551.4 $(M+Na)^+$, 1429.4 $(M+H-Boc)^+$. Anal. Calcd for $C_{106}H_{88}N_4O_7{\cdot}4H_2O$ (1601.860): C, 79.47; H, 6.04; N, 3.50. Found: C, 79.78; H, 6.01; N, 3.46.

4.13. Boc-[(*S*)-β^{2,2}-HBin]$_4$-OMe (*SSSS*)-4

Prepared in the same way as (*RRRR*)-**4** by coupling (*S*)-**1a**[19] (0.080 g; 0.171 mmol) with crude H-[(*S*)-β^{2,2}-HBin]$_3$-OMe, obtained by N-deprotection of (*SSS*)-**3** (0.150 g; 0.127 mmol), in THF (2 mL) and CH_2Cl_2 (2 mL). The crude product was purified by column chromatography on silica gel with eluant (V) to afford 0.199 g (75%) of pure (*SSSS*)-**4** as a solid. Mp = 285 °C. ^{1}H NMR and ^{13}C NMR ($CDCl_3$): see (*RRRR*)-**4**. $[\alpha]^{25}_{589} = +79$; $[\alpha]^{25}_{578} = +71$; $[\alpha]^{25}_{546} = +67$; $[\alpha]^{25}_{436} = -64$; $[\alpha]^{25}_{365} = -1184$ (*c* 0.10, CH_2Cl_2). ESI$^+$ MS *m*/*z*: 1551.8 $(M+Na)^+$, 784.9 $(M+H+K)^{2+}$. Anal. Calcd for $C_{106}H_{88}N_4O_7{\cdot}3H_2O$ (1583.844): C, 80.38; H, 5.98; N, 3.54. Found: C, 80.21; H, 6.04; N, 3.69.

4.14. Boc-[(*R*)-β^{2,2}-HBin]$_5$-OMe (*RRRRR*)-5

Tetrapeptide (*RRRR*)-**4** (0.091 g; 0.060 mmol) was N-deprotected in TFA/CH_2Cl_2 1:1 (2 mL) according to the general procedure A2. The obtained crude H-[(*R*)-β^{2,2}-HBin]$_4$-OMe (0.080 g) was coupled with (*R*)-**1a**[19] (0.031 g; 0.065 mmol) in THF (1 mL) and CH_2Cl_2 (2 mL), according to the general procedure C. The crude product was purified by preparative TLC on silica gel with eluant (I) to afford 0.070 g (62%) of pure (*RRRRR*)-**5** as a solid. Mp = 281 °C. $R_f = 0.4$ (VII). ^{1}H NMR ($CDCl_3$): δ 8.02–7.05 [m, 60H, ArH], 6.73 [m (t-like), 1H, NH], 6.53 [m (t-like), 2H, NH], 5.79 [m (t-like), 1H, NH], 5.31 [m (t-like), 1H, NH–Boc], 3.05 [s, 3H, OCH_3], 3.49–1.90 [m, 30H, Ar–CH_2 and

N–CH_2], 1.37 [s, 9H, 3CH_3 Boc]. ^{13}C NMR ($CDCl_3$): δ 175.0, 174.9, 174.8, 174.5, 174.4 (C=O), 156.2 (C=O Boc), 135.6, 135.3, 134.9, 134.8, 134.5, 134.4, 134.3, 134.2, 134.18, 134.1, 134.0, 133.9, 133.8, 133.0, 132.94, 132.9, 132.8, 132.7, 131.7, 131.6 (CAr), 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 127.2, 127.1, 127.0, 126.0, 125.9, 125.7, 125.4, 125.3, 125.2, 125.1 (CHAr), 79.3 (C–O Boc), 59.2, 58.9, 58.7, 58.6 (Cα), 51.7 (OCH_3), 46.0, 45.0, 44.7, 43.8, 43.1 (N–CH_2), 39.4, 38.8, 38.5, 37.1, 36.9, 36.3, 35.8 (Ar–CH_2), 28.4 (CH_3 Boc). $[\alpha]^{25}_{589} = -7$; $[\alpha]^{25}_{578} = -8$; $[\alpha]^{25}_{546} = -6$; $[\alpha]^{25}_{436} = +82$; $[\alpha]^{25}_{365} = +990$ (*c* 0.26, CH_2Cl_2). MALDI MS *m*/*z*: 1916.8 $(M+K)^+$, 1900.8 $(M+Na)^+$, 1778.8 $(M+H-Boc)^+$. Anal. Calcd for $C_{131}H_{107}N_5O_8{\cdot}4H_2O$ (1951.270): C, 80.63; H, 5.94; N, 3.59. Found: C, 80.56; H, 6.01; N, 3.64.

