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Synthesis of enantiopure, axially chiral, C^{α}-tetrasubstituted α-amino acids with binaphthyl-based crowned side chains and 3D-structural analysis of their peptides

Karen Wright [a,*], Jean-François Lohier [a], Michel Wakselman [a], Jean-Paul Mazaleyrat [a], Fernando Formaggio [b], Cristina Peggion [b], Marta De Zotti [b], Claudio Toniolo [b,*]

[a] *ILV, UMR CNRS 8180, University of Versailles, F-78035 Versailles, France*
[b] *Institute of Biomolecular Chemistry, CNR, Padova Unit, Department of Chemistry, University of Padova, I-35131 Padova, Italy*

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Abstract

The syntheses of the terminally protected, crowned, C^{α}-tetrasubstituted α-amino acids with only axial chirality, the two diastereomers Boc-(*S*)-Bip[(*R*)-Binol-22-C-6]-OMe and Boc-(*R*)-Bip[(*R*)-Binol-22-C-6]-OMe, and their respective enantiomers Boc-(*R*)-Bip[(*S*)-Binol-22-C-6]-OMe and Boc-(*S*)-Bip[(*S*)-Binol-22-C-6]-OMe, all derived from 2′,1′:1,2; 1″,2″:3,4-dibenzcyclohepta-1,3-diene-6-amino-6-carboxylic acid (Bip), were performed by bis-alkylation with cyclization of racemic (*R*+*S*)-Boc-$[HO]_2$-Bip-OMe, possessing two phenolic OH groups at the 6,6′-positions of the biphenyl frame of Bip, using (+)-(*R*)- and (−)-(*S*)-Binol$[(OCH_2CH_2)_2OTs]_2$ (2,2′-bis[5-tosyloxy-3-oxa-1-pentyloxy]-1,1′-binaphthyl), respectively, as the alkylating agent followed by chromatographic separation. Two series of terminally protected model peptides to the hexamer level, containing the (*R*)-Bip[(*S*)-Binol-22-C-6] residue at *i* and *i*+3 positions of the sequence, combined with either L-Ala or L-Ala/Aib, were synthesized by solution methods. Their 3D-structural analyses by FTIR absorption and NMR suggest that these peptides preferentially adopt folded secondary structures.

Keywords: Atropoisomerism; Binaphthyl; Biphenyl; Crowned amino acids; C^{α}-Tetrasubstituted α-amino acids; NMR; Infrared absorption; Peptide conformation

1. Introduction

In the past few years, a series of crown-carrier derivatives of L-DOPA,[1–19] lysine,[20] or glutamic acid,[21] were synthesized and shown to be of interest for the construction of peptide receptors specific for alkali metal, ammonium, and di-ammonium ions, and for the preparation of artificial ion channels. Application of this concept to C^{α}-tetrasubstituted α-amino acids with well-defined stereochemical properties was expected to result in more predictable peptide structures, as these residues are known to be able to induce folded 3_{10}-helical conformations in short peptide backbones.[22–33] Accordingly, we previously designed crown-carrier C^{α}-tetrasubstituted α-amino acids as interesting targets allowing control of the spatial organization of the crown-ether receptors in short-chain peptide structures for the construction of new molecular receptors and supramolecular devices.[34–37] Peptides based on L-Mdp[CROWN] residues derived from C^{α}-methyl-L-DOPA (L-Mdp) with [CROWN]=[15-C-5], [18-C-6], [Benzo-24-C-8], and [(*S*)-Binol-20-C-6] (Fig. 1), the latter containing a binaphthyl unit as a part of the crown moiety, were shown to have a strong propensity for folded/helical secondary structures.[38,39] Other groups synthesized indane-based,[40] as well as α-hydroxymethylserine-based,[41,42] achiral, C^{α}-tetrasubstituted α-amino acid derivatives with various crown-ether side chains. However, X-ray

* Corresponding authors. Fax: +33 01 39 25 44 52 (K.W.); fax: +39 049 827 5239 (C.T.).
E-mail addresses: wright@chimie.uvsq.fr (K. Wright), claudio.toniolo@unipd.it (C. Toniolo).

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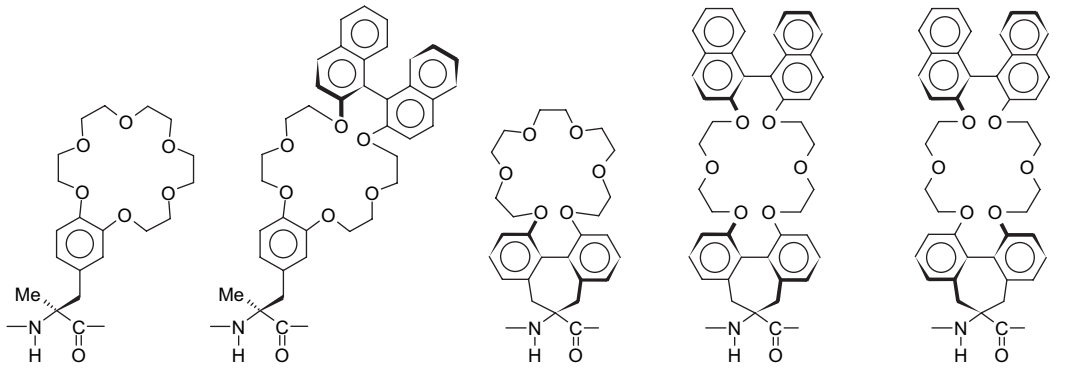

Figure 1. Chemical structures of L-Mdp[18-C-6], L-Mdp[(*S*)-Binol-20-C-6], (*R*)-Bip[20-C-6], (*R*)-Bip[(*S*)-Binol-22-C-6], and (*S*)-Bip[(*S*)-Binol-22-C-6] residues.

diffraction 3D-structural analyses of only single amino acids or cyclic dipeptides (2,5-dioxopiperazines) have been performed.[40]

To the same end, peptides based on the more rigid, cyclic, 6-amino-1,11-(20-crown-6)-6,7-dihydro-5*H*-dibenzo [*a*,*c*]cycloheptene-6-carboxylic acid (Bip[20-C-6]) residue (Fig. 1) were previously investigated in our groups.[34–36] However, we were unable to prepare this amino acid in an enantiomerically pure state, because of extensive racemization occurring at several stages of the synthesis. Therefore, only limited 3D-structural information on some of its short peptides could be obtained.[36] We envisioned that introduction of either a (*R*)- or a (*S*)-binaphthyl unit as a part of the crown receptor would not only impart extended chiral barriers to the Bip[20-C-6] residue, as an amino acid analogue of the famous binaphthyl crown-ether series designed many years ago by Cram and co-workers,[43–46] but could also allow access to the resulting diastereomeric (*R*)-Bip[(*S*)-Binol-22-C-6] and (*S*)-Bip[(*S*)-Binol-22-C-6] residues (Fig. 1), as well as their respective enantiomers (*S*)-Bip[(*R*)-Binol-22-C-6] and (*R*)-Bip[(*R*)-Binol-22-C-6] (not shown), in an enantiomerically pure state.[47]

In this paper, we wish to present our detailed results of the synthesis of the binaphthyl-crowned, atropisomeric, terminally protected, C^{α}-tetrasubstituted α-amino acid isomers Boc-(*S*)-Bip[(*R*)-Binol-22-C-6]-OMe (Boc, *tert*-butyloxycarbonyl; OMe, methoxy), Boc-(*R*)-Bip[(*R*)-Binol-22-C-6]-OMe, Boc-(*R*)-Bip[(*S*)-Binol-22-C-6]-OMe, and Boc-(*S*)-Bip[(*S*)-Binol-22-C-6]-OMe. The solution synthesis of two series of terminally protected model peptides to the hexamer level, where the (*R*)-Bip[(*S*)-Binol-22-C-6] residue is placed at the *i* and *i*+3 positions of the sequence, combined with either L-Ala or L-Ala/Aib (α-aminoisobutyric acid), and their 3D-structural analysis by FTIR absorption and NMR are also presented.

2. Results and discussion

2.1. Synthesis

The two phenolic hydroxy groups of the racemic, N^{α}-protected, α-amino ester 6-*tert*-butyloxycarbonylamino-1,11-dihydroxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptene-6-carboxylic acid methyl ester Boc-(*R*+*S*)-Bip[OH]$_2$-OMe (Fig. 2), previously obtained from 2,2′-bis(bromomethyl)-6,6′-dimethoxy-1,1′-biphenyl,[36] served to introduce the (*R*)- or (*S*)-binaphthyl-crowned side chain, by using the well established procedure reported by Voyer and co-workers,[3,6,14] with Cs_2CO_3 as a base in DMF (*N*,*N*-dimethylformamide) at 60 °C, and enantiomerically pure (+)-(*R*)- or (−)-(*S*)-Binol[$(OCH_2CH_2)_2OTs]_2$ (2,2′-bis[5-tosyloxy-3-oxa-1-pentyloxy]-1,1′-binaphthyl)[46] as the alkylating agent to afford a mixture of either Boc-(*S*)-Bip[(*R*)-Binol-22-C-6]-OMe (*SR*)-**1** and its diastereomer Boc-(*R*)-Bip[(*R*)-Binol-22-C-6]-OMe (*RR*)-**1** (not shown), or Boc-(*R*)-Bip[(*S*)-Binol-22-C-6]-OMe (*RS*)-**1** and its diastereomer Boc-(*S*)-Bip[(*S*)-Binol-22-C-6]-OMe (*SS*)-**1** (Fig. 2), which could be separated by chromatography on silica gel. The compounds (*SR*)-**1** and (*RR*)-**1** were obtained from a small-scale experiment in 26% yield (52% of theoretical yield) and 25% yield (50% of theoretical yield), respectively,[47] while (*RS*)-**1** (37% of theoretical yield) and (*SS*)-**1** (45% of theoretical yield) resulted from a medium-scale experiment in which repeated chromatography was necessary for efficient and complete separation.

This separation represents a resolution of the Bip part of the molecule after crown formation with access to both configurations in an enantiopure state. This is especially interesting since, as pointed out above, racemization was shown previously to be an inherent process during crown formation by etherification of the di-cesium salt of the enantiomerically pure Boc-(*R*)- or (*S*)-Bip[OH]$_2$-OMe in DMF at 60 °C, to afford crowned, α-amino esters Boc-(*R*)-Bip[20-C-6]-OMe (Fig. 1) with only ca. 64% ee or Boc-(*S*)-Bip[20-C-6]-OMe with only ca. 48% ee, respectively.[36]

The absolute configuration of (*RR*)-**1** was easily assigned by considering its relationship with the absolute configurations of the two products resulting from chemical cleavage of the ArO–R ether bonds. Treatment of the postulated (*RR*)-**1** isomer with a large excess of boron tribromide in dichloromethane,[48] followed by re-esterification of the crude product with thionyl chloride in methanol (Fig. 3), allowed the recovery of Binol with $[\alpha]_D^{25}$ +29 (*c* 0.84, THF), and of H-Bip[OH]$_2$-OMe with $[\alpha]_{436}^{25}$ −93 (*c* 0.14, MeOH), both of known absolute configuration (+)-(*R*)[46] and (−)-(*R*),[36] respectively. From this

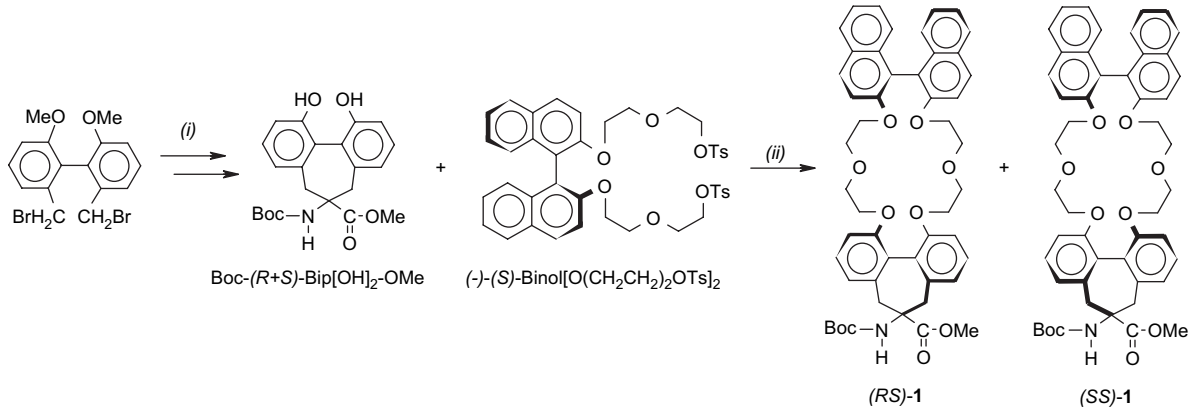

Figure 2. Synthesis of Boc-(*R*)-Bip[(*S*)-Binol-22-C-6]-OMe (*RS*)-**1** and Boc-(*S*)-Bip[(*S*)-Binol-22-C-6]-OMe (*SS*)-**1**. (i) Ref. 36; (ii) Cs_2CO_3; DMF; 60 °C.

