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Induced Axial Chirality in the Biphenyl Core of the Proatropoisomeric, C^{α}-Tetrasubstituted α-Amino Acid Residue Bip in Peptides**

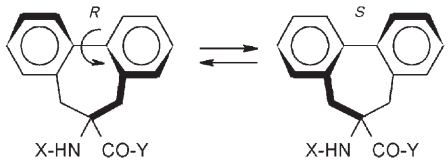
Jean-Paul Mazaleyrat,[b] Karen Wright,[b] Anne Gaucher,[b] Nathalie Toulemonde,[b] Laurence Dutot,[b] Michel Wakselman,[b] Quirinus B. Broxterman,[c] Bernard Kaptein,[c] Simona Oancea,[a] Cristina Peggion,[a] Marco Crisma,[a] Fernando Formaggio,[a] and Claudio Toniolo*[a]

Abstract: An induced axial chirality in the biphenyl core of the 2′,1′:1,2;1″,2″:3,4-dibenzcyclohepta-1,3-diene-6-amino-6-carboxylic acid (Bip) residue, a conformationally labile, atropoisomeric, C^{α}-tetrasubstituted α-amino acid, was observed by CD and ^{1}H NMR spectroscopic techniques in the linear dipeptides Boc-Bip-Xaa*-OMe where Boc = *tert*-butoxycarbonyl, OMe = methoxy, and Xaa* = D- and/or L-Ala, -Val, -Leu, -Phe, -(αMe)Val and -(αMe)Leu. Chiral induction was significantly lower in the isomeric dipeptides Boc-Xaa*-Bip-OMe, with the Xaa* residue located at the N-terminus of Bip, as well as in the cyclic dipeptide cyclo-[Bip-L-Ala]. The results obtained in solution were confirmed by X-ray diffraction analysis of a crystalline sample of Boc-(R)-Bip-D-Ala-OMe.

Keywords: atropoisomerism · biphenyl compounds · chirality · circular dichroism · peptides

Introduction

In the past few years, several peptides based on the 2′,1′:1,2;1″,2″:3,4-dibenzcyclohepta-1,3-diene-6-amino-6-carboxylic acid residue (Bip),[1,2] a C^{α}-tetrasubstituted α-amino acid formally derived from 1-amino-cycloheptane-1-carboxylic acid,[3] have been prepared and investigated by our groups.[4–6] These studies revealed that Bip behaves as a turn/helix inducer and favors the 3_{10}-helical secondary structure[7] in the homopeptides $(Bip)_n$ as well as in selected Bip/Ala and Bip/Gly peptides. Bip is also a conformationally labile, atropoisomeric amino acid with interconverting, nonresolvable *R* and *S* enantiomers.[2,4–6] This phenomenon is characterized by a rotational energy barrier of about 14 kcal mol^{-1}, as observed for other seven-membered 2,2′-bridged biphenyl derivatives.[8,9] As such, Bip may exhibit induced atropoisomerism and act as a reporter for chiral interactions with other amino acids in peptides of the type X-Bip-Y (X and/or Y = chiral amino acid residue Xaa*; Scheme 1).



Scheme 1. Conformational equilibrium (proatropoisomerism) of the X-Bip-Y peptides.

Induction of axial chirality in conformationally flexible biphenyl systems by interaction with chiral auxiliaries is well documented and has been exploited in molecular recognition studies as well as in asymmetric catalysis.[10–14] Central-

[a] Dr. S. Oancea, Dr. C. Peggion, Dr. M. Crisma, Prof. F. Formaggio, Prof. C. Toniolo
Institute of Biomolecular Chemistry, CNR, Department of Chemistry
University of Padova, via Marzolo 1, 35131 Padova (Italy)
Fax: (+39) 049-827-5239
E-mail: claudio.toniolo@unipd.it

[b] Dr. J.-P. Mazaleyrat, Dr. K. Wright, Dr. A. Gaucher, N. Toulemonde, L. Dutot, Dr. M. Wakselman
SIRCOB, UMR CNRS 8086
University of Versailles, 78035 Versailles (France)

[c] Dr. Q. B. Broxterman, Dr. B. Kaptein
DSM Research, Life Sciences, Advanced Synthesis and Catalysis
P.O. Box 18, 6160 MD Geleen (The Netherlands)

[**] Bip = 2′,1′:1,2;1″,2″:3,4-dibenzcyclohepta-1,3-diene-6-amino-6-carboxylic acid.