4.15. Boc-[(*R*)-β^{2,2}-HBin]$_6$-OMe (*RRRRRR*)-6

The pentapeptide (*RRRRR*)-**5** (0.049 g; 0.026 mmol) was N-deprotected in TFA/CH_2Cl_2 1:1 (1 mL) according to the general procedure A2. The obtained crude H-[(*R*)-β^{2,2}-HBin]$_4$-OMe (0.047 g) was coupled with (*R*)-**1a**[19] (0.013 g; 0.029 mmol) in THF (1 mL) and CH_2Cl_2 (2 mL), according to the general procedure C. The crude product was purified by preparative TLC on silica gel with eluant (I) to afford 0.025 g (43%) of pure (*RRRRRR*)-**6** as a solid. Mp = 276 °C. $R_f = 0.4$ (VII). ^{1}H NMR ($CDCl_3$): δ 8.05–7.02 [m, 72H, ArH], 6.89 [m (broad), 1H, NH], 6.72 [m (broad), 1H, NH], 6.62 [m (broad), 2H, NH], 6.02 [m (broad), 1H, NH], 5.34 [m (broad), 1H, NH–Boc], 3.08 [s, 3H, OCH_3], 3.49–1.96 [m, 36H, Ar–CH_2 and N–CH_2], 1.35 [s, 9H, 3 CH_3 Boc]. ^{13}C NMR ($CDCl_3$): δ 175.6, 175.1, 174.9, 174.7, 174.6, 174.5 (C=O), 156.2 (C=O Boc), 135.0, 134.8, 134.4, 134.2, 134.0, 133.9, 133.8, 133.0, 132.9, 132.8, 132.7, 131.8, 131.7, 131.6 (CAr), 128.3, 128.2, 128.0, 127.8, 127.1, 126.9, 125.9, 125.7, 125.6, 125.5, 125.1 (CHAr), 79.3 (C–O Boc), 59.6, 59.1, 58.8, 58.7, 58.5, 58.4 (Cα), 51.8 (OCH_3), 45.0, 44.9, 44.3, 44.2, 43.6, 43.4 (N–CH_2), 38.9, 38.4, 36.8, 36.7, 36.6, 36.5 (Ar–CH_2), 28.4 (CH_3 Boc). $[\alpha]^{25}_{589} = -13$; $[\alpha]^{25}_{578} = -12$; $[\alpha]^{25}_{546} = -11$; $[\alpha]^{25}_{436} = +75$; $[\alpha]^{25}_{365} = +980$ (*c* 0.13, CH_2Cl_2). MALDI MS *m*/*z*: 2266.2 $(M+K)^+$, 2250.2 $(M+Na)^+$, 2128.2 $(M+H-Boc)^+$. Anal. Calcd for $C_{156}H_{126}N_6O_9{\cdot}4H_2O$ (2300.680): calcd C, 81.43; H, 5.87; N, 3.65. Found: C, 81.86; H, 5.84; N, 3.53.