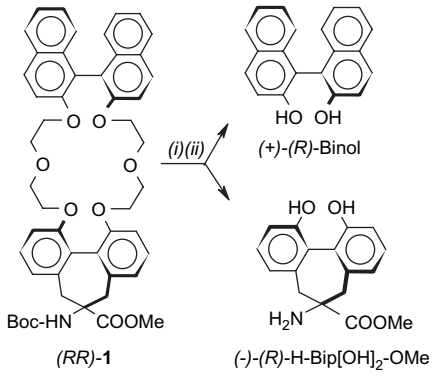

Figure 3. Cleavage of the postulated (*RR*)-**1** isomer to (+)-(*R*)-Binol and (−)-(*R*)-H-Bip[OH]$_2$-OMe. (i) BBr_3, CH_2Cl_2, −10 °C to rt; (ii) MeOH, $SOCl_2$, rt.

result the absolute configuration of its diastereomer (*SR*)-**1** and those of their enantiomeric pairs (*SS*)-**1** and (*RS*)-**1** were inferred.

It can be observed that as the maximum value reported for (+)-(*R*)-Binol was $[\alpha]_D^{25}$ +34 (*c* 1.1, THF)[46] and for (−)-(*R*)-H-Bip[OH]$_2$-OMe was $[\alpha]_{436}^{25}$ −137 (*c* 0.1, MeOH),[36] these two compounds were obtained by chemical cleavage of (*RR*)-**1** with only ca. 85% ee and ca. 68% ee, respectively. However, we believe that this result does not bring into question the ee of the starting (*RR*)-**1**, expected to be enantiomerically pure or nearly so, but rather that it reflects a racemization of the dihydroxy-substituted binaphthyl and biphenyl moieties of the products (*R*)-Binol and (*R*)-H-Bip[OH]$_2$-OMe, respectively. Indeed, Binol has been reported to be configurationally stable at 100 °C for 24 h in dioxane/water, but to racemize to an extent of 72% in a 1.2 N HCl solution.[46] It is perhaps therefore not surprising that Binol racemizes 15%, and that the more flexible dihydroxy-biphenyl skeleton of H-Bip[OH]$_2$-OMe racemizes 32% at room temperature under the acidic conditions required for both ether cleavage and re-esterification. To clarify the question of the enantiomeric purity of the adducts **1**, the N^{α}-Boc protecting group of (*SS*)-**1** and (*RS*)-**1** was cleaved by acidolysis in TFA (trifluoroacetic acid)/CH_2Cl_2 and the resulting free amino esters were reacted with a large excess of the symmetrical anhydrides resulting from reaction of both (−)-(*S*)-MTPA (Mosher's reagent,[49] α-methoxy-α-trifluoromethyl-α-phenyl-acetic acid) and (+)-(*R*)-MTPA with a half-equivalent of EDC (*N*-ethyl, *N*′-[3-dimethylaminopropyl]-carbodiimide) in acetonitrile. This led to the pairs of diastereomeric amido esters *S*(*SS*)-**1**, MTPA/*R*(*SS*)-**1**, MTPA (Fig. 4) and *S*(*RS*)-**1**, MTPA/*R*(*RS*)-**1**, MTPA (not shown), respectively. These compounds showed distinct ^{1}H NMR signals in $CDCl_3$ solution for the −COOMe singlet (see Section 4) and distinct ^{19}F NMR signals in either $CDCl_3$ or toluene-d_8 solution (with a much better signal separation in the latter case) for the $-CF_3$ singlet (Fig. 5), allowing

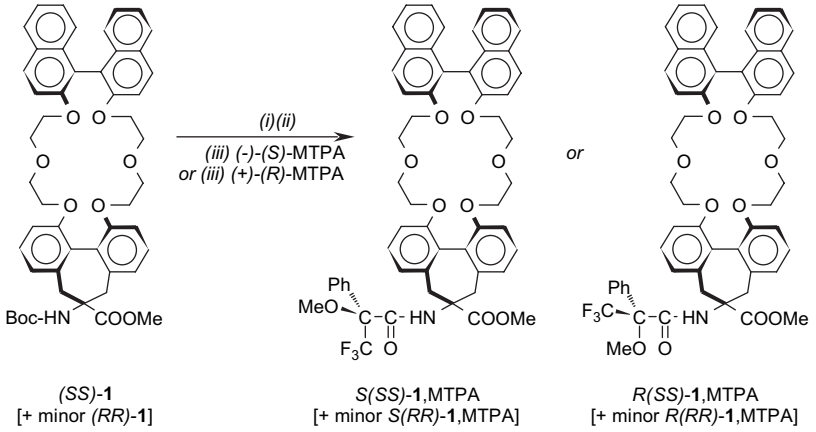

Figure 4. Synthesis of the diastereomeric Mosher's amides *S*(*SS*)-**1**, MTPA and *R*(*SS*)-**1**, MTPA from (*SS*)-**1**. (i) TFA/CH_2Cl_2 1:3, 0 °C to rt; (ii) EDC, CH_3CN, rt.

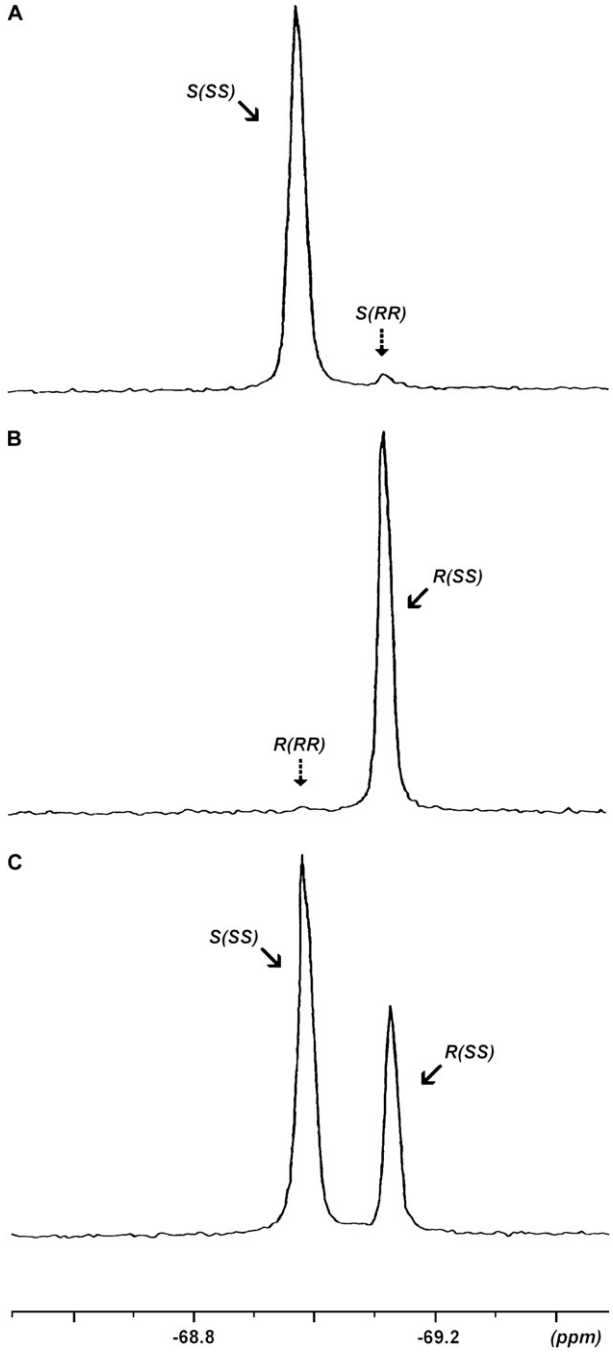

Figure 5. ^{19}F NMR spectra of the Mosher's amido esters *S*(*SS*)-**1**, MTPA (**A**) and *R*(*SS*)-**1**, MTPA (**B**) in toluene-d_8 solution, as compared to the spectrum of an artificial mixture of both solutions of *S*(*SS*)-**1**, MTPA (major) and *R*(*SS*)-**1**, MTPA (minor) (**C**).

localization of the corresponding minor isomers and determination of the diastereomeric excess (de). An average ≥95% de was found for both pairs of isomers *S*(*SS*)-**1**, MTPA/*S*(*RR*)-**1**, MTPA and *R*(*SS*)-**1**, MTPA/*R*(*RR*)-**1**, MTPA (Fig. 5) as well as *S*(*RS*)-**1**, MTPA/*S*(*SR*)-**1**, MTPA and *R*(*RS*)-**1**, MTPA/*R*(*SR*)-**1**, MTPA (not shown), demonstrating the formation of the adducts (*SS*)-**1** and (*RS*)-**1** in an enantiopure state or nearly so, taking into account the synthetic nature (<100% ee) of the MTPA reagents.

Peptides based on the (*R*)-Bip[(*S*)-Binol-22-C-6] residue combined with either L-Ala (**a** series) or L-Ala/Aib (**b** series) residues, were prepared by stepwise coupling in solution. The urethane-protected *N*-carboxyanhydrides (UNCAs),[50,51] Fmoc-L-Ala-NCA (Fmoc, 9-fluorenylmethyloxycarbonyl), and Boc-Aib-NCA were used for coupling at the N^{α}-terminus of either C^{α}-tetrasubstituted α-amino acid residue, (*R*)-Bip[(*S*)-Binol-22-C-6] or Aib, while coupling of H-L-Ala-OMe or H-L-Ala-peptide ester at the C-terminus of the (*R*)-Bip[(*S*)-Binol-22-C-6] residue was performed by HATU (2-[7-aza-1*H*-benzotriazole-1-yl]-1,1,3,3-tetramethyluronium hexafluorophosphate)[52] activation, more efficient in our hands than the EDC/HOAt (7-aza-1-hydroxy-1,2,3-benzotriazole) method.[53]

For the (*R*)-Bip[(*S*)-Binol-22-C-6]/L-Ala (**a**) series (Fig. 6), saponification of (*RS*)-**1** in 1 N NaOH/MeOH (methanol) at 50 °C gave its C-deprotected analogue Boc-(*R*)-Bip[(*S*)-Binol-22-C-6]-OH, which was coupled with HCl·H-L-Ala-OMe by the HATU method to afford Boc-(*R*)-Bip[(*S*)-Binol-22-C-6]-L-Ala-OMe **2a** in 94% yield. This dipeptide was N^{α}-deprotected in TFA/CH_2Cl_2 1:3 and the resulting crude TFA·H-(*R*)-Bip[(*S*)-Binol-22-C-6]-L-Ala-OMe was coupled with Fmoc-L-Ala-NCA in the presence of an excess of DIEA (*N*,*N*,*N*-diisopropylethylamine) to give the tripeptide Fmoc-L-Ala-(*R*)-Bip[(*S*)-Binol-22-C-6]-L-Ala-OMe **3a** in 63% overall yield. Coupling of Boc-L-Ala-OH at the deprotected N^{α}-terminus of **3a** (using $Et_2NH/CH_3CN-CH_2Cl_2$) by the EDC/HOAt method gave Boc-{L-Ala}$_2$-(*R*)-Bip[(*S*)-Binol-22-C-6]-L-Ala-OMe **4a** in 74% overall yield. Coupling of Boc-(*R*)-Bip[(*S*)-Binol-22-C-6]-OH at the deprotected N^{α}-terminus of **4a** (HCl/dioxane/CH_2Cl_2) by the HATU method furnished Boc-(*R*)-Bip[(*S*)-Binol-22-C-6]-{L-Ala}$_2$-(*R*)-Bip[(*S*)-Binol-22-C-6]-L-Ala-OMe **5a** in 62% overall yield, and coupling of Fmoc-L-Ala-NCA at the deprotected N^{α}-terminus of **5a** (HCl/dioxane/CH_2Cl_2) afforded the hexapeptide Fmoc-{L-Ala-(*R*)-Bip[(*S*)-Binol-22-C-6]-L-Ala}$_2$-OMe **6a** in 61% yield.