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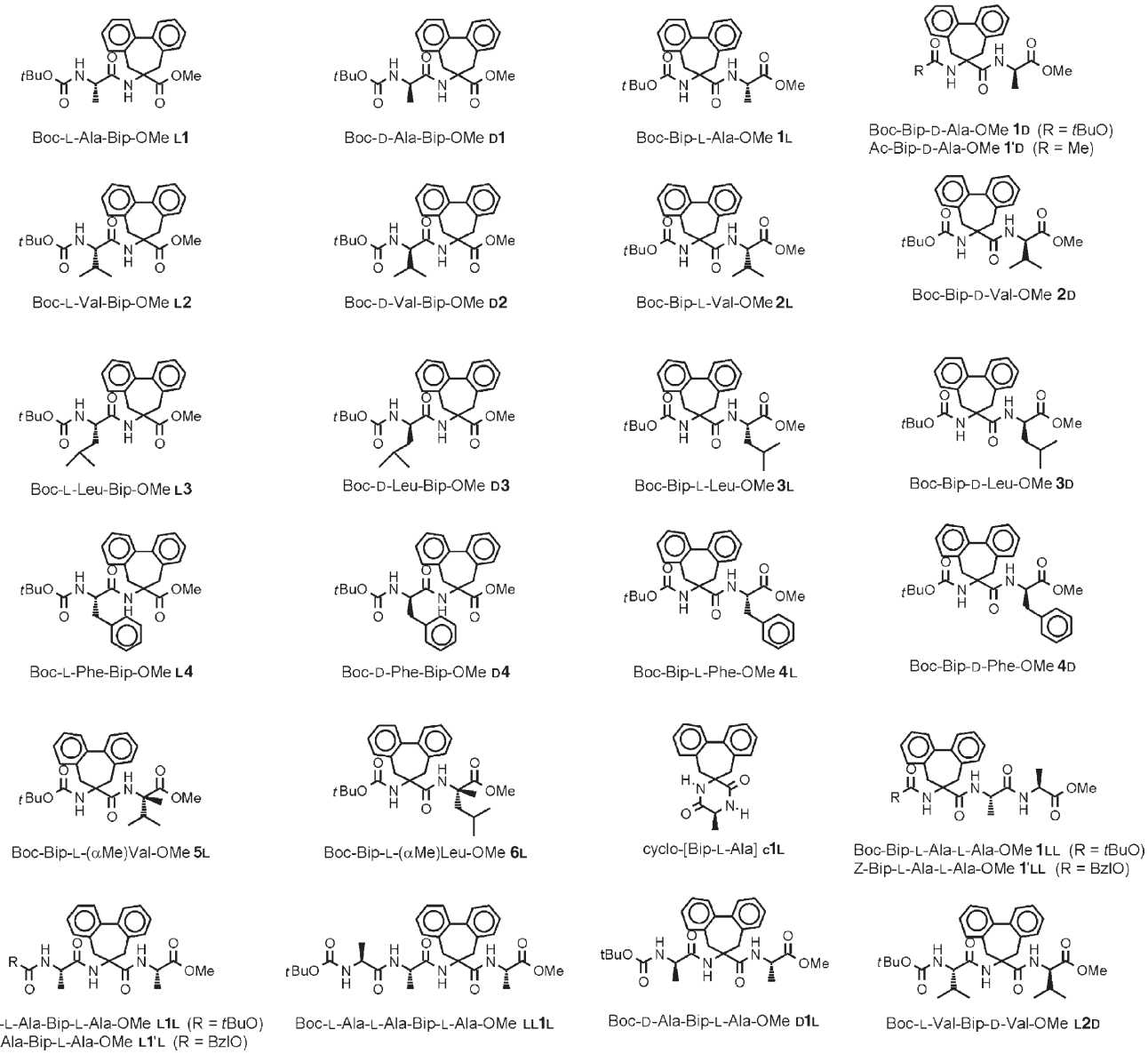
to-axial transfer of chirality results in an induced circular dichroism (ICD)[15] of the biphenyl chromophore, which has been used as a tool for determination of the absolute configuration of chiral 1,2- and 1,3-diols by means of biphenyldioxolane derivatives[9] and of chiral secondary alcohols in dinitrodiphenic esters[16] (or 2,2′-binaphthyl esters[17]). ICD was also observed in diphenimides,[18,19] with a concomitant induced homohelicity being demonstrated in diphenimide bis-propellers.[18] Recently, by taking advantage of both the atropoisomeric nature and the conformational lability of the Bip residue, we have demonstrated the occurrence of a central-to-axial transfer of chirality in terminally protected Bip/Val dipeptides as well as a novel process of chiral propagation/amplification in a series of $(Bip)_n$/Val 3_{10}-helical oligopeptides.[20] Herein we report the full set of our results relative to the induced axial chirality in the biphenyl core of the Bip residue in an extended series of Bip/Xaa* linear dipeptides and some tri/tetrapeptides with Xaa* = Ala (**1**), Val (**2**), Leu (**3**), Phe (**4**), C^{α}-methyl valine ((αMe)Val; **5**), and (C^{α}-methyl leucine ((αMe)Leu; **6**) residues of L and/or D configuration at the C- and/or N-terminal positions of Bip, as well as in the cyclic dipeptide cyclo-[Bip-L-Ala] (**c1L**) (Scheme 2).[21]

Results and Discussion

Synthesis: The starting derivatives Boc-Bip-OH,[2] Z-Bip-OH,[2] and H-Bip-OMe,[20] were readily obtained from the α-amino ester H-Bip-O*t*Bu (O*t*Bu = *tert*-butoxy), which was



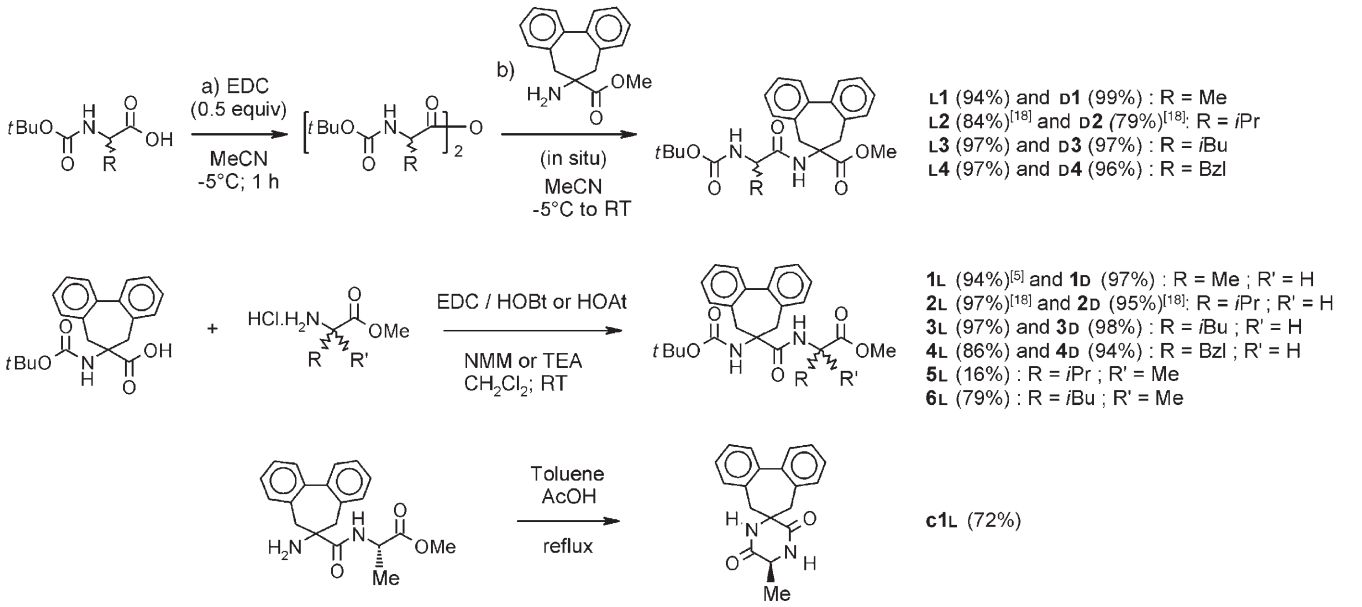
Scheme 2. Peptides discussed in this work. Boc = *tert*-butoxycarbonyl, Z = benzyloxycarbonyl, OMe = methoxy.