4.16. c[(*R*)-β^{2,2}-HBin]$_3$

The tripeptide (*RRR*)-**3** (0.105 g; 0.089 mmol) was saponified with 1 M NaOH (1.8 mL) in MeOH (4 mL) according to the general procedure B. The obtained crude Boc-[(*R*)-β^{2,2}-HBin]$_3$-OH (0.101 g) was converted to the corresponding pentafluorophenyl ester according to the general procedure D. The obtained crude Boc-[(*R*)-β^{2,2}-HBin]$_3$-OPfp (0.107 g) was N-deprotected in TFA/CH_2Cl_2 1:1 (2 mL) according to the general procedure A1, to afford crude TFA·H-[(*R*)-β^{2,2}-HBin]$_3$-OPfp (0.129 g). A solution of this compound (0.108 g; 0.08 mmol) in CH_3CN (43 mL) and CH_2Cl_2 (18 mL), was added to a hot solution of DIEA (0.020 mL; 0.15 mmol) in CH_3CN (9 mL), for cyclization according to the general procedure E. The crude product was purified by preparative TLC on silica gel with eluant (V) to afford 0.048 g (57%) of pure c[(*R*)-β^{2,2}-HBin]$_3$ as a solid. Mp = 253 °C. $R_f = 0.3$ (V). ^{1}H NMR ($CDCl_3$): δ 7.91–7.26 [m, 36H, ArH], 6.25 [m (broad t-like), 3H, NH], 3.68 and 3.20 [dd, $J = 13.6$; 6.7, 3H and dd (partly masked), 3H, N–CH_2], 3.18 and 2.25 [d (partly masked), $J \sim 13.1$, 3H and d, $J = 13.4$, 3H, Ar–CH_2], 2.90 [m (s-like AB quartet), 6H, Ar–CH_2]. ^{13}C NMR ($CDCl_3$): δ 174.2 (C=O), 135.2, 134.6, 134.4, 133.8, 133.2, 133.1, 131.9 (CAr), 128.7, 128.6, 128.5, 128.4, 128.3, 127.8, 127.4, 127.3, 126.0, 125.9, 125.5, 125.3 (CHAr), 60.0 (Cα), 44.7 (N–CH_2), 40.1, 36.5 (Ar–CH_2). $[\alpha]^{25}_{589} = -104$; $[\alpha]^{25}_{578} = -107$; $[\alpha]^{25}_{546} = -124$; $[\alpha]^{25}_{436} = -158$; $[\alpha]^{25}_{365} = +339$ (*c* 0.20, CH_2Cl_2). ESI$^+$ MS *m*/*z*: 1086.9 $(M+K)^+$, 1070.8 $(M+Na)^+$, 1048.8 $(M+H)^+$. Anal. Calcd for $C_{75}H_{57}N_3O_3{\cdot}4H_2O$ (1120.284): C, 80.40; H, 5.85; N, 3.75. Found: C, 80.05; H, 5.23; N, 3.33.