The corresponding (*R*)-Bip[(*S*)-Binol-22-C-6]/L-Ala/Aib (**b**) series (Fig. 7) was prepared in a different way, as we expected that competitive cyclization of the N^{α}-deprotected dipeptide TFA·H-(*R*)-Bip[(*S*)-Binol-22-C-6]-L-Ala-OMe to the corresponding 2,5-dioxopiperazine during coupling with the more hindered Boc-Aib-NCA (as compared to Fmoc-L-Ala-NCA) could occur, as we had previously observed in similar cases.[37] The tripeptide **3b** was prepared by first coupling Boc-Aib-NCA with the fully deprotected crude amino acid TFA·H-(*R*)-Bip[(*S*)-Binol-22-C-6]-OH, which gave Boc-Aib-(*R*)-Bip[(*S*)-Binol-22-C-6]-OH **2b** in 69% yield, and then coupling of **2b** with HCl·H-L-Ala-OMe by the HATU method, which afforded Boc-Aib-(*R*)-Bip[(*S*)-Binol-22-C-6]-L-Ala-OMe **3b** in 72% yield. In the next step, Fmoc-L-Ala-NCA was used for coupling at the hindered, N^{α}-deprotected (using TFA/CH_2Cl_2) terminus of **3b**, which afforded Fmoc-L-Ala-Aib-(*R*)-Bip[(*S*)-Binol-22-C-6]-L-Ala-OMe **4b** in 85% overall yield. Finally, in a similar manner as in the **a** series, coupling of Boc-(*R*)-Bip[(*S*)-Binol-22-C-6]-OH at the deprotected N^{α}-terminus of **4b** (using $Et_2NH/CH_3CN-CH_2Cl_2$) by the HATU method furnished Boc-(*R*)-Bip[(*S*)-Binol-22-C-6]-L-Ala-Aib-(*R*)-Bip[(*S*)-Binol-22-C-6]-L-Ala-OMe **5b** in 61%

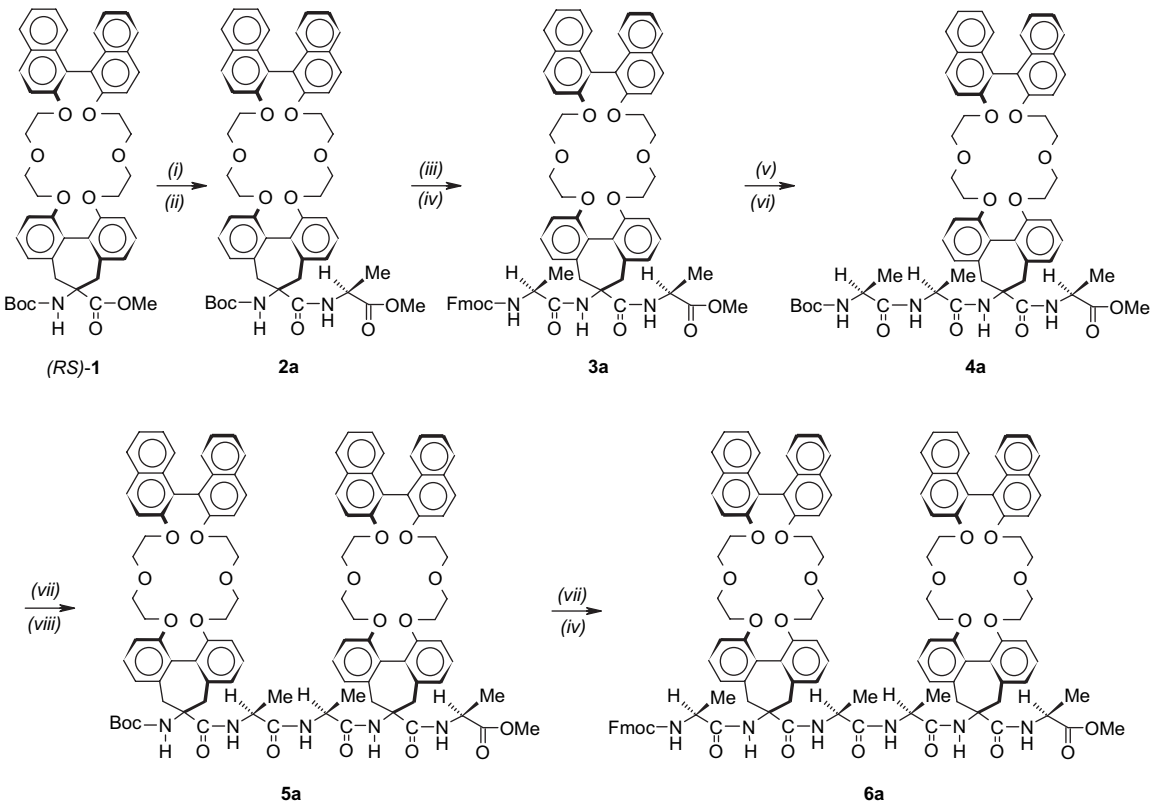

Figure 6. Synthesis of peptides based on (*R*)-Bip[(*S*)-Binol-22-C-6] combined with L-Ala (**a** series). (i) 1 N NaOH, MeOH, 50 °C; (ii) HCl·H-L-Ala-OMe, HATU, DIEA, CH_2Cl_2/THF; (iii) TFA/CH_2Cl_2 1:3; (iv) Fmoc-L-Ala-NCA, DIEA, THF; (v) 10% (v/v) $Et_2NH/CH_3CN-CH_2Cl_2$; (vi) Boc-L-Ala-OH, EDC, HOAt, CH_2Cl_2; (vii) HCl/dioxane ≈ 4 N, CH_2Cl_2; (viii) Boc-(*R*)-Bip[(*S*)-Binol-22-C-6]-OH, HATU, DIEA, CH_2Cl_2/THF.

overall yield, and coupling of Boc-Aib-NCA at the deprotected N^{α}-terminus of **5b** (using TFA/CH_2Cl_2) afforded the hexapeptide Boc-{Aib-(*R*)-Bip[(*S*)-Binol-22-C-6]-L-Ala}$_2$-OMe **6b** in 33% overall yield.

2.2. Conformational analysis

FTIR absorption and ^{1}H NMR techniques were used to assess the preferred conformations of the two terminally protected (*R*)-Bip[(*S*)Binol-22-C-6]/L-Ala **2a**–**6a** and (*R*)-Bip[(*S*)-Binol-22-C-6]/L-Ala/Aib **2b**–**5b** oligopeptide series at various concentrations in the structure supporting solvent $CDCl_3$ (paucity of material precluded the analysis of compound **6b**).

Figure 8 shows the FTIR absorption spectra of the two peptide series at 1 mM concentration in the conformationally informative 3530–3200 cm^{-1} region. An intense band at 3360–3330 cm^{-1}, assigned to the N–H stretching mode of strongly H-bonded –CONH– groups,[54,55] was seen at the level of the trimer in the **b** series, but only at the level of the pentamer in the **a** series. The bands found in the regions 3462–3424 cm^{-1} (with a major contribution at 3434–3424 cm^{-1}) and 3520–3480 cm^{-1}, the latter seen only in the dipeptide carboxylic acid **2b**, were assigned to the N–H stretching mode of free (solvated) –CONH– groups and the O–H stretching mode of the –COOH group,[56] respectively. In the longest peptides of both series, a band of very low intensity centered near 3395(±5) cm^{-1} and associated to weakly H-bonded –CONH– groups of extended conformers was also observed. Upon peptide dilution from 10 to 0.1 mM peptide concentration, the spectra change only slightly (not shown), indicating that the C=O···H–N H-bonding is almost exclusively of the intramolecular type. A comparison of the spectra for the two peptide series strongly supports the view that the major finding of this analysis is the rank order propensities of the three α-amino acids studied to induce strong intramolecular C=O···H–N H-bonds, and, as a result, to stabilize folded conformers: Aib>(*R*)-Bip[(*S*)Binol-22-C-6]>L-Ala. In particular, the remarkably higher helicogenic tendency of Aib compared to L-Ala, already known,[22–33] was confirmed by considering the spectral patterns of peptide **3a** versus **3b**, and peptide **4a** versus **4b**. Moreover, if the spectra of peptides **3a**→**4a**→**5a** and **3b**→**4b**→**5b** are compared, it stands out clearly that more folding is produced by the incorporation of an N-terminal (*R*)-Bip[(*S*)Binol-22-C-6] residue than an L-Ala residue in the sequence. The observation that peptide **3a** is not folded, as compared with the partially folded tripeptide with two L-Ala and one Aib residue,[55] points to a greater capability to generate turn species for Aib than for (*R*)-Bip[(*S*)Binol-22-C-6].

More detailed information on the conformational preferences of the longest peptides of the two series was derived from an NMR analysis in $CDCl_3$ solution (1 mM concentration) despite the complexity of the spectra in the 7.5–6.5 ppm region due to overlapping of the informative NH proton signals with those of the (*R*)-Bip[(*S*)Binol-22-C-6] aromatic CH protons.

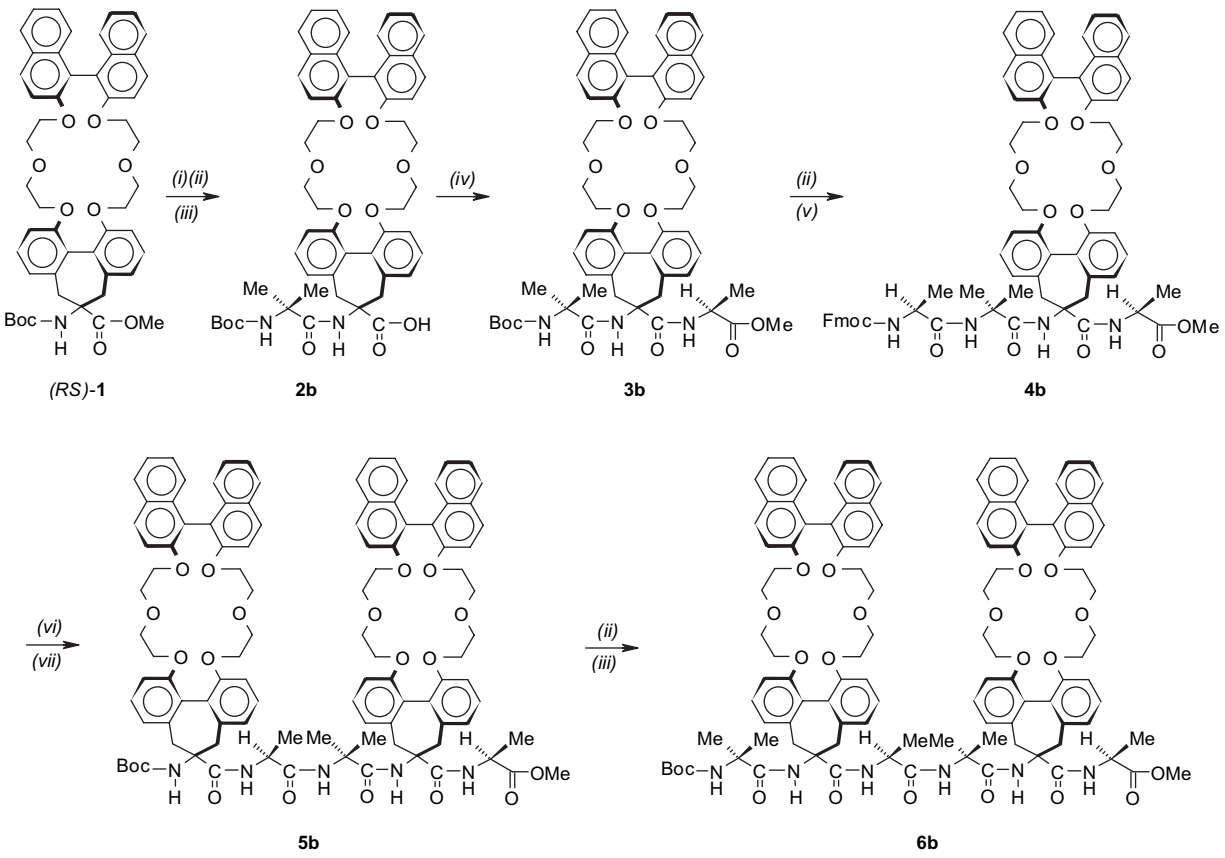

Figure 7. Synthesis of peptides based on (*R*)-Bip[(*S*)-Binol-22-C-6] combined with L-Ala and Aib (**b** series). (i) 1 N NaOH, MeOH, 50 °C; (ii) TFA/CH_2Cl_2 1:3; (iii) Boc-Aib-NCA, DIEA, THF; (iv) HCl·H-L-Ala-OMe, HATU, DIEA, CH_2Cl_2/THF; (v) Fmoc-L-Ala-NCA, DIEA, THF; (vi) 10% (v/v) Et_2NH/CH_2Cl_2; (vii) Boc-(*R*)-Bip[(*S*)-Binol-22-C-6]-OH, HATU, DIEA, CH_2Cl_2/THF.

As an illustrative example, Figure 9 presents a section of the ROESY spectrum of peptide **5a** in the region where the amide NH proton signals are found. The urethane NH proton, NH(1), is known to be remarkably upfield shifted (≅5.0 ppm) with respect to the amide NH protons in this halohydrocarbon solution.[55] All other NH proton resonances were assigned by virtue of their peak multiplicities and TOCSY/ROESY experiments.