synthesized by phase-transfer bis-alkylation of a glycine *tert*-butyl ester Schiff base, as previously reported.[2] The Bip/Xaa* dipeptides **L1–4**, **D1–4**, **1–6L**, and **1–4D** were prepared in solution by using symmetrical anhydride activation[22] for coupling at the N-terminus of Bip and *N*-ethyl-*N*′-(3-dimethylaminopropyl)-carbodiimide (EDC)/1-hydroxy-1,2,3-benzotriazole (HOBt)[23] or EDC/7-aza-1-hydroxy-1,2,3-benzotriazole (HOAt)[24] activation for coupling at its C-terminus (Scheme 3). These methods are all known to be efficient in difficult cases involving sterically demanding C^{α}-tetrasubstituted α-amino acids.[25] High yields (79–99%) were generally obtained, except for the coupling of Boc-Bip-OH with H-L-(αMe)Val-OMe by the EDC/HOAt method, which gave **5L** in a much lower yield (16%) than the similar coupling of Boc-Bip-OH with H-L-(αMe)Leu-OMe to give **6L** (79%), apparently because of more severe steric interference.

In the same manner, coupling of Boc-Bip-OH or Z-Bip-OH with H-(L-Ala)$_2$-OMe by the EDC/HOBt method furnished the tripeptides **1LL** (97%) and **1′LL**,[6] respectively, while the symmetrical anhydride method was applied for the acylation of the *N*-deprotected dipeptides H-Bip-L-Ala-OMe and H-Bip-D-Val-OMe to afford the tripeptides with a central Bip residue: **L1L**[6] (chain elongated to **LL1L**[6]), **L1′L**,[6] **D1L** (81%), and **L1D** (42%). Finally, direct cyclization of H-Bip-L-Ala-OMe in toluene/AcOH at 110°C[26] gave **c1L** (72%).

^{1}H NMR analysis: In general, the ^{1}H NMR spectra of the Bip/Xaa* peptides exhibit broadened signals at room temperature, especially for the Bip benzylic protons. At about 233 K, two different sets of signals could be observed, corresponding to the presence of two diastereomeric conformers slowly exchanging on the NMR timescale, with either unequal or nearly equal populations depending on both the peptide sequence and the solvent ($CDCl_3$ or CD_3OD). Fast-interconverting conditions, which resulted in the presence of only a single set of signals, were reached at about 333 K, as is expected from the rotational energy barrier of 14 kcal mol^{-1} along the 1–1′ bond of the biphenyl moiety.[1,2] Evolution of the ^{1}H NMR signals as a function of temperature for the dipeptides Boc-Bip-D-Ala-OMe (**1D**) and Boc-D-Ala-Bip-OMe (**D1**) in CD_3OD is shown as a representative example (Figure 1). The Bip benzylic protons were generally resolved at 333 K into two pairs of doublets reflecting the inequivalency of both the β-carbon atoms and β-protons $ArC_{\beta}H_AH_B$-$ArC_{\beta'}H_AH_B$ of the Bip residue. In most cases, the two doublets at lower field were better resolved (sharper peaks) than the two doublets at higher field, which remained more or less broad, because of a higher coalescence temperature related to a higher difference of the corresponding chemical shifts of the two diastereomeric conformers. At 233 K, the slow exchange between these two conformers resulted in a complex superposition of pairs of doublets for the Bip benzylic protons. However, in some cases (compounds **3L** and **L3** in $CDCl_3$, for example), all pairs of doublets of both conformers (16 peaks) were clearly seen.

The diastereomeric ratio (d.r.) was determined at 233 K by integration of the best separated sets of signals. In this respect, the singlets relating to the NH (Bip) amide group, the COOMe group, and the Boc group are especially suitable for higher accuracy. For *all* of the Boc-Bip-Xaa*-OMe dipeptides, in both $CDCl_3$ and CD_3OD (and also CD_3CN in the case of **1D**), the singlets corresponding to the COOMe group of both diastereomers appeared at a different chemical shift (see the Supporting Information). For this series of N-terminal Bip dipeptides, the Me_3C singlets corresponding to the Boc group were well separated only in the case of **2L** ($CDCl_3$), **3L** ($CDCl_3$), **4L** (CD_3OD), and **5L** ($CDCl_3$). In con-



Scheme 3. Synthesis of the linear and cyclic Bip/Xaa* dipeptides. NMM = *N*-methylmorpholine, TEA = triethylamine.

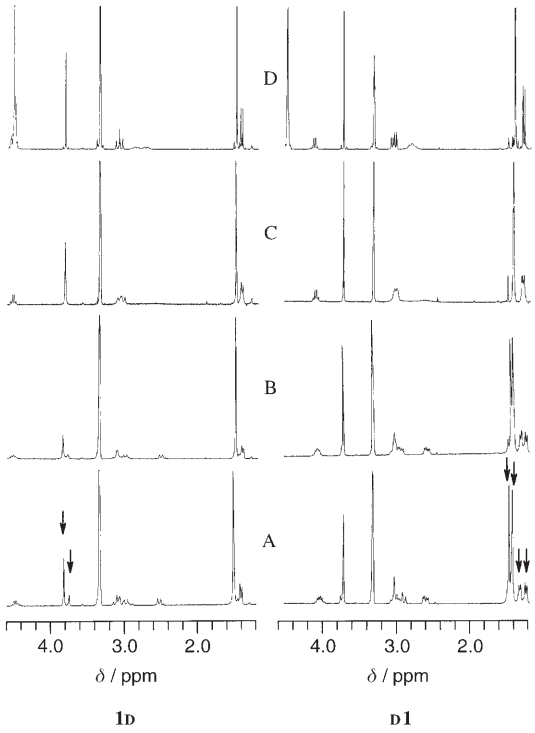


Figure 1. ^{1}H NMR signals ($\delta = 1.2$–4.6 ppm) of the dipeptides Boc-Bip-D-Ala-OMe (**1D**) and Boc-D-Ala-Bip-OMe (**D1**) in CD_3OD, as a function of temperature: A) 233 K (the arrows indicate the separation of the COOMe singlets and the Boc $(CH_3)_3C$/Ala CH_3 signals, in both diastereomeric conformers of **1D** and **D1**, respectively), B) 263 K, C) 293 K, and D) 333 K.

trast, for the Boc-Xaa*-Bip-OMe dipeptides, in both $CDCl_3$ and CD_3OD (and also CD_3CN in the case of **D1**), the Boc Me_3C singlets of both diastereomers were *always* separated, while the COOMe singlets gave a unique (or shouldered) signal in most cases (except for **L4**). Separation of the NH (Bip) amide singlets in $CDCl_3$ was observed for all dipeptides (except **4L**) in both the N-terminal and C-terminal Bip series. The signals relating to NH (Xaa*), H^α (Xaa*), and CH_3 (Xaa*) were separated in some cases, thereby allowing more or less accurate determinations of the d.r. values, which generally confirmed the values obtained from the singlets described above.