4.17. c[(*S*)-β^{2,2}-HBin]$_4$

The tetrapeptide (*SSSS*)-**4** (0.199 g; 0.130 mmol) was saponified with 1 M NaOH (2.6 mL) in MeOH (6 mL) according to the general procedure B to afford crude Boc-[(*R*)-β^{2,2}-HBin]$_3$-OH (0.171 g). This compound (0.091 g; 0.06 mmol) was converted to the corresponding pentafluorophenyl ester according to the general procedure D to afford crude Boc-[(*S*)-β^{2,2}-HBin]$_4$-OPfp (0.083 g). This compound (0.075 g; 0.044 mmol), in turn, was N-deprotected in TFA/CH_2Cl_2 1:1 (1 mL) according to the general procedure A1 to afford crude TFA·H-[(*S*)-β^{2,2}-HBin]$_4$-OPfp (0.077 g). A solution of this latter compound (0.075 g; 0.044 mmol) in CH_3CN (24 mL) and CH_2Cl_2 (10 mL), was added to a hot solution of DIEA (0.015 mL; 0.09 mmol) in CH_3CN (5 mL), for cyclization according to the general procedure E. The crude product was purified by preparative TLC on silica gel with eluant (VII) to afford 0.027 g (44%) of pure c[(*S*)-β^{2,2}-HBin]$_4$ as a solid. Mp > 300 °C. $R_f = 0.3$ (VII). ^{1}H NMR ($CDCl_3$): δ 7.96–7.23 [m, 48H, ArH], 6.60 [m (broad t-like), $J \sim 5.9$, 4H, NH], 3.67 and 3.32 [dd, $J = 14.1$; 6.7, 4H and dd, $J = 13.8$; 5.1, 4H, N–CH_2], 3.14 and 2.56 [d, $J = 13.7$, 4H and d, $J = 13.6$, 4H, Ar–CH_2], 2.82 and 2.69 [d, $J = 12.9$, 4H and d, $J = 12.8$, 4H, Ar–CH_2]. ^{13}C NMR ($CDCl_3$): δ 175.6 (C=O), 134.9, 134.5, 134.2, 134.1, 133.20, 133.18, 132.0, 131.9 (CAr), 128.9, 128.5, 127.4, 127.3, 126.1, 126.0, 125.6, 125.2 (CHAr), 60.3 (Cα), 45.7 (N–CH_2), 40.6, 38.0 (Ar–CH_2). $[\alpha]^{25}_{589} = -50$; $[\alpha]^{25}_{578} = -58$; $[\alpha]^{25}_{546} = -75$; $[\alpha]^{25}_{436} = -249$; $[\alpha]^{25}_{365} = -1020$ (*c* 0.10; CH_2Cl_2). ESI$^+$ MS *m*/*z*: 1419.8 $(M+Na)^+$.

4.18. Ultraviolet absorption and fluorescence

The electronic absorption spectra were recorded between 260 and 350 nm using a Shimadzu model UV-2501 PC spectrophotometer (scan speed: 50 nm/min; response time: 2 s; slit size: 1.0 nm; accumulations: 1; no smoothing; processing: normalization to 0.01 mM). The fluorescence spectra were measured between 320 and 450 nm (upon excitation at 307 nm) using a

Perkin–Elmer model LS-50B spectrofluorimeter (scan speed: 30 nm/min; response time: 2.5 s; $slit_{exc}$ size = $slit_{em}$ size: 5.0 nm; accumulations: 1; smoothing: adjacent averaging 10 points; processing: normalization to 0.01 mM by concentration correction according to the UV absorption measurements). Spectrograde methylene chloride, dried by distillation over P_2O_5, was purchased from C. Erba.

4.19. Circular dichroism

Electronic CD spectra were recorded between 205 and 340 nm on a Jasco model J-715 spectropolarimeter (scan speed: 50 nm/min; response time: 2 s; bandwidth: 1.0 nm; accumulations: 6; no smoothing; processing: solvent subtraction, conversion to molar ellipticity, normalization to 0.5 mM by concentration correction according to the UV absorption measurements). The data are expressed in terms of $[\theta]_T$, the total molar ellipticity (deg cm^2 dmol^{-1}). Spectrograde MeOH (Fluka), TFE (Acros), and $CHCl_3$ (Fluka) were used as solvents.

4.20. FT-IR absorption

The solution IR absorption spectra of the N^{α}-protected (*S*)-Bin derivative and peptide esters in the 3550–3200 cm^{-1} region were recorded using a Perkin–Elmer model 1720X FT-IR spectrophotometer, nitrogen flushed, equipped with a sample-shuttle device, at 2 cm^{-1} nominal resolution, averaging 100 scans. Solvent (baseline) spectra were obtained under the same conditions. After solvent subtraction, the spectra were smoothed by a Savitsky-Golay weighted 9-point window. Peak positions of shoulders and partially overlapping bands were estimated with the aid of the second derivative spectra. All calculations were performed using the Spectra Calc (Galactic) software. Cells with path lengths of 1.0 and 10 mm (with CaF_2 windows) were used. Spectrograde deuterochloroform (99.8% d) was purchased from Fluka.

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