From an inspection of Figure 9 it is evident that a complete set of cross-peaks of the NH(i)→NH(i+1) type is exhibited by the pentapeptide ester, indicative of the onset of an at least partially developed helical structure.[57] We believe that the type of helix formed would be most probably of the 3_{10}-type in view of the well established conformational tendencies of short peptides (with less than six residues) rich in C^{α}-tetrasubstituted α-amino acids.[22–33]

3. Conclusion

In the present study we prepared all isomers Boc-(*S*)-Bip[(*R*)-Binol-22-C-6]-OMe, Boc-(*R*)-Bip[(*R*)-Binol-22-C-6]-

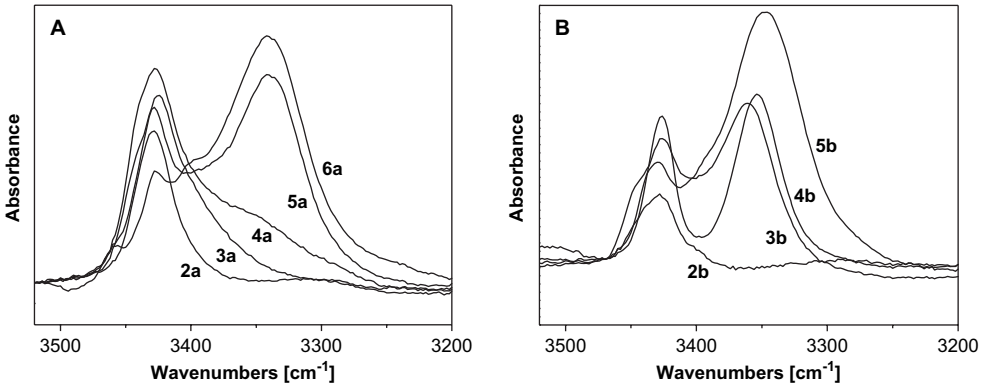

Figure 8. FTIR absorption spectra in the N–H stretching region of the (*R*)-Bip[(*S*)Binol-22-C-6]/L-Ala peptide series **2a**–**6a** (**A**) and the (*R*)-Bip[(*S*)Binol-22-C-6]/L-Ala/Aib series **2b**–**5b** (**B**) in $CDCl_3$ solution (peptide concentration: 1 mM).

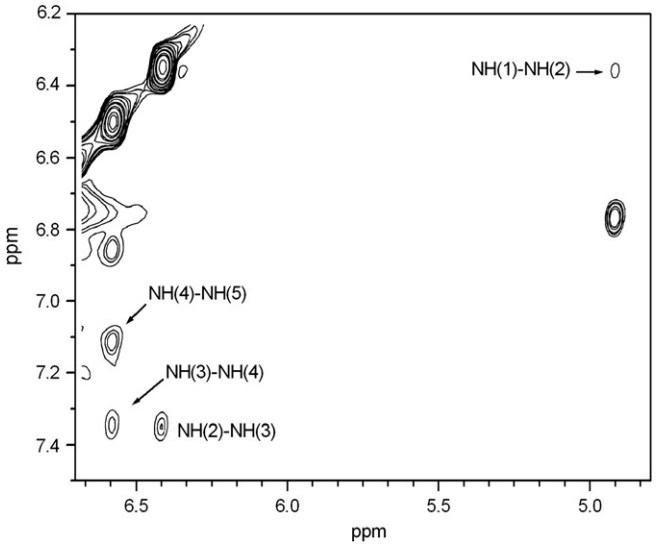

Figure 9. Section of the ROESY spectrum of the (*R*)-Bip[(*S*)Binol-22-C-6]/L-Ala pentapeptide **5a** in $CDCl_3$ solution (peptide concentration: 1 mM) showing the NH(i)→NH(i+1) connectivities.

OMe, Boc-(*R*)-Bip[(*S*)-Binol-22-C-6]-OMe, and Boc-(*S*)-Bip[(*S*)-Binol-22-C-6]-OMe, of a new, terminally protected, C^{α}-tetrasubstituted α-amino acid with only axial chirality, characterized by a 2,2′,6,6′-tetrasubstituted biphenyl architecture and a binaphthyl-based crown-ether side chain. The presence of a binaphthyl unit as chiral selector allowed resolution of the biphenyl part of the molecule after crown formation to afford enantiomerically pure adducts, overcoming the racemization problems previously encountered in the synthesis of the related Boc-Bip[20-C-6]-OMe series.[36]

Model peptides to the hexamer level, based on the (*R*)-Bip[(*S*)-Binol-22-C-6] residue combined with either L-Ala or L-Ala/Aib and introduced at i and i+3 positions of the sequence, were synthesized by solution methods and shown to preferentially adopt folded secondary structures, as their binaphthyl-crowned analogues derived from C^{α}-methyl-L-DOPA.[38,39]

The Bip[Binol-22-C-6] residue presents interesting features for future developments. (i) It belongs to the class of C^{α}-tetrasubstituted α-amino acids, well known for their high tendency to induce β-bends and 3_{10}-helices in peptides.[22–33] (ii) Its crown-ether receptor site is in a totally rigid and controlled spatial disposition relative to the C^{α} atom, in contrast with the previously described flexible[1–21] or semi-rigid[38,39] crown-carrier α-amino acids. (iii) The crown-ether side chains of two residues, introduced at positions i and i+3 of a peptide sequence, should be located one on top of the other in the ternary 3_{10}-helix, favoring cooperative cation binding.[39] (iv) As pointed out earlier, Bip[Binol-22-C-6] may be considered as a building block amino acid equivalent of the well known binaphthyl crown-ether hosts previously designed by Cram and co-workers.[43–46] Here, the chirality of the binaphthyl unit could function in synergy with the chirality of the peptide chain in new peptide-based catalysts[58,59] for enhanced chiral recognition properties in enantioselective crown-ether catalyzed reactions.[60–65]

4. Experimental

4.1. General experimental information

Melting points were measured on a Mettler apparatus with a final temperature raise of 3 °C/min or by means of a capillary tube immersed in an oil bath (Tottoli apparatus, Büchi) and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker WM300 spectrometer operating at 300 MHz and 77 MHz, respectively, the solvent being used as the internal standard: $CDCl_3$ (^{1}H: δ=7.27 ppm; ^{13}C: δ=77.00 ppm). Splitting patterns are abbreviated as follows: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet. Elemental analyses were performed by the C.N.R.S. Service of Microanalyses in Gif-sur-Yvette. High resolution mass spectra were performed by the Service of Mass Spectrometry of the ENS, Paris. Mass spectra (electrospray mode) were recorded on a Hewlett–Packard HP5989MS spectrometer, by Mr. Vincent Steinmetz (ILV). Analytical TLC and preparative column chromatography were performed on Kieselgel F 254 and Kieselgel 60 (0.040–0.063 mm) (Merck), respectively, with the following eluant systems: 1% MeOH–99% CH_2Cl_2 (I); 5% MeOH–95% CH_2Cl_2 (II); 10% MeOH–90% CH_2Cl_2 (III); 40% *c*Hex (cyclohexane)–60% EtOAc (ethyl acetate) (IV). UV light (λ=254 nm) allowed visualization of the spots after TLC runs for all compounds. Except when noted, all starting materials and solvents were obtained from commercial suppliers and were used as received. (+)-(*R*)-1,1′-Bi(2-naphthol) (Binol) (≥98% ee) and (−)-(*S*)-1,1′-bi(2-naphthol) (≥98% ee) were purchased from Fluka. (−)-(*S*)-α-Methoxy-α-trifluoromethyl-α-phenyl-acetic acid (gold label, 99+%) and (+)-(*R*)-α-methoxy-α-trifluoromethyl-α-phenyl-acetic acid (ee>99%) were purchased from Aldrich. Fmoc-L-Ala-NCA and Boc-Aib-NCA were Fluka and Isochem products, respectively.

4.2. 6-tert-Butyloxycarbonylamino-1,11-(Binol-22-crown-6)-6,7-dihydro-5H-dibenzo[a,c]cycloheptene-6-carboxylic acid methyl ester: Boc-(R)-Bip[(R)-Binol-22-C-6]-OMe (RR)-1, Boc-(S)-Bip[(R)-Binol-22-C-6]-OMe (SR)-1, Boc-(S)-Bip[(S)-Binol-22-C-6]-OMe (SS)-1, and Boc-(R)-Bip[(S)-Binol-22-C-6]-OMe (RS)-1

A solution of racemic 6-*tert*-butyloxycarbonylamino-1,11-dihydroxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptene-6-carboxylic acid methyl ester Boc-(*R*+*S*)-Bip[OH]$_2$-OMe[36] (0.101 g; 0.25 mmol) and Cs_2CO_3 (0.099 g; 0.30 mmol) in degassed MeOH (5 mL) was stirred under argon at 45 °C for 15 min, then evaporated to dryness in vacuo. To the residue was added DMF (5 mL) under an argon stream and the resulting solution was evaporated under high vacuum at 45 °C to remove the residual MeOH. Again, DMF (15 mL) was added to the residue, generating a greenish-orange solution which was magnetically stirred under argon at 60 °C while a solution of 2,2′-bis[5-tosyloxy-3-oxa-1-pentyloxy]-1,1′-binaphthyl (+)-(*R*)-Binol[$(OCH_2CH_2)_2OTs]_2$ (0.200 g; 0.27 mmol), prepared from (+)-(*R*)-Binol according to Cram and co-workers,[46] in DMF (5 mL) was added dropwise over a 1 h period. The solution

was stirred at 60 °C overnight and evaporated to dryness under high vacuum. The residue was dissolved in a mixture of CH_2Cl_2 (150 mL) and 5% $NaHCO_3$ (100 mL). The decanted CH_2Cl_2 solution was washed with a 5% $NaHCO_3$ solution (2×100 mL), then with H_2O (3×100 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product (0.200 g) showed two main spots of close R_f values but well separated in several eluant systems. It was purified by chromatography on four preparative TLC plates of silica gel with eluant (I) (five consecutive elutions) to afford 0.052 g (25%) of Boc-(*R*)-Bip[(*R*)-Binol-22-C-6]-OMe (*RR*)-**1** and 0.054 g (26%) of Boc-(*S*)-Bip[(*R*)-Binol-22-C-6]-OMe (*SR*)-**1**. In a similar manner, a mixture of Boc-(*R*+*S*)-Bip[OH]$_2$-OMe[36] (2.410 g; 6.04 mmol) and Cs_2CO_3 (2.340 g; 7.18 mmol) in DMF (150 mL) was treated with a solution of (−)-(*S*)-Binol[$(OCH_2CH_2)_2OTs]_2$ (4.770 g; 6.19 mmol) prepared from (−)-(*S*)-Binol,[46] in DMF (80 mL) at 60 °C for 16 h. Extraction as above gave 5.550 g of a brown foam, which was purified by chromatography on a column of silica gel (0.040−0.063 mm) with eluant (II). The resulting product (4.480 g) was purified by chromatography on a second column of silica gel (0.020−0.040 mm) with eluant (I), to afford 0.800 g of pure Boc-(*S*)-Bip[(*S*)-Binol-22-C-6]-OMe (*SS*)-**1**, 0.950 g of pure Boc-(*R*)-Bip[(*S*)-Binol-22-C-6]-OMe (*RS*)-**1**, and 0.680 g of a mixture of the two isomers. This mixture was repeatedly purified by chromatography on preparative TLC plates of silica gel eluted with eluant (I) (several consecutive elutions) to afford 0.114 g of pure (*SS*)-**1** for a total of 0.914 g (18%) and 0.171 g of pure (*RS*)-**1** for a total of 1.121 g (23%).

4.3. Boc-(R)-Bip[(R)-Binol-22-C-6]-OMe (RR)-1

Amorphous solid, mp 170 °C, R_f 0.18 (I). ^{1}H NMR ($CDCl_3$): δ 7.94 [d, J=9.0 Hz, 2H, ArH Binol], 7.88 [d, J=8.2 Hz, 2H, ArH Binol], 7.53 [d, J=9.0 Hz, 2H, ArH Binol], 7.35 [m (t-like), 2H, ArH Binol], 7.27−7.20 [m, 4H, 2ArH Binol and 2ArH Bip], 7.14 [d, J=8.0 Hz, 2H, ArH Binol], 6.89−6.80 [m, 4H, ArH Bip], 4.77 [br s, 1H, NH Bip], 4.29−4.22 [m, 2H, OCH_2], 4.06−3.80 [m, 6H, OCH_2], 3.73 [s, 3H, OCH_3], 3.60−3.40 [m, 8H, OCH_2], 3.14 [d, J=13.1 Hz, 1H, $ArCH_A$ Bip], 2.91 [br s, 2H, $ArC'H_2$ Bip], 2.21 [d, J=13.1 Hz, 1H, $ArCH_B$ Bip], 1.45 [s, 9H, CH_3 Boc]. ^{13}C NMR ($CDCl_3$): δ 173.1 [C=O Bip], 156.5, 156.3, 154.74, 154.69, 154.5 [C=O Boc and $C_{Ar}O$], 136.2, 134.0, 129.6, 129.2, 128.4, 128.2, 127.9, 126.2, 125.5, 125.3, 123.8, 122.2, 122.1, 120.8, 117.2, 117.1, 112.2 [C_{Ar}], 80.1 [C−O Boc], 70.6, 70.3, 70.2, 70.1, 69.9, 68.5 [OCH_2], 67.8 [C^{α} Bip], 52.3 [OCH_3], 41.4 [$ArCH_2$ Bip], 38.0 [$ArC'H_2$ Bip], 28.2 [CH_3 Boc]. $[\alpha]_{589}^{25}$ −10, $[\alpha]_{578}^{25}$ −10, $[\alpha]_{546}^{25}$ −14, $[\alpha]_{436}^{25}$ −7, $[\alpha]_{365}^{25}$ +181 (*c* 0.1, MeOH). ESI$^+$ MS *m/z* (relative intensity): 864 (15) $[M+K]^+$, 848 (100) $[M+Na]^+$, 826 (3) $[M+H]^+$. Anal. Calcd for $C_{50}H_{51}NO_{10}\cdot 1.5H_2O$ (852.940): C, 70.40; H, 6.38; N, 1.64. Found: C, 70.75; H, 6.39; N, 1.65.