Interestingly, for the C^α-tetrasubstituted α-amino acid residues αMeVal (in **5L**) and αMeLeu (in **6L**), the singlets relating to the C^α-methyl group were well separated. Unfortunately, the very low solubility of the Bip/Ala 2,5-dioxopiperazine **c1L** at 233 K in both $CDCl_3$ and CD_3OD prevented any ^{1}H NMR measurement at this temperature. Finally, for the Bip/Ala tripeptides **1LL**, **L1L**, **L1′L**, **D1L**, and **L2D** and for the tetrapeptide **LL1L**, all containing an Xaa* residue (Ala or Val) at the C-terminal position of Bip, the d.r. values could be easily determined from the COOMe and NH (Bip) singlets, which were always separated at 233 K (see the Supporting Information).

The d.r. values for the various peptides (summarized in Table 1) were found to be remarkably dependent on the

Table 1. d.r. values for the two diastereomeric conformers of Bip/Xaa* di-, tri-, and tetrapeptides in $CDCl_3$ and CD_3OD at approximately 233 K.

Xaa*	Boc-Bip-Xaa*-OMe		Boc-Xaa*-Bip-OMe	
	CD_3OD	$CDCl_3$	CD_3OD	$CDCl_3$
Ala	81:19	56:44[a]	51:49	53:47[b]
Val	77:23	52:48	58:42	53:47
Leu	89:11	58:42	57:43	54:46
Phe	58:42	58:42	51:49	56:44
(αMe)Val	80:20	66:34		
(αMe)Leu	70:30	58:42		

Tri- and tetrapeptides	CD_3OD	$CDCl_3$
Z-Bip-L-Ala-L-Ala-OMe	–	55:45[c]
Z-L-Ala-Bip-L-Ala-OMe	–	75:25[c]
Boc-L-Ala-Bip-L-Ala-OMe	–	62:38
Boc-D-Ala-Bip-L-Ala-OMe	84:16	90:10[d]
Boc-L-Val-Bip-D-Val-OMe	–	79:21
Boc-L-Ala-L-Ala-Bip-L-Ala-OMe	–	62:38

[a] 76:24 in CD_3CN. [b] 54:46 in CD_3CN. [c] Reference [6]. [d] 88:12 in CD_3CN.

nature of the solvent. Our initial measurements were performed in $CDCl_3$ and showed relatively low values, in the range of 50:50–60:40, for all the dipeptides (except **5L**) of both the Bip-Xaa* and Xaa*-Bip series. For the tripeptides, the d.r. value of **L1L**, in which an L-Ala residue is located at both the C- and N-terminal positions of Bip, remained low, but this value increased when the Boc protecting group was replaced by the Z group (in the analogue **L1′L**). Low d.r. values were again recorded when two consecutive L-Ala residues, instead of one, were introduced either at the C-terminal position of Bip (**1′LL** compared to **1D**) or at its N-terminal position (**LL1L** compared to **L1L**). Interestingly, the only relatively high d.r. values observed in $CDCl_3$ were those of the tripeptides **D1L** (90:10) and **L2D** (79:21) in which *an Xaa* residue (Ala or Val) of opposite absolute configuration is located on each side of Bip*. It is noteworthy that the d.r. value of **D1L** (the only case examined) remained high when the solvent was changed to either CD_3CN (88:12) or CD_3OD (84:16). For the dipeptides, important changes of the d.r. values could be observed when the ^{1}H NMR spectra were performed in CD_3OD (and also CD_3CN in the case of **1D** and **D1**) instead of $CDCl_3$, depending on the relative position of the Bip and Xaa* residues. Remarkably, while the d.r. values in CD_3OD remained in the same low range (50:50–60:40) as those in $CDCl_3$ for the Xaa*-Bip dipeptides, a significant increase was observed for all of the Bip-Xaa* dipeptides except **4L**, thereby highlighting *the extreme importance of the C-terminal rather than the N-terminal position of the Xaa* residue for the occurrence of a central-to-axial transfer of chirality*, at least in the series of compounds studied in this work. It is worth recalling that CD_3OD is also the solvent that was used in our CD experiments (see below).

CD analysis: The biphenyl chromophore is characterized by an intense electronic transition at about 240–250 nm, assigned to the A band of Suzuki,[27] followed by a very intense transition at approximately 210–215 nm (the C band).

The wavelength of the absorption maximum of the A band is strongly dependent on θ, the biphenyl axial torsion angle.[28–30] Several studies have established that in the CD spectra of biphenyl-based chiral molecules, a negative maximum corresponding to the A band is related to a *P* torsion of the C_{Ar}–C_{Ar} bond.[28–30]

We carried out a detailed CD analysis in MeOH solution of all of the terminally protected Bip di-, tri-, and tetrapeptides depicted in Scheme 2. The most relevant spectra are shown in Figures 2–4. A strong and negative Cotton effect is visible at 250 nm in the spectrum of the Bip-Ala dipeptide **1L**, followed by a couplet, negative at longer wavelength, centered at 215 nm (Figure 2). Not unexpectedly, the CD

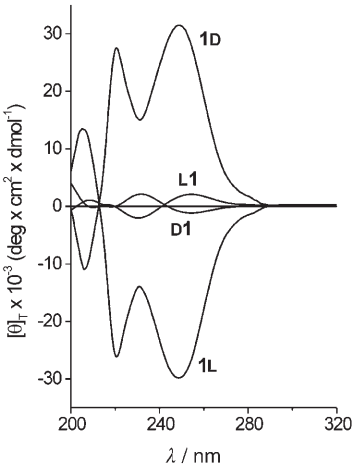


Figure 2. CD spectra (320–200 nm region) in MeOH solution of the Boc/OMe terminally protected Bip/Ala dipeptides **L1**, **D1**, **1L**, and **1D**.

spectrum of **1L** is the mirror image of that of its enantiomer **1D**. Notably, if the Bip residue is located at the C-terminus of the dipeptide sequence (**L1** and **D1**), the CD bands are significantly less intense. Moreover, the relationship between the Ala configuration and the signs of the CD bands in the **L1** and **D1** dipeptides is reversed with respect to that typical of the **1L** and **1D** dipeptides. In any case, here too enantiomeric peptides (**L1** and **D1**) exhibit mirror image CD spectra.