4.4. Boc-(S)-Bip[(S)-Binol-22-C-6]-OMe (SS)-1

Mp, R_f, ^{1}H NMR and ^{13}C NMR ($CDCl_3$): see above (*RR*)-**1**. $[\alpha]_{589}^{25}$ +10, $[\alpha]_{578}^{25}$ +9, $[\alpha]_{546}^{25}$ +9, $[\alpha]_{436}^{25}$ −4, $[\alpha]_{365}^{25}$ −204 (*c* 0.1, MeOH) [*Note*: The experimental absolute values $[\alpha]_{\lambda}^{25}$ are not the same as for the enantiomer (*RR*)-**1** (vide supra) because of measurement imprecision. Even the sign of $[\alpha]_{436}^{25}$ is opposite, as compared to (*RR*)-**1**, in the sensitive zone close to zero]. ESI$^+$ MS *m/z* (relative intensity): 848 (100) $[M+Na]^+$ Anal. Calcd for $C_{50}H_{51}NO_{10}\cdot 0.5H_2O$ (834.924): C, 71.92; H, 6.28; N, 1.68. Found: C, 71.91; H, 6.17; N, 1.36.

4.5. Boc-(S)-Bip[(R)-Binol-22-C-6]-OMe (SR)-1

Amorphous solid, mp 152 °C, R_f 0.14 (I). ^{1}H NMR ($CDCl_3$): δ 8.00 [d, J=9.0 Hz, 2H, ArH Binol], 7.91 [d, J=8.0 Hz, 2H, ArH Binol], 7.42 [d, J=9.0 Hz, 1H, ArH Binol], 7.41 [d, J=8.9 Hz, 1H, ArH Binol], 7.37−7.21 [m, 6H, 4ArH Binol and 2ArH Bip], 7.15 [d, J=8.4 Hz, 2H, ArH Binol], 6.87−6.80 [m, 4H, ArH Bip], 4.82 [br s, 1H, NH Bip], 4.22−4.16 [m, 2H, OCH_2], 4.00−3.86 [m, 6H, OCH_2], 3.75 [s, 3H, OCH_3], 3.57−3.33 [m, 8H, OCH_2], 3.15 [d, J=12.9 Hz, 1H, $ArCH_A$ Bip], 2.95 [br s, 2H, $ArC'H_2$ Bip], 2.25 [d, J=12.9 Hz, 1H, $ArCH_B$ Bip], 1.48 [s, 9H, CH_3 Boc]. ^{13}C NMR ($CDCl_3$): δ 173.2 [C=O Bip], 156.4, 156.2, 154.5, 154.0, 153.9 [C=O Boc and $C_{Ar}O$], 136.4, 134.2, 129.3, 129.2, 128.3, 128.1, 127.8, 126.2, 125.4, 125.2, 125.0, 123.7, 123.6, 121.9, 121.8, 120.4, 120.3, 115.4, 115.2, 115.1, 111.0, 110.9 [C_{Ar}], 80.1 [C−O Boc], 69.6, 69.50, 69.47, 69.2, 67.9, 67.8 [OCH_2], 67.7 [C^{α} Bip], 52.3 [OCH_3], 41.5 [$ArCH_2$ Bip], 37.9 [$ArC'H_2$ Bip], 28.2 [CH_3 Boc]. $[\alpha]_{589}^{25}$ +240, $[\alpha]_{578}^{25}$ +241, $[\alpha]_{546}^{25}$ +284, $[\alpha]_{436}^{25}$ +567, $[\alpha]_{365}^{25}$ +1300 (*c* 0.1, MeOH). ESI$^+$ MS *m/z* (relative intensity): 864 (10) $[M+K]^+$, 848 (100) $[M+Na]^+$, 826 (3) $[M+H]^+$. Anal. Calcd for $C_{50}H_{51}NO_{10}\cdot 1.5H_2O$ (852.940): C, 70.40; H, 6.38; N, 1.64. Found: C, 70.53; H, 6.26; N, 1.64.

4.6. Boc-(R)-Bip[(S)-Binol-22-C-6]-OMe (RS)-1

Mp, R_f, ^{1}H NMR and ^{13}C NMR ($CDCl_3$): see above (*SR*)-**1**. $[\alpha]_{589}^{25}$ −236, $[\alpha]_{578}^{25}$ −250, $[\alpha]_{546}^{25}$ −293, $[\alpha]_{436}^{25}$ −586, $[\alpha]_{365}^{25}$ −1321 (*c* 0.1, MeOH). ESI$^+$ MS *m/z* (relative intensity): 848 (100) $[M+Na]^+$. Anal. Calcd for $C_{50}H_{51}NO_{10}\cdot 0.5H_2O$ (834.924): C, 71.92; H, 6.28; N, 1.68. Found: C, 72.14; H, 6.36; N, 1.68.

4.7. Cleavage of (RR)-1 by boron tribromide

To a solution of (*RR*)-**1** (0.045 g; 0.054 mmol) in CH_2Cl_2 (5 mL) kept under argon atmosphere and cooled to −10 °C was added a 1 M solution of BBr_3 in CH_2Cl_2 (1.5 mL; 1.5 mmol). The reaction mixture was stirred at room temperature for 40 h, cooled to 0 °C, quenched with MeOH (25 mL), concentrated in vacuo at 30 °C to ca. 15 mL (CH_2Cl_2 off), and diluted to ca. 40 mL by addition of MeOH. The solution was then cooled to 0 °C and $SOCl_2$ (5 mL) was added dropwise. The reaction mixture was stirred at room temperature for 4 days, and then evaporated in vacuo. To the residue were successively added ice (ca. 25 mL), H_2O (ca. 25 mL), and EtOAc (ethyl acetate) (ca. 25 mL). The mixture was magnetically stirred and made basic by addition of solid $NaHCO_3$ (by

portions). The diluted organic phase (EtOAc, ca. 100 mL) was decanted, washed with H_2O (2×100 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was purified by chromatography on a preparative TLC plate of silica gel using eluant (II) to afford 0.0084 g (54%) of (*R*)-Binol, pure by ^1H NMR and TLC, with $[\alpha]_{589}^{25}$ +29 (*c* 0.84, THF), maximum lit.[46] $[\alpha]_D^{25}$ +34 (*c* 1.1, THF), and 0.068 g (42%) of (*R*)-H-Bip[OH]$_2$-OMe, identified by comparison with an authentic sample,[36] pure by ^1H NMR and TLC, with $[\alpha]_{436}^{25}$ −93 (*c* 0.14, MeOH), maximum lit.[36] $[\alpha]_{436}^{25}$ −137 (*c* 0.1, MeOH).

4.8. Mosher's amido ester derivatives of (SS)-1 and (RS)-1

To a solution of (*SS*)-**1** (16.5 mg; 0.020 mmol) in CH_2Cl_2 (3 mL) cooled to 0 °C was added TFA (1 mL). The solution was magnetically stirred at 0 °C for 1 h, then at room temperature for 2 h, and evaporated in vacuo at 25 °C. The residue was dissolved in CH_2Cl_2 (100 mL), the solution was successively washed with 5% aq $NaHCO_3$ (50 mL) and H_2O (50 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The resulting crude amino ester was dissolved in CH_2Cl_2 (1 mL) and the solution divided into two portions of ca. 0.5 mL each, to which were, respectively, added the symmetrical anhydrides previously prepared in situ by stirring at room temperature for 2 h: (a) a solution of (−)-(*S*)-MTPA (24.5 mg; 0.105 mmol) and EDC (10.0 mg; 0.052 mmol) in CH_3CN (1 mL), and (b) a solution of (+)-(*R*)-MTPA (19.5 mg; 0.083 mmol) and EDC (8.0 mg; 0.042 mmol) in CH_3CN (1 mL). The solutions were magnetically stirred at room temperature for 48 h, diluted with CH_2Cl_2 (100 mL), successively extracted with 0.5 N HCl (50 mL), H_2O (100 mL), 5% $NaHCO_3$ (50 mL), and H_2O (100 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude products were purified by chromatography on preparative TLC plates of silica gel with eluant (I), care being taken not to exercise a mechanical separation of one of the diastereomers on top of the other, to afford: (a) the amido ester *S*(*SS*)-**1**, MTPA (6.9 mg; 73%). ^1H NMR ($CDCl_3$): δ 7.94 [d, $J\approx$9.0 Hz, 2H], 7.88 [d, $J\approx$8.1 Hz, 2H], 7.65−7.61 [m, 2H], 7.55−7.46 [m, 5H], 7.37−7.32 [m (t-like), 2H], 7.26−7.19 [m, 2H], 7.16−7.11 [m, 3H], 7.08−7.03 [m (t-like), 2H], 6.88−6.82 [m, 4H], and 6.48 [d, $J\approx$7.1 Hz, 1H] [23 ArH and NHCO], 4.29−4.21 [m, 2H, OCH_2], 4.06−3.83 [m, 6H, OCH_2], 3.73 [s (integration≈97.5%), 3H, $COOCH_3$], 3.67 [s (integration≈2.5%), $COOCH_3$ from the *S*(*RR*)-**1**, MTPA isomer (vide infra)], 3.61−3.39 [m, 8H, OCH_2], 3.45 [m, 3H, OCH_3 MTPA], 3.25 [d, J=12.9 Hz, 1H, $ArCH_AH_B$ Bip], 2.95 [d, J=14.0 Hz, 1H, $ArC'H_AH_B$ Bip], 2.86 [d, J=14.1 Hz, 1H, $ArC'H_AH_B$ Bip], 2.32 [d, J=12.9 Hz, 1H, $ArCH_AH_B$ Bip]. ^{19}F NMR ($CDCl_3$): −69.1680 [s, CF_3], [CF_3 from the *S*(*RR*)-**1**, MTPA isomer at −69.2085 (vide infra) not seen]. For a better separation of the two signals: ^{19}F NMR (toluene-d_8): −68.9857 [s (integration≈97.5%), CF_3], −69.1275 [s (integration≈2.5%), CF_3 from the *S*(*RR*)-**1**, MTPA isomer (vide infra)]. (b) The amido ester *R*(*SS*)-**1**, MTPA (6.4 mg; 68%). ^1H NMR ($CDCl_3$): δ 7.94 [d, $J\approx$8.9 Hz, 2H], 7.88 [d, $J\approx$8.1 Hz, 2H], 7.55−7.51 [m, 4H], 7.42−7.32 [m, 5H], 7.23−7.08 [m, 7H], 6.92−6.86 [m (t-like), 2H], 6.81 [d, $J\approx$7.1 Hz, 1H], and 6.75 [d, $J\approx$7.3 Hz, 1H] [23 ArH and NHCO], 4.31−4.22 [m, 2H, OCH_2], 4.10−3.83 [m, 6H, OCH_2], 3.73 [s (integration≈1.5%), $COOCH_3$ from the *S*(*SS*)-**1**, MTPA isomer (vide supra)], 3.67 [s (integration≈98.5%), 3H, $COOCH_3$], 3.62−3.40 [m, 8H, OCH_2], 3.31 [m, 3H, OCH_3 MTPA], 3.09 [d, J=12.9 Hz, 1H, $ArCH_AH_B$ Bip], 3.08 [d, J=14.0 Hz, 1H, $ArC'H_AH_B$ Bip], 3.01 [d, J=14.0 Hz, 1H, $ArC'H_AH_B$ Bip], 2.40 [d, J=12.9 Hz, 1H, $ArCH_AH_B$ Bip]. ^{19}F NMR ($CDCl_3$): −69.2085 [s, CF_3], [CF_3 from the *S*(*SS*)-**1**, MTPA isomer at −69.1680 (vide supra) not seen]. For a better separation of the two signals: ^{19}F NMR (toluene-d_8): −68.9857 [s (integration≈1.5%), CF_3 from the *S*(*SS*)-**1**, MTPA isomer (vide supra)], −69.1275 [s (integration≈98.5%), CF_3].

In the same manner, to a solution of (*RS*)-**1** (16.5 mg; 0.020 mmol) in CH_2Cl_2 (3 mL) cooled to 0 °C was added TFA (1 mL). The solution was treated as above. The resulting crude amino ester was dissolved in CH_2Cl_2 (1 mL) and the solution divided into two portions of ca. 0.5 mL each, which were, respectively, added to the symmetrical anhydrides previously prepared in situ by stirring at room temperature for 2 h: (a) a solution of (−)-(*S*)-MTPA (20.7 mg; 0.088 mmol) and EDC (8.6 mg; 0.045 mmol) in CH_3CN (1 mL), and (b) a solution of (+)-(*R*)-MTPA (19.8 mg; 0.084 mmol) and EDC (8.0 mg; 0.04 mmol) in CH_3CN (1 mL). The solutions were magnetically stirred at room temperature for 48 h, diluted with CH_2Cl_2 (100 mL), and extracted as above. The crude products were purified by chromatography on preparative TLC plates of silica gel with eluant (I), care being taken not to exercise a mechanical separation of one of the diastereomers on top of the other, to afford: (a) the amido ester *S*(*RS*)-**1**, MTPA (6.2 mg; 66%). ^1H NMR ($CDCl_3$): δ 7.99 [d, $J\approx$9.0 Hz, 2H], 7.90 [d, $J\approx$8.1 Hz, 2H], 7.56−7.52 [m, 2H], 7.44−7.20 [m, 11H], 7.14−7.08 [m, 3H], 6.87−6.81 [m, 3H], and 6.77 [d, $J\approx$7.3 Hz, 1H] [23 ArH and NHCO], 4.24−4.12 [m, 2H, OCH_2], 4.02−3.81 [m, 6H, OCH_2], 3.73 [s (integration≈2.5%), $COOCH_3$ from the *S*(*SR*)-**1**, MTPA isomer (vide infra)], 3.67 [s (integration≈97.5%), 3H, $COOCH_3$], 3.61−3.35 [m, 8H, OCH_2], 3.31 [m, 3H, OCH_3 MTPA], 3.10 [d, J=12.9 Hz, 1H, $ArCH_AH_B$ Bip], 3.08 [d, $J\approx$14.1 Hz, 1H, $ArC'H_AH_B$ Bip], 3.03 [d, $J\approx$14.1 Hz, 1H, $ArC'H_AH_B$ Bip], 2.40 [d, J=12.9 Hz, 1H, $ArCH_AH_B$ Bip]. ^{19}F NMR ($CDCl_3$): −69.2355 [s, CF_3], [CF_3 from the *S*(*SR*)-**1**, MTPA isomer at −69.2018 (vide infra) not seen]. For a better separation of the two signals: ^{19}F NMR (toluene-d_8): −68.9924 [s (integration≈2.5%), CF_3 from the *S*(*SR*)-**1**, MTPA isomer (vide infra)], −69.1477 [s (integration≈97.5%), CF_3]. (b) The amido ester *R*(*RS*)-**1**, MTPA (5.9 mg; 63%). ^1H NMR ($CDCl_3$): δ 7.99 [d, $J\approx$8.7 Hz, 2H], 7.89 [d, $J\approx$8.1 Hz, 2H], 7.67−7.60 [m, 2H], 7.51−7.45 [m, 3H], 7.41 [d, $J\approx$9.1 Hz, 2H], 7.34 [m (t-like), $J\approx$7.3 Hz, 2H], 7.24−7.19 [m, 3H], 7.17−7.10 [m, 3H], 6.89−6.80 [m, 4H], and 6.50 [d, $J\approx$7.3 Hz, 1H] [23 ArH and NHCO], 4.24−4.11 [m, 2H, OCH_2], 4.01−3.79 [m, 6H, OCH_2], 3.73 [s (integration≈97.5%), 3H, $COOCH_3$], 3.67 [s (integration≈2.5%), $COOCH_3$ from the *R*(*SR*)-**1**, MTPA isomer (vide supra)], 3.60−3.31 [m, 8H, OCH_2], 3.42 [m, 3H, OCH_3 MTPA], 3.26 [d, J=13.1 Hz, 1H, $ArCH_AH_B$ Bip], 2.97 [d, J=13.9 Hz, 1H, $ArC'H_AH_B$ Bip], 2.86 [d, J=13.9 Hz, 1H, $ArC'H_AH_B$ Bip], 2.32

[d, J=12.9 Hz, 1H, $ArCH_B$ Bip]. ^{19}F NMR ($CDCl_3$): −69.2018 [s, CF_3], [CF_3 from the *R*(*SR*)-**1**, MTPA isomer at −69.2355 (vide supra) not seen]. For a better separation of the two signals: ^{19}F NMR (toluene-d_8): −68.9924 [s (integration ≈97.5%), CF_3], −69.1477 [s (integration ≈2.5%), CF_3 from the *R*(*SR*)-**1**, MTPA isomer (vide supra)].

4.9. Boc-(R)-Bip[(S)-Binol-22-C-6]-L-Ala-OMe (2a)

The amino ester (*RS*)-**1** (360 mg; 0.43 mmol) was dissolved in a mixture of THF (10 mL) and MeOH (7 mL), and water (3.5 mL) was added. Sodium hydroxide (300 mg) was added, and the mixture was heated on a 50 °C bath for 16 h. The mixture was allowed to cool, and the organic solvents were removed under reduced pressure. The resulting mixture was cooled on an ice bath, and the pH was adjusted to ≈1 by addition of 1 N HCl. The mixture was diluted with water and extracted with CH_2Cl_2 three times. The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to give Boc-(*R*)-Bip[(*S*)-Binol-22-C-6]-OH (354 mg; 99%), which was pure by TLC, R_f 0.21 (II), and was not characterized further. This compound (246 mg; 0.29 mmol) was dissolved in THF (7 mL) and CH_2Cl_2 (7 mL), and HCl·H-L-Ala-OMe (121 mg; 0.876 mmol) was added. The mixture was cooled on an ice bath, and DIEA (0.3 mL) and HATU (165 mg; 0.435 mmol) were added. The mixture was stirred at room temperature for 16 h. The mixture was concentrated and the resulting residue was taken up in CH_2Cl_2. The solution was washed successively with 0.5 N HCl, water, and a saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (IV) to give **2a** (246 mg; 94%). Amorphous solid, mp 148 °C, R_f 0.43 (IV). ^1H NMR ($CDCl_3$): δ 7.99 [d, J=8.8 Hz, 2H, ArH], 7.88 [d, J=8.1 Hz, 2H, ArH], 7.43–7.11 [m, 10H, ArH], 6.91–6.78 [m, 5H, ArH, NH], 4.69 [br s, 1H, NH], 4.61 [m, 1H, CH^{α} Ala], 4.23–4.12 [m, 2H, OCH_2], 3.99–3.82 [m, 6H, OCH_2], 3.77 [s, 3H, OCH_3], 3.58–3.35 [m, 8H, OCH_2], 3.17 [d, J=13.1 Hz, 1H, $ArCH_2$], 2.98–2.94 [br m, 2H, $ArCH_2$ Bip], 2.17 [d, J=12.9 Hz, 1H, $ArC'H_2$], 1.47 [s, 9H, CH_3 Boc], 1.39 [d, 3H, CH_3 Ala]. ^{13}C NMR ($CDCl_3$): δ 174.6 [C=O], 156.6, 156.3, 154.8, 154.2 [C=O Boc, $C_{Ar}O$], 143.7, 136.7, 134.5, 129.5, 129.5, 128.4, 128.0, 126.5, 125.6, 123.8, 121.9, 120.6, 115.5, 115.4, 111.2 [C_{Ar}], 81.3 [CO Boc], 69.7, 69.7, 69.4, 69.4, 68.0, 67.9 [C^{α} Bip, OCH_2], 52.5 [OCH_3], 50.5 [C^{α} Ala], 42.5 [$ArCH_2$ Bip], 39.9 [$ArC'H_2$ Bip], 28.5 [CH_3 Boc], 18.1 [CH_3 Ala]. $[\alpha]_{589}^{25}$ −187, $[\alpha]_{578}^{25}$ −196, $[\alpha]_{546}^{25}$ −227, $[\alpha]_{436}^{25}$ −454, $[\alpha]_{365}^{25}$ −1057 (*c* 0.2, CH_2Cl_2). ESI^+ MS *m/z* (relative intensity): 919 (100) $[M+Na]^+$. Anal. Calcd for $C_{53}H_{56}N_2O_{11}\cdot H_2O$ (915.01): C, 69.56; H, 6.39; N, 3.06. Found: C, 69.19; H, 6.33; N, 3.09.

4.10. Fmoc-L-Ala-(R)-Bip[(S)-Binol-22-C-6]-L-Ala-OMe (3a)

The dipeptide **2a** (252 mg; 0.28 mmol) was dissolved in CH_2Cl_2 (6 mL) and the solution was cooled on an ice bath. TFA (1.5 mL) was added. The mixture was kept at 0 °C for 15 min, then at room temperature for 2 h. The mixture was concentrated, then CH_2Cl_2 was added twice to the residue and the resulting solution was evaporated in vacuo. The residue was dissolved in THF (7 mL) and cooled on an ice bath. DIEA (0.12 mL; 0.70 mmol) and Fmoc-L-Ala-NCA (237 mg; 0.70 mmol) were added. The mixture was stirred at room temperature for 48 h. The mixture was concentrated and the resulting residue was taken up in CH_2Cl_2. The solution was washed successively with 0.5 N HCl, water, and a saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (IV) to give **3a** (191 mg; 63%). Amorphous solid, mp 152 °C, R_f 0.32 (IV). ^1H NMR ($CDCl_3$): δ 7.99 [d, J=13.8 Hz, 2H, ArH Binol], 7.88 [d, J=12.1 Hz, 2H, ArH Binol], 7.79–7.01 [m, 17H, ArH], 6.91–6.70 [m, 5H, ArH], 6.06 [br s, 1H, NH], 5.32 [br s, 1H, NH], 4.55 [m, 1H, CH^{α} Ala], 4.36 [m, 2H, CH_2 Fmoc], 4.21–4.15 [m, 3H, CH^{α} Ala, OCH_2], 4.06–3.84 [m, 7H, CH Fmoc, OCH_2], 3.72 [s, 3H, OCH_3], 3.47–3.26 [m, 8H, OCH_2], 3.24–2.96 [m, 3H, $ArCH_2$ Bip], 2.27 [d, J=12.9 Hz, 1H, $ArC'H_2$ Bip], 1.39–1.30 [m, 6H, 2 CH_3 Ala]. ^{13}C NMR ($CDCl_3$): δ 173.8, 172.2, 171.2 [C=O], 156.6, 156.3, 154.3, 154.2 [$C_{Ar}O$], 143.9, 141.5, 137.3, 136.3, 134.5, 129.6, 129.5, 128.5, 128.4, 128.0, 127.4, 127.3, 126.5, 125.6, 125.6, 125.2, 123.8, 122.7, 121.9, 120.7, 120.6, 120.2, 115.6, 115.4, 111.4, 111.1 [C_{Ar}], 69.8, 69.7, 69.7, 69.5, 69.4, 69.1, 68.0, 67.3 [CH_2 Fmoc, C^{α} Bip, OCH_2], 52.4 [OCH_3], 51.5, 48.5 [C^{α} Ala], 47.3 [CH Fmoc], 42.2 [$ArCH_2$ Bip], 36.3 [$ArC'H_2$ Bip], 18.1, 17.9 [CH_3 Ala]. $[\alpha]_{589}^{25}$ −173, $[\alpha]_{578}^{25}$ −183, $[\alpha]_{546}^{25}$ −213, $[\alpha]_{436}^{25}$ −430, $[\alpha]_{365}^{25}$ −996 (*c* 0.2, CH_2Cl_2). ESI^+ MS *m/z* (relative intensity): 1128 (26) $[M+K]^+$, 1112 (100) $[M+Na]^+$. Anal. Calcd for $C_{66}H_{63}N_3O_{12}\cdot H_2O$ (1108.204): C, 71.53; H, 5.91; N, 3.79. Found: C, 71.34; H, 5.88; N, 3.58.