Figure 3 shows that our conclusions for the Bip/Ala dipeptides can be extended to all protein Xaa* residues with an aliphatic side chain. The same effect is seen for the corresponding C^{α}-methylated α-amino acids, even if the CD signals are somewhat weaker for these dipeptides. Conversely, the CD spectra of the Bip/Phe dipeptides **L4**, **D4**, **4L**, and **4D** (not shown) are dominated by the contribution of the aromatic chromophore present in the amino acid side chain.[31–33] The role of solvent (methanol, acetonitrile), temperature (10–50 °C), and bulkiness of the N^{α}-protecting (blocking) group (Boc, as in **1D**, versus Ac, as in **1′D**) are of modest significance (not shown). However, dipeptide cyclization (**c1L**) dramatically changes the CD pattern (not shown) relative to those of both linear dipeptides **L1** and **1L**.

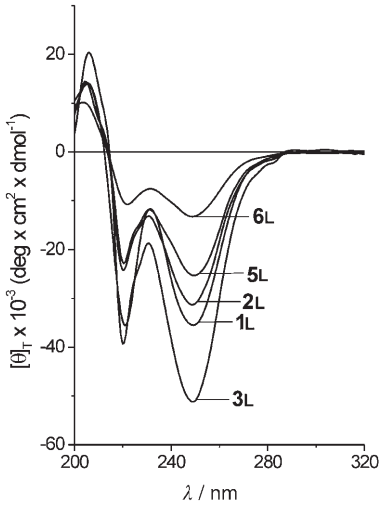


Figure 3. CD spectra (320–200 nm region) in MeOH solution of the Boc/OMe terminally protected Bip-Xaa* dipeptides **1L**, **2L**, **3L**, **5L**, and **6L**.

Indeed, in **c1L** a very weak and positive CD band at 260 nm is followed by two intense and positive bands at 235 and 222 nm.

In the tripeptides of general formula Xaa*-Bip-Yaa* (**L1L**, **D1L**, and **L2D**), CD bands are governed by the configuration of the residue *following* Bip (Yaa*; Figure 4). A strictly

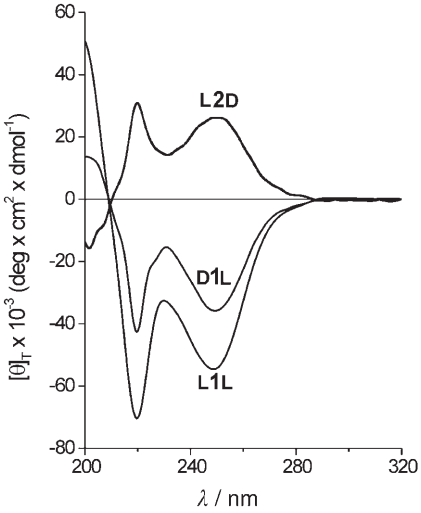


Figure 4. CD spectra (320–200 nm region) in MeOH solution of the Boc/OMe terminally protected Xaa*-Bip-Yaa* tripeptides **L1L**, **D1L**, and **L2D**.

comparable effect is also visible in the CD spectrum of the tetrapeptide **LL1L** (not shown), with two L-Ala residues preceding and one folllowing the Bip residue. Not unexpectedly, the overall CD pattern of the tripeptide **1LL**, with two L-Ala residues following Bip (not shown), resembles that of the Bip-L-Ala dipeptide **1L**, although the Cotton effects are generally of lower intensity. Also, in the tripeptides a change in the N^{α} protection (from Boc to Z: **L1L** versus **L1′L**,

and **1LL** versus **1′LL**) does not produce any remarkable effect on the CD spectra (not shown).

In conclusion, our CD investigation of the Bip-containing peptides, in particular the dipeptides, clearly demonstrated that a *chirality transfer* from L- or D-residues to the atropoisomeric Bip does indeed take place and that this phenomenon occurs more efficiently when the chiral amino acid residue is located at the C-terminus of Bip. In this latter case, a *P* torsion of the Bip biphenyl axial bond is the one that is preferentially induced by an L residue (and an *M* torsion is induced by a D residue). As a consequence, the exploitation of a Bip-Xaa* dipeptide system as a probe permits the chirality of the covalently linked, nonaromatic α-amino acid to be directly correlated to the features of the CD spectrum at approximately 250 nm. Finally, if one compares the diastereomeric ratios obtained by NMR spectroscopy in CD_3OD solution (Table 1) with the relative intensities of the CD spectra in MeOH (Figures 2–4), it turns out that the two sets of data match nicely.

X-ray diffraction analysis: We have grown a single crystal and solved the 3D structure of the terminally protected dipeptide Boc-(*R*)-Bip-D-Ala-OMe (**1D**). Two independent molecules (**A** and **B**) are found in the asymmetric unit (Figure 5). The most significant difference between the two molecules is seen in the conformation of the D-Ala residue, which is a distorted, left-handed helical conformation ($\varphi =$ 83.2(7)°, "ψ" = 17.9(11)°) in molecule **A** and a quasiextended conformation ($\varphi = 117.4(5)°$, "ψ" = 139.3(4)°) in molecule **B**.[34] Conversely, the Bip residue is in a regular, right-handed helical conformation in both molecules ($\varphi = -52.0(5)°$, $\psi = -51.9(5)°$ in molecule **A**, and $\varphi = -64.0(5)°$, $\psi = -45.9(5)°$ in molecule **B**). The Bip configuration, induced by the D-Ala residue, is *R* in both molecules. Interestingly, the relationship between the configuration of the C^{α}-tetrasubstituted Bip residue and its helical screw sense is opposite to that commonly observed for C^{α}-trisubstituted (protein) amino acids.[3] However, it is the same as that found in the crystal state for a related binaphthyl-based α-amino acid in a terminally protected helical hexapeptide.[35] The characteristic Bip biphenyl bond length and side-chain torsion angle in dipeptide **1D** are quite close to those reported for the simple amino acid derivative H-Bip-O*t*Bu:[1] C11–C11′ = 1.498(4) Å (molecule **A**) and C31–C31′ = 1.504(3) Å (molecule **B**); C12–C11–C11′–C12′ = −43.9(3)° (molecule **A**) and C32–C31–C31′–C32′ = −42.7(3)° (molecule **B**).

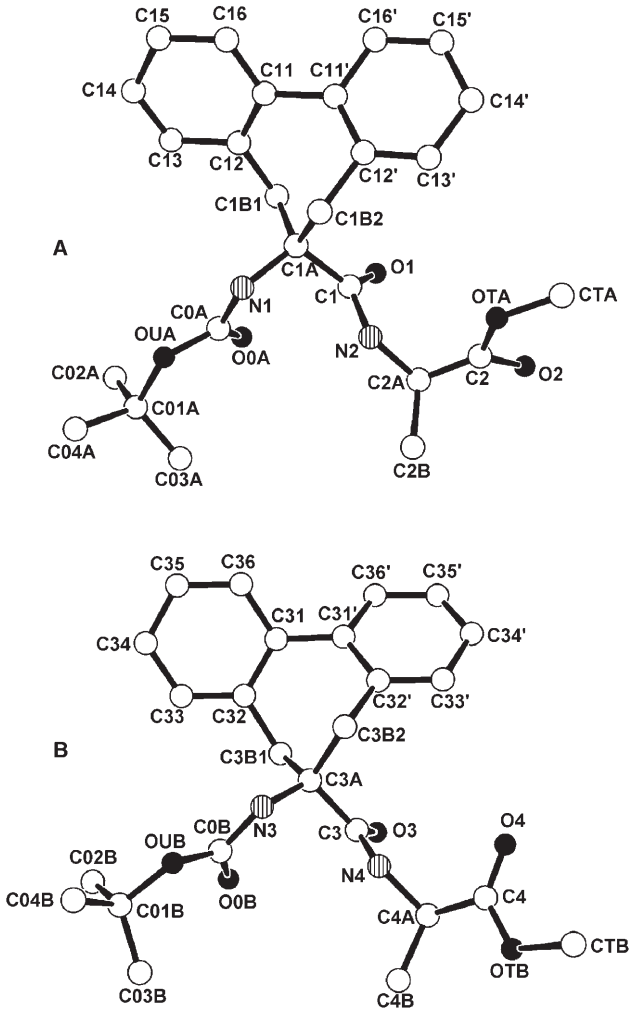


Figure 5. X-ray diffraction structures of the two independent molecules (**A** and **B**) in the asymmetric unit of the terminally protected dipeptide Boc-(*R*)-Bip-D-Ala-OMe (**1D**) with atom numbering.

Conclusion

Bip is a conformationally labile, atropoisomeric, α-amino acid. In this work we have clearly shown by CD and ^{1}H NMR spectroscopic techniques that an axial chirality can be induced in the biphenyl moiety of the Bip residue in peptides containing one or more chiral α-amino acids (Xaa*/Yaa*). We believe that this phenomenon is purely intramolecular in nature. Indeed, self-association is not expected to take place in these systems in view of the relatively high polarity of the solvent used (MeOH) and the low concentration (1×10^{-3} M) and short main-chain lengths (dimers and trimers) of the peptides investigated. Interestingly, the magnitude of this effect is particularly remarkable when the chiral amino acid is positioned at the C-terminus of Bip. At the present stage of our research, the reasons for the observed unidirectionality of the chiral induction are not clear. However, a plausible explanation could be a different degree of steric interference taking place between the extremely bulky Bip side chain and that of the preceding (versus the following) residue. Also, the CD response always correlates with the absolute configuration of the aliphatic Xaa* residue. This phenomenon of chirality transfer, as detected by CD spectroscopy, represents the basis for the *Bip method*, an easy and fast configurational assignment of chiral amino acids, amines, and alcohols currently being developed in our laboratories. More specifically, C-terminal L-Xaa* and D-Xaa* residues preferentially induce *P* and *M* torsions, respectively, in the biphenyl chromophore, as is evi-

dent from the negative and positive ellipticities at 250 nm. In addition, the preferential onset of the Bip *S* and *R* configurations, respectively, has been unambiguously demonstrated by X-ray diffraction. Interestingly, this latter property can be exploited for the construction of foldameric[36] polypeptide structures with a predetermined screw sense. Our combined CD, ^{1}H NMR, and X-ray diffraction results on linear peptides closely match those reported for other biphenyl-based systems (ethers,[9] imides,[19] and lactams[37,38]).

Experimental Section

Synthesis of peptides: Melting points were measured on a Mettler apparatus with a final temperature raise of 3 °C min^{-1} 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, with the solvent, $CDCl_3$ (^{1}H: $\delta = 7.27$ ppm; ^{13}C: $\delta = 77.00$ ppm) or CD_3OD (^{1}H: $\delta = 3.31$ ppm), being used as the internal standard. Splitting patterns are abbreviated as follows: s singlet, d doublet, t triplet, q quartet, and m multiplet. The optical rotations were measured in a 1 dm thermostated cell on a Perkin–Elmer 241 polarimeter, with an accuracy of 0.3%. Elemental analyses were performed by the C.N.R.S. Service of Microanalyses in Gif-sur-Yvette (France). 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: A: MeOH/CH_2Cl_2 (2.5:97.5); B: MeOH/CH_2Cl_2 (5:95). UV light ($\lambda = 254$ nm) allowed visualization of the spots after TLC runs for all compounds. Unless noted otherwise, all starting materials and solvents were obtained from commercial suppliers and were used as received. The syntheses and characterizations of the Bip derivatives Boc-Bip-OH,[2] Z-Bip-OH,[2] and H-Bip-OMe,[20] as well as the peptides Boc-Bip-L-Ala-OMe (**1L**),[6] Z-Bip-L-Ala-L-Ala-OMe (**1′LL**),[6] Boc-L-Ala-Bip-L-Ala-OMe (**L1L**),[6] Z-L-Ala-Bip-L-Ala-OMe (**L1′L**),[6] Boc-L-Ala-L-Ala-Bip-L-Ala-OMe (**LL1L**),[6] Boc-Bip-L-Val-OMe (**2L**),[20] Boc-Bip-D-Val-OMe (**2D**),[20] Boc-L-Val-Bip-OMe (**L2**),[20] and Boc-D-Val-Bip-OMe (**D2**),[20] have already been published. The ^{1}H and ^{13}C NMR data for all of the compounds described below may be found in the Supporting Information.