4.11. Boc-L-Ala-L-Ala-(R)-Bip[(S)-Binol-22-C-6]-L-Ala-OMe (4a)

The tripeptide **3a** (144 mg; 0.132 mmol) was dissolved in CH_2Cl_2 (5 mL) and diethylamine (1 mL) was added. The mixture was stirred at room temperature for 7 h. The mixture was concentrated, then CH_2Cl_2 was added twice to the residue and the solution was evaporated in vacuo. The resulting residue was dissolved in CH_2Cl_2 (7 mL), and Boc-L-Ala-OH (50 mg; 0.264 mmol) was added. The mixture was cooled on an ice bath, and HOAt (36 mg; 0.264 mmol) and NMM (0.08 mL) were added. The mixture was stirred for 10 min, and EDC (76 mg; 0.396 mmol) was added. The mixture was then stirred at room temperature for 48 h. The mixture was diluted with CH_2Cl_2, washed successively with 0.5 N HCl, water, then a saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (II) to give **4a** (101 mg; 74%). Amorphous solid, mp 138–141 °C, R_f 0.30 (II). ^1H NMR ($CDCl_3$): δ 7.99 [d, J=8.8 Hz, 2H, ArH Binol], 7.88 [d, J=8.1 Hz, 2H, ArH Binol], 7.42–7.04 [m, 10H, ArH], 6.87–6.80 [m, 4H, ArH], 6.30 [br s, 1H, NH Bip], 4.99 [br s, 1H, NH Ala], 4.52 [m, 1H, CH^{α} Ala], 4.18–4.09 [m, 4H, 2 CH^{α} Ala, OCH_2], 3.97–3.79 [m, 6H, OCH_2], 3.75 [s, 3H, OCH_3], 3.55–3.38 [m, 8H, OCH_2], 3.15 [2d, 2H, $ArCH_2$ Bip], 2.98 [d, J=13.9 Hz, 1H, $ArC'H_2$ Bip], 2.27 [d,

J=12.9 Hz, 1H, ArC′H_2 Bip], 1.42 [s, 9H, CH_3 Boc], 1.37–1.24 [m, 9H, 3 CH_3 Ala]. ^{13}C NMR ($CDCl_3$): δ 173.9, 173.3, 171.9, 171.4 [C=O], 156.6, 156.3, 154.3, 154.2 [C=O Boc and $C_{Ar}O$], 137.4, 136.3, 134.5, 129.6, 129.5, 129.5, 128.5, 128.3, 128.1, 126.6, 126.5, 125.6, 125.6, 125.2, 123.8, 122.7, 122.1, 120.7, 120.6, 115.6, 115.4, 115.4, 111.4, 111.1 [C_{Ar}], 80.6 [C–O Boc], 69.8, 69.7, 69.7, 69.6, 69.5, 69.4, 69.1, 68.0 [OCH_2], 66.7 [C^{α} Bip], 52.5 [OCH_3], 50.2, 48.5 [C^{α} Ala], 42.2 [ArCH_2 Bip], 36.1 [ArC′H_2 Bip], 28.5 [CH_3 Boc], 17.9, 17.7, 17.6 [CH_3 Ala]. $[\alpha]_{589}^{25}$ −287, $[\alpha]_{578}^{25}$ −301, $[\alpha]_{546}^{25}$ −349, $[\alpha]_{436}^{25}$ −683, $[\alpha]_{365}^{25}$ −1466 (c 0.23, MeOH). ESI$^+$ MS m/z (relative intensity): 1061 (100) $[M+Na]^+$. Anal. Calcd for $C_{59}H_{66}N_4O_{13}\cdot H_2O$ (1057.166): C, 67.03; H, 6.48; N, 5.30. Found: C, 66.61; H, 6.17; N, 4.85.

4.12. Boc-(R)-Bip[(S)-Binol-22-C-6]L-Ala-L-Ala-(R)-Bip[(S)-Binol-22-C-6]-L-Ala-OMe (**5a**)

The tetrapeptide **4a** (60 mg; 0.058 mmol) was dissolved in CH_2Cl_2 (5 mL) and the solution was cooled on an ice bath. A solution of HCl in dioxane (approx. 4 N; 1 mL) was added. The mixture was kept at 0 °C for 15 min, then at room temperature for 2 h. The mixture was concentrated, then CH_2Cl_2 was added twice to the residue and the solution was evaporated in vacuo. The residue was dissolved in THF (2 mL) and CH_2Cl_2 (2 mL), and Boc-(*R*)-Bip[(*S*)-Binol-22-C-6]-OH (50 mg; 0.061 mmol) was added. The mixture was cooled on an ice bath, and DIEA (0.06 mL) and HATU (33 mg; 0.087 mmol) were added. The mixture was stirred at room temperature for 16 h. The mixture was concentrated and the resulting residue was taken up in CH_2Cl_2. The solution was washed successively with 0.5 N HCl, water, then a saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by TLC (II) to give **5a** (63 mg; 62%). Amorphous solid, mp 191–194 °C, R_f 0.45 (II). ^{1}H NMR ($CDCl_3$): δ 7.99 [d, 4H, ArH Binol], 7.89 [d, 4H, ArH Binol], 7.42–7.12 [m, 20H, ArH], 6.94–6.74 [m, 8H, ArH], 6.59 [br s, 1H, NH], 6.50 [br s, 1H, NH], 4.95 [br s, 1H, NH], 4.55 [m, 1H, CH^{α} Ala], 4.16 [m, 6H, 2 CH^{α} Ala, OCH_2], 3.96–3.76 [m, 12H, OCH_2], 3.74 [s, 3H, OCH_3], 3.56–3.25 [m, 18H, ArCH_2 Bip, OCH_2], 3.21 [d, J=14.6 Hz, 1H, ArCH_2 Bip], 3.05 [d, J=13.8 Hz, 1H, ArCH_2 Bip], 2.76 [2d, 2H, ArCH_2 Bip], 2.43 [d, J=12.9 Hz, 1H, ArCH_2 Bip], 2.13 [d, J=12.5 Hz, 1H, ArCH_2 Bip], 1.44 [s, 9H, CH_3 Boc], 1.38 [m, 9H, 3 CH_3 Ala]. ^{13}C NMR ($CDCl_3$): δ 174.0, 173.1, 172.7, 172.2, 171.7 [C=O], 156.8, 156.4, 156.2, 156.1, 154.3, 154.2, 154.1 [C=O Boc and $C_{Ar}O$], 137.8, 136.8, 134.4, 129.5, 129.4, 128.0, 126.5, 125.6, 123.8, 122.6, 120.6, 120.5, 115.6, 115.5, 115.4, 115.2, 111.4, 111.2, 111.1 [C_{Ar}], 81.3 [C–O Boc], 69.7, 69.6, 69.3, 69.1, 68.0 [C^{α} Bip, OCH_2], 52.3 [OCH_3], 51.0, 50.9, 48.4 [C^{α} Ala], 42.4, 42.2, 38.7, 35.8 [ArCH_2 Bip], 28.5 [CH_3 Boc], 17.7, 17.2, 16.8 [CH_3 Ala]. $[\alpha]_{589}^{25}$ −219, $[\alpha]_{578}^{25}$ −230, $[\alpha]_{546}^{25}$ −268, $[\alpha]_{436}^{25}$ −551, $[\alpha]_{365}^{25}$ −1304 (c 0.27, CH_2Cl_2). ESI$^+$ MS m/z (relative intensity): 1755.7 (5) $[M+Na]^+$, 897.4 (24) $[M+K+Na]^{2+}$, 889.4 (100) $[M+2Na]^{2+}$. HR-ESI-TOF MS m/z calcd for $C_{103}H_{105}N_5O_{20}Na$: 1754.7251; found: 1754.7181. Anal. Calcd for $C_{103}H_{105}N_5O_{20}\cdot H_2O$ (1750.926): C, 70.65; H, 6.16; N, 4.00. Found: C, 70.59; H, 6.11; N, 4.21.

4.13. Fmoc-{L-Ala-(R)-Bip[(S)-Binol-22-C-6]-L-Ala}$_2$-OMe (**6a**)

The pentapeptide **5a** (29 mg; 0.017 mmol) was dissolved in CH_2Cl_2 (5 mL) and the solution was cooled on an ice bath. A solution of HCl in dioxane (appx. 4 N; 0.5 mL) was added. The mixture was kept at 0 °C for 15 min, then at room temperature for 5 h. The mixture was concentrated, then CH_2Cl_2 was added twice to the residue and the solution was evaporated in vacuo. The residue was dissolved in THF (2 mL) and cooled on an ice bath. DIEA (0.015 mL) and Fmoc-L-Ala-NCA (17 mg; 0.05 mmol) were added. The mixture was stirred at room temperature for 48 h. The mixture was concentrated and the resulting residue was taken up in CH_2Cl_2. The solution was washed successively with 0.5 N HCl, water, then a saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (II) to give **6a** (20 mg; 61%). Amorphous solid, mp 169–172 °C, R_f 0.38 (II). ^{1}H NMR ($CDCl_3$): δ 7.99 [d, 4H, ArH], 7.88 [d, 4H, ArH], 7.73 [m, 2H, ArH], 7.40–7.09 [m, 25H, ArH], 6.95–6.53 [m, 9H, ArH], 6.36 [br s, 1H, NH], 6.05 [br s, 1H, NH], 4.58 [m, 1H, CH^{α} Ala], 4.18 [m, 9H, 3 CH^{α} Ala, CH_2 Fmoc, OCH_2], 3.94–3.76 [m, 13H, CH Fmoc, OCH_2], 3.70 [s, 3H, OCH_3], 3.52–3.24 [m, 16H, OCH_2], 3.04–2.90 [m, 3H, ArCH_2 Bip], 2.73 [d, 1H, ArCH_2 Bip], 2.56 [d, 2H, ArCH_2 Bip], 2.37 [m, 2H, ArCH_2 Bip], 1.44–1.34 [m, 12H, 4 CH_3 Ala]. $[\alpha]_{589}^{25}$ −159, $[\alpha]_{578}^{25}$ −166, $[\alpha]_{546}^{25}$ −194, $[\alpha]_{436}^{25}$ −400 (c 0.23, CH_2Cl_2). ESI$^+$ MS m/z (relative intensity): 986.0 (100) $[M+2Na]^{2+}$. HR-ESI-TOF MS m/z calcd for $C_{116}H_{112}N_6O_{21}Na$: 1947.7778; found: 1947.7802. Anal. Calcd for $C_{116}H_{112}N_6O_{21}\cdot 3H_2O$ (1980.152): C, 70.35; H, 6.01; N, 4.25. Found: C, 70.24; H, 6.17; N, 4.25.

4.14. Boc-Aib-(R)-Bip[(S)-Binol-22-C-6]-OH (**2b**)

The amino ester (*RS*)-**1** (171 mg; 0.207 mmol) was dissolved in a mixture of THF (6 mL), and MeOH (4 mL) and water (2 mL) was added. Sodium hydroxide (250 mg) was added, and the mixture was heated on a 50 °C bath for 16 h. The mixture was allowed to cool, and the organic solvents were removed under reduced pressure. The resulting mixture was cooled on an ice bath, and the pH was adjusted to ≈1 with 1 N HCl. The mixture was diluted with water and extracted with CH_2Cl_2 three times. The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to give crude Boc-(*R*)-Bip[(*S*)-Binol-22-C-6]-OH. This compound was dissolved in CH_2Cl_2 (6 mL) and the solution was cooled on an ice bath. TFA (2 mL) was added. The mixture was kept at 0 °C for 10 min, then at room temperature for 3 h. The mixture was concentrated, then CH_2Cl_2 was added twice to the residue and the solution was evaporated in vacuo to give crude TFA·H-(*R*)-Bip[(*S*)-Binol-22-C-6]-OH as a light brown solid, which was not characterized further. To this compound was added THF (7 mL), and the mixture was cooled on an ice bath. DIEA (0.1 mL) and

Boc-Aib-NCA (142 mg; 0.62 mmol) were added. The mixture was kept at 0 °C for 5 min then stirred at 50 °C for 60 h. The mixture was concentrated and the resulting residue was taken up in CH_2Cl_2. The solution was washed with 0.5 N HCl, the phases separated, and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (II) to give **2b** (128 mg; 69%). Amorphous solid, mp 229 °C, R_f 0.57 (III). ^{1}H NMR ($CDCl_3$): δ 7.99 [d, J=13.1 Hz, 2H, ArH], 7.88 [d, J=12.2 Hz, 2H, ArH], 7.43–7.10 [m, 9H, ArH], 6.96–6.79 [m, 5H, ArH Bip], 5.38 [br s, 1H, NH Aib], 4.15–4.11 [m, 2H, OCH_2], 3.91–3.74 [m, 6H, OCH_2], 3.47–3.39 [m, 8H, OCH_2], 3.16 [br d, 1H, $ArCH_A$ Bip], 2.87 [br s, 2H, $ArC'H_2$ Bip], 2.07 [br d, 1H, $ArCH_B$ Bip], 1.43–1.31 [m, 15H, $2CH_3$ Aib, CH_3 Boc]. ^{13}C NMR ($CDCl_3$): δ 177.9, 174.6 [C=O], 156.4, 156.0, 155.1, 154.3, 154.2 [C=O Boc and $C_{Ar}O$], 139.3, 138.1, 134.4, 129.5, 129.4, 128.1, 126.5, 125.6, 125.2, 123.8, 120.7, 120.6, 115.6, 110.6 [C_{Ar}], 80.4 [C–O Boc], 69.6, 69.3 [OCH_2], 67.9 [C^{α} Bip], 57.0 [C^{α} Aib], 28.5 [CH_3 Boc], 26.4, 25.0 [CH_3 Aib]. $[\alpha]_{589}^{25}$ −138, $[\alpha]_{578}^{25}$ −146, $[\alpha]_{546}^{25}$ −171, $[\alpha]_{436}^{25}$ −364, $[\alpha]_{365}^{25}$ −937 (c 0.2, CH_2Cl_2). ESI$^+$ MS m/z (relative intensity): 941 (29) $[M+2Na]^+$, 919 (100) $[M+Na]^+$. Anal. Calcd for $C_{53}H_{56}N_2O_{11}\cdot 2.5H_2O$ (942.034): C, 67.57; H, 6.52; N, 2.97. Found: C, 67.64; H, 6.51; N, 2.64.