Boc-Bip-D-Ala-OMe (1D): TEA (0.070 mL; 0.5 mmol) was added to a suspension of Boc-Bip-OH (0.088 g; 0.25 mmol), HCl·H-D-Ala-OMe (0.070 g; 0.5 mmol), and HOBt (0.068 g; 0.5 mmol) in CH_2Cl_2 (4 mL), and this was followed by addition of EDC (0.058 g, 0.30 mmol). The reaction mixture was magnetically stirred at RT for 16 h and then evaporated in vacuo at 25 °C. The residue was diluted with EtOAc (50 mL) and the organic solution was washed with 0.5 N HCl (2×15 mL), H_2O (2×15 mL), 5% $NaHCO_3$ (2×15 mL), and H_2O (2×15 mL), dried over $MgSO_4$, filtered, and evaporated in vacuo. The crude product was chromatographed on a 1.5×24 cm column of silica gel with eluant B to afford pure **1D** (0.106 g; 97%) as a solid. Crystallization from EtOAc/cyclohexane (slow diffusion) gave crystals suitable for an X-ray diffraction analysis: m.p. 203 °C; $[\alpha]_{589}^{25} = +106$; $[\alpha]_{578}^{25} = +115$; $[\alpha]_{546}^{25} = +130$; $[\alpha]_{436}^{25} = +248$; $[\alpha]_{365}^{25} = +472$ ($c = 0.30$ in MeOH); $R_f = 0.60$ (B); elemental analysis calcd (%) for $C_{25}H_{30}N_2O_5$ ($M_W = 438.51$): C 68.47, H 6.90, N 6.39; found: C 68.46, H 7.05, N 6.24.

Boc-D-Ala-Bip-OMe (D1): EDC (0.210 g; 1.1 mmol) was added to a solution of Boc-D-Ala-OH (0.416 g; 2.2 mmol) in CH_3CN (3 mL) cooled to approximately −10 °C (ice/salt bath). The solution was magnetically stirred at temperatures of −10 °C to −5 °C for 1 h and, with the assumption that complete formation of the anhydride [Boc-D-Ala]$_2$O had occurred, a solution of H-Bip-OMe (0.104 g; 0.39 mmol) in CH_3CN (2 mL) and CH_2Cl_2 (5 mL) was then added. The reaction mixture was magnetically stirred at RT for 48 h and evaporated in vacuo at 25 °C. The residue was then diluted with EtOAc (100 mL) and the organic solution was extracted with 0.5 N HCl (2×50 mL), H_2O (50 mL), 5% $NaHCO_3$ (2×50 mL), and H_2O (2×50 mL), dried over $MgSO_4$, filtered, and evaporated in vacuo. The crude product was chromatographed on a 1.5×24 cm column of silica gel with eluant A to afford pure **D1** (0.170 g; 99%) as a solid: m.p. 86 °C; $[\alpha]_{589}^{25} = +26$; $[\alpha]_{578}^{25} = +26$; $[\alpha]_{546}^{25} = +24$; $[\alpha]_{436}^{25} = +39$; $[\alpha]_{365}^{25} = +73$ ($c = 0.07$ in MeOH); $R_f = 0.60$ (B); elemental analysis calcd (%) for $C_{25}H_{30}N_2O_5 \cdot 0.5\,H_2O$ ($M_W = 447.51$): C 67.09, H 6.98, N 6.26; found: C 66.84, H 7.06, N 6.27.

Boc-L-Ala-Bip-OMe (L1): The same experimental procedure as for dipeptide **D1** was used but with H-Bip-OMe (0.067 g; 0.25 mmol). After work-up, the crude product was chromatographed on a 1.5×24 cm column of silica gel with eluant B to afford pure **L1** (0.104 g; 94%) as a solid: m.p. 86 °C; $[\alpha]_{589}^{25} = -21$; $[\alpha]_{578}^{25} = -21$; $[\alpha]_{546}^{25} = -27$; $[\alpha]_{436}^{25} = -45$; $[\alpha]_{365}^{25} = -69$ ($c = 0.20$ in MeOH); $R_f = 0.60$ (B); elemental analysis calcd (%) for $C_{25}H_{30}N_2O_5$ ($M_W = 438.51$): C 68.47, H 6.90, N 6.39; found: C 67.89, H 7.04, N 6.17.

Boc-Bip-L-Leu-OMe (3L): NMM (0.05 mL; 0.4 mmol) was added to a suspension of Boc-Bip-OH (0.0357 g; 0.1 mmol), HCl·H-L-Leu-OMe (0.055 g; 0.5 mmol), and HOAt (0.028 g; 0.2 mmol) in CH_2Cl_2 (2 mL), and this was followed by addition of EDC (0.029 g, 0.15 mmol). The reaction mixture was magnetically stirred at RT for 24 h. Workup as for **1D**, followed by chromatography of the crude product on a 1.5×38 cm column of silica gel with eluant A, afforded pure **3L** (0.0474 g; 98%) as a solid: m.p. 178 °C; $[\alpha]_{589}^{25} = -138$; $[\alpha]_{578}^{25} = -145$; $[\alpha]_{546}^{25} = -168$; $[\alpha]_{436}^{25} = -321$; $[\alpha]_{365}^{25} = -602$ ($c = 0.23$ in MeOH); $R_f = 0.50$ (A); elemental analysis calcd (%) for $C_{28}H_{36}N_2O_5$ ($M_W = 480.58$): C 69.97, H 7.55, N 5.83; found: C 69.88, H 7.61, N 5.69.

Boc-Bip-D-Leu-OMe (3D): The same experimental procedure as for dipeptide **3L** was used but with Boc-Bip-OH (0.0355 g; 0.1 mmol), HCl·H-D-Leu-OMe (0.055 g; 0.5 mmol), HOAt (0.029 g; 0.2 mmol), NMM (0.05 mL; 0.4 mmol), and EDC (0.029 g, 0.15 mmol) in CH_2Cl_2 (2 mL). Workup as for **3L**, followed by chromatography of the crude product on a 1.5×40 cm column of silica gel with eluant A, afforded pure **3D** (0.0474 g; 98%) as a solid: m.p. 175–178 °C; $[\alpha]_{589}^{25} = +139$; $[\alpha]_{578}^{25} = +150$; $[\alpha]_{546}^{25} = +169$; $[\alpha]_{436}^{25} = +324$; $[\alpha]_{365}^{25} = +611$ ($c = 0.20$ in MeOH); $R_f = 0.50$ (A); elemental analysis calcd (%) for $C_{28}H_{36}N_2O_5$ ($M_W = 480.58$): C 69.97, H 7.55, N 5.83; found: C 70.21, H 7.55, N 5.53.