4.15. Boc-Aib-(R)-Bip[(S)-Binol-22-C-6]-L-Ala-OMe (3b)

The dipeptide **2b** (90 mg; 0.1 mmol) was dissolved in THF (3 mL) and CH_2Cl_2 (3 mL), and HCl·H-L-Ala-OMe (41 mg; 0.3 mmol) was added. The mixture was cooled on an ice bath, and DIEA (0.1 mL) and HATU (57 mg; 0.15 mmol) were added. The mixture was stirred at room temperature for 48 h and then evaporated. The resulting residue was taken up in CH_2Cl_2. The solution was washed successively with 0.5 N HCl, water, then a saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by TLC (II) to give **3b** (71 mg; 72%). Amorphous solid, mp 157 °C, R_f 0.63 (II). ^{1}H NMR ($CDCl_3$): δ 7.99 [d, 2H, ArH], 7.88 [d, 2H, ArH], 7.60–7.09 [m, 11H, ArH], 6.83–6.78 [m, 3H, ArH Bip], 6.68 [br d, 1H, NH], 6.16 [br s, 1H, NH], 4.85 [br s, 1H, NH], 4.57 [m, 1H, CH^{α} Ala], 4.48–4.11 [m, 2H, OCH_2], 4.00–3.79 [m, 6H, OCH_2], 3.76 [s, 3H, OCH_3], 3.56–3.36 [m, 8H, OCH_2], 3.15 [br s, 2H, $ArCH_2$ Bip], 2.87 [d, 1H, $ArCH_2$ Bip], 2.25 [d, 1H, $ArCH_2$ Bip], 1.50–1.43 [m, 18H, CH_3 Aib, CH_3 Ala, CH_3 Boc]. ^{13}C NMR ($CDCl_3$): δ 174.4, 172.9, 171.2 [C=O], 156.5, 156.0, 155.3, 154.3, 154.1 [C=O Boc and $C_{Ar}O$], 138.6, 136.0, 134.4, 134.4, 129.5, 129.5, 129.4, 128.4, 128.0, 126.5, 126.4, 125.6, 125.1, 123.8, 122.9, 122.5, 120.7, 120.6, 115.6, 115.3, 111.4, 110.7 [C_{Ar}], 81.3 [C–O Boc], 69.9, 69.8, 69.6, 69.4, 69.4, 68.5, 68.0 [OCH_2, C^{α} Bip], 57.3 [C^{α} Aib], 52.2 [OCH_3], 48.4 [C^{α} Ala], 28.4 [CH_3 Boc], 27.7, 23.4 [CH_3 Aib], 17.2 [CH_3 Ala]. $[\alpha]_{589}^{25}$ −154, $[\alpha]_{578}^{25}$ −162, $[\alpha]_{546}^{25}$ −190, $[\alpha]_{436}^{25}$ −385, $[\alpha]_{365}^{25}$ −920 (c 0.23, CH_2Cl_2). ESI$^+$ MS m/z (relative intensity): 1020 (22) $[M+K]^+$, 1004 (52) $[M+Na]^+$. Anal. Calcd for $C_{57}H_{63}N_3O_{12}\cdot H_2O$ (1000.114): C, 68.45; H, 6.55; N, 4.20. Found: C, 68.38; H, 6.71; N, 3.91.

4.16. Fmoc-L-Ala-Aib-(R)-Bip[(S)-Binol-22-C-6]-L-Ala-OMe (4b)

The tripeptide **3b** (79 mg; 0.08 mmol) was dissolved in CH_2Cl_2 (3 mL) and the solution was cooled on an ice bath. TFA (0.75 mL) was added. The mixture was kept at 0 °C for 15 min, then at room temperature for 3 h. The mixture was concentrated, then CH_2Cl_2 was added twice to the residue and the solution was evaporated in vacuo. The residue was dissolved in THF (3 mL) and cooled on an ice bath. DIEA (0.04 mL) and Fmoc-L-Ala-NCA (81 mg; 0.24 mmol) were added. The mixture was stirred at room temperature for 72 h. The mixture was concentrated and the resulting residue was taken up in CH_2Cl_2. The solution was washed successively with 0.5 N HCl, water, then a saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by TLC (II) to give **3a** (80 mg; 85%). Amorphous solid, mp 163–165 °C, R_f 0.43 (II). ^{1}H NMR ($CDCl_3$): δ 7.99 [d, 2H, ArH], 7.89 [d, 2H, ArH], 7.75 [d, 2H, ArH], 7.61 [m, 2H, ArH], 7.42–7.11 [m, 14H, ArH], 6.80–6.65 [m, 4H, ArH], 6.45 [br d, 1H, NH], 5.38 [br s, 1H, NH], 4.52 [m, 2H, CH^{α} Ala], 4.29–4.15 [m, 4H, CH_2 Fmoc, OCH_2], 3.95–3.76 [m, 7H, CH Fmoc, OCH_2], 3.67 [s, 3H, OCH_3], 3.49–3.38 [m, 8H, OCH_2], 3.22 [d, 1H, $ArCH_2$ Bip], 3.10 [d, 1H, $ArCH_2$ Bip], 3.01 [d, 1H, $ArCH_2$ Bip], 2.35 [d, 1H, $ArCH_2$ Bip], 1.48–1.27 [m, 12H, 2 CH_3 Aib, 2 CH_3 Ala]. ^{13}C NMR ($CDCl_3$): δ 174.4, 173.1, 172.6, 171.8 [C=O], 156.7, 156.4, 156.0, 154.3, 154.2 [$C_{Ar}O$], 144.4, 143.6, 141.5, 141.4, 138.7, 136.5, 134.4, 129.5, 129.5, 129.4, 128.2, 128.0, 128.0, 127.9, 127.8, 127.2, 126.5, 125.8, 125.6, 125.5, 125.4, 125.3, 125.2, 123.8, 123.0, 122.5, 120.7, 120.6, 120.1, 115.6, 115.4, 111.3, 110.7 [C_{Ar}], 69.8, 69.7, 69.7, 69.5, 69.4, 69.1, 68.9, 68.0, 67.9, 67.6 [CH_2 Fmoc, C^{α} Bip, OCH_2], 57.4 [C^{α} Aib], 52.1 [OCH_3], 51.4, 48.4 [C^{α} Ala], 47.1 [CH Fmoc], 42.9 [$ArCH_2$ Bip], 34.4 [$ArC'H_2$ Bip], 27.7, 23.1 [CH_3 Aib] 17.3, 17.1 [CH_3 Ala]. $[\alpha]_{589}^{25}$ −161, $[\alpha]_{578}^{25}$ −170, $[\alpha]_{546}^{25}$ −198, $[\alpha]_{436}^{25}$ −409, $[\alpha]_{365}^{25}$ −970 (c 0.26, CH_2Cl_2). ESI$^+$ MS m/z (relative intensity): 1198 (100) $[M+Na]^+$. Anal. Calcd for $C_{70}H_{70}N_4O_{13}\cdot 2H_2O$ (1211.324): C, 69.40; H, 6.16; N, 4.62. Found: C, 69.49; H, 5.98; N, 4.65.

4.17. Boc-(R)-Bip[(S)-Binol-22-C-6]-L-Ala-Aib-(R)-Bip[(S)-Binol-22-C-6]-L-Ala-OMe (5b)

The tetrapeptide **4b** (23 mg; 0.019 mmol) was dissolved in CH_2Cl_2 (2 mL) and diethylamine (0.5 mL) was added. The mixture was stirred at room temperature for 5 h. The mixture was concentrated, then CH_2Cl_2 was added twice to the residue and the solution was evaporated in vacuo. The residue was dissolved in THF (1 mL) and CH_2Cl_2 (1 mL), and Boc-(*R*)-Bip[(*S*)-Binol-22-C-6]-OH (20 mg; 0.025 mmol) was added. The mixture was cooled on an ice bath, and DIEA (0.05 mL) and HATU (14 mg, 0.037 mmol) were added. The mixture was stirred at room temperature for 16 h. The mixture was concentrated and the resulting residue was taken up in CH_2Cl_2. The solution was washed successively with 0.5 N HCl, water, then a saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and evaporated. The

residue was purified by TLC (II) to give **5b** (21 mg; 61%). Amorphous solid, mp 202–205 °C, R_f 0.43 (II). ^{1}H NMR ($CDCl_3$): δ 7.99 [d, 4H, ArH], 7.88 [d, 4H, ArH], 7.42–7.03 [m, 21H, NH, ArH], 6.86–6.64 [m, 9H, NH, ArH], 5.07 [br s, 1H, NH], 4.53 [m, 1H, CH^{α} Ala], 4.13 [m, 4H, OCH_2], 3.93–3.87 [m, 7H, CH^{α} Ala, OCH_2], 3.81–3.62 [m, 6H, OCH_2], 3.72 [s, 3H, OCH_3], 3.48–3.33 [m, 17H, $ArCH_2$ Bip, OCH_2], 3.23–2.98 [m, 4H, $ArCH_2$ Bip], 2.55 [d, 1H, J=13.7 Hz, $ArCH_2$ Bip], 2.40 [d, J=12.7 Hz, 1H, $ArCH_2$ Bip], 2.11 [d, J=12.5 Hz, 1H, $ArCH_2$ Bip], 1.51–1.47 [m, 9H, $2CH_3$ Aib, CH_3 Ala], 1.43 [s, 9H, CH_3 Boc], 1.38 [m, 3H, CH_3 Ala]. ^{13}C NMR ($CDCl_3$): δ 175.1, 173.5, 173.1, 172.8, 171.9 [C=O], 156.6, 156.2, 155.9, 154.3, 154.2, 154.1, 153.4 [C=O Boc and $C_{Ar}O$], 136.8, 136.4, 134.4, 129.5, 129.4, 128.3, 128.1, 126.5, 126.4, 125.7, 125.6, 125.5, 123.8, 121.7, 120.8, 120.7, 120.5, 115.8, 115.6, 111.2, 111.1 [C_{Ar}], 80.9 [C–O Boc], 69.7, 69.6, 69.5, 69.3, 69.1, 68.9, 68.5, 68.2, 68.1, 68.0, 67.9, 67.8 [C^{α} Bip, OCH_2], 57.4 [C^{α} Aib], 52.3 [OCH_3], 50.8, 48.2 [C^{α} Ala], 42.8, 41.4, 36.8, 34.3 [$ArCH_2$ Bip], 28.5 [CH_3 Boc], 27.6, 23.3 [CH_3 Aib] 17.3 [CH_3 Ala]. $[\alpha]^{25}_{589}$ −184, $[\alpha]^{25}_{578}$ −194, $[\alpha]^{25}_{546}$ −226, $[\alpha]^{25}_{436}$ −459, $[\alpha]^{25}_{365}$ −1085 (c 0.25, CH_2Cl_2). ESI$^+$ MS m/z (relative intensity): 912 (14) $[M+2K]^{2+}$, 904 (63) $[M+K+Na]^{2+}$, 896 (100) $[M+2Na]^{2+}$. HR-ESI-TOF MS m/z calcd for $C_{104}H_{107}N_5O_{20}Na$: 1768.7407; found: 1768.7404. Anal. Calcd for $C_{104}H_{107}N_5O_{20}\cdot 3H_2O$ (1800.984): C, 69.35; H, 6.32; N, 3.89. Found: C, 69.31; H, 6.31; N, 3.89.

*4.18. Boc-{Aib-(R)-Bip[(S)-Binol-22-C-6]-L-Ala}$_2$-OMe (**6b**)*

The pentapeptide **5b** (9 mg; 0.005 mmol) was dissolved in CH_2Cl_2 (1 mL) and the solution was cooled on an ice bath. TFA (0.3 mL) was added. The mixture was kept at 0 °C for 15 min, then at room temperature for 4 h. The mixture was concentrated, then CH_2Cl_2 was added twice to the residue and the solution was evaporated in vacuo. To this residue was added THF (1 mL), and the mixture was cooled on an ice bath. DIEA (0.05 mL) and Boc-Aib-NCA (15 mg, 0.065 mmol) were added. The mixture was kept at 0 °C for 5 min, then stirred at 50 °C for 10 days. The mixture was concentrated and the residue was purified by TLC (II) to give **6b** (3 mg; 33%). Amorphous solid, mp 229 °C, R_f 0.59 (II). [*Note*: ^{1}H NMR and ^{13}C NMR spectra, optical rotation $[\alpha]^{25}_{\lambda}$ measurements, and elemental analysis were not performed because of the low amount of compound available]. ESI$^+$ MS m/z (relative intensity): 939 (100) $[M+2Na]^{2+}$. HR-ESI-TOF MS m/z calcd for $C_{108}H_{114}N_6O_{21}Na$: 1853.7935; found: 1853.7919.

4.19. FTIR absorption analysis

The FTIR absorption spectra were recorded with a Perkin–Elmer model 1720X spectrophotometer, nitrogen-flushed, equipped with a sample shuttle device, at 2 cm^{-1} nominal resolution, averaging 100 scans. Cells with path lengths of 0.1, 1.0, and 10 mm (with CaF_2 windows) were used. Spectrograde deuteriochloroform (99.8% D) was purchased from Aldrich. Solvent (baseline) spectra were recorded under the same conditions.

4.20. ^{1}H NMR analysis

The NMR spectra for conformational analysis were recorded with a Bruker AM 400 spectrometer. Measurements were performed in deuteriochloroform (99.96% D, Acros Organics) with tetramethylsilane as the internal standard.

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