Boc-L-Leu-Bip-OMe (L3): The same experimental procedure and workup as for dipeptide **D1** was used but with H-Bip-OMe (0.0301 g; 0.113 mmol) and the symmetrical anhydride [Boc-L-Leu]$_2$O, with the latter being prepared in situ from Boc-L-Leu-OH (0.105 g; 0.45 mmol) and EDC (0.043 g, 0.22 mmol), in CH_3CN (2 mL). The crude product was chromatographed on a 1.5×38 cm column of silica gel with eluant A to afford pure **L3** (0.0525 g; 97%) as a solid: m.p. 72 °C; $[\alpha]_{589}^{25} = -20$; $[\alpha]_{578}^{25} = -20$; $[\alpha]_{546}^{25} = -22$; $[\alpha]_{436}^{25} = -31$; $[\alpha]_{365}^{25} = -32$ ($c = 0.21$ in MeOH); $R_f = 0.35$ (A); elemental analysis calcd (%) for $C_{28}H_{36}N_2O_5 \cdot 0.7\,H_2O$ ($M_W = 493.20$): C 68.18, H 7.64, N 5.68; found: C 68.25, H 7.81, N 5.74.

Boc-D-Leu-Bip-OMe (D3): The same experimental procedure as for dipeptide **L3** was used but with H-Bip-OMe (0.0281 g; 0.105 mmol) and the symmetrical anhydride [Boc-D-Leu]$_2$O, with the latter being prepared in situ from Boc-D-Leu-OH (0.0973 g; 0.42 mmol) and EDC (0.041 g, 0.21 mmol), in CH_3CN (2 mL). The crude product was chromatographed on a 1.5×38 cm column of silica gel with eluant A to afford pure **D3** (0.0491 g; 97%) as a solid: m.p. 72 °C; $[\alpha]_{589}^{25} = +19$; $[\alpha]_{578}^{25} = +20$; $[\alpha]_{546}^{25} = +21$; $[\alpha]_{436}^{25} = +33$; $[\alpha]_{365}^{25} = +40$ ($c = 0.22$ in MeOH); $R_f = 0.35$ (A); elemental analysis calcd (%) for $C_{28}H_{36}N_2O_5 \cdot 0.5\,H_2O$ ($M_W = 489.59$): C 68.69, H 7.62, N 5.72; found: C 69.06, H 7.71, N 5.71.

Boc-Bip-L-Phe-OMe (4L): The same experimental procedure and workup as for dipeptide **3L** was used but with Boc-Bip-OH (0.0359 g; 0.1 mmol), HCl·H-L-Phe-OMe (0.065 g; 0.3 mmol), HOAt (0.029 g; 0.2 mmol), NMM (0.044 mL; 0.4 mmol), and EDC (0.0292 g, 0.15 mmol) in CH_2Cl_2 (2 mL). The crude product was chromatographed on a 1.5×40 cm column of silica gel with eluant A to afford pure **4L** (0.0452 g; 86%) as a solid: m.p. 172 °C; $[\alpha]_{589}^{25} = -0.5$; $[\alpha]_{578}^{25} = -1.0$; $[\alpha]_{546}^{25} = -2.4$; $[\alpha]_{436}^{25} = +1.9$; $[\alpha]_{365}^{25} = +24$ ($c = 0.21$ in MeOH); $R_f = 0.60$ (A); elemental analysis calcd (%) for $C_{31}H_{34}N_2O_5$ ($M_W = 514.60$): C 72.35, H 6.66, N 5.44; found: C 72.76, H 6.66, N 5.41.

Boc-Bip-D-Phe-OMe (4D): The same experimental procedure and workup as for dipeptide **4L** was used but with Boc-Bip-OH (0.0358 g;

0.1 mmol), HCl·H-D-Phe-OMe (0.065 g; 0.3 mmol), HOAt (0.028 g; 0.2 mmol), NMM (0.05 mL; 0.45 mmol), and EDC (0.029 g, 0.15 mmol) in CH_2Cl_2 (2 mL). The crude product was chromatographed on a 1.5× 40 cm column of silica gel with eluant A to afford pure **4D** (0.0490 g; 94%) as a solid: m.p. 170°C; $[\alpha]_{589}^{25}=0.0$; $[\alpha]_{578}^{25}=0.0$; $[\alpha]_{546}^{25}=0.0$; $[\alpha]_{436}^{25}=-5.1$; $[\alpha]_{365}^{25}=-23$ ($c=0.22$ in MeOH); $R_f=0.60$ (A); elemental analysis calcd (%) for $C_{31}H_{34}N_2O_5\cdot0.5\,H_2O$ ($M_W=523.61$): C 71.10, H 6.74, N 5.35; found: C 70.99, H 6.77, N 5.01.

Boc-L-Phe-Bip-OMe (L4): The same experimental procedure and workup as for dipeptide **D1** was used but with H-Bip-OMe (0.0274 g; 0.103 mmol) and the symmetrical anhydride $[Boc\text{-}L\text{-}Phe]_2O$, with the latter being prepared in situ from Boc-L-Phe-OH (0.111 g; 0.42 mmol) and EDC (0.039 g, 0.20 mmol), in CH_3CN (2 mL). The crude product was chromatographed on a 1.5×38 cm column of silica gel with eluant A to afford pure **L4** (0.0517 g; 97%) as a solid: m.p. 77°C; $[\alpha]_{589}^{25}=-11$; $[\alpha]_{578}^{25}=-14$; $[\alpha]_{546}^{25}=-16$; $[\alpha]_{436}^{25}=-31$; $[\alpha]_{365}^{25}=-39$ ($c=0.21$ in MeOH); $R_f=0.30$ (A); elemental analysis calcd (%) for $C_{31}H_{34}N_2O_5$ ($M_W=514.60$): C 72.35, H 6.66, N 5.44; found: C 72.01, H 6.81, N 5.38.

Boc-D-Phe-Bip-OMe (D4): The same experimental procedure as for dipeptide **L4** was used but with H-Bip-OMe (0.0279 g; 0.105 mmol) and the symmetrical anhydride $[Boc\text{-}D\text{-}Phe]_2O$, with the latter being prepared in situ from Boc-D-Phe-OH (0.0973 g; 0.42 mmol) and EDC (0.041 g, 0.21 mmol), in CH_3CN (2 mL). The crude product was chromatographed on a 1.5×40 cm column of silica gel with eluant A to afford pure **D4** (0.0516 g; 96%) as a solid: m.p. 77°C; $[\alpha]_{589}^{25}=+15$; $[\alpha]_{578}^{25}=+16$; $[\alpha]_{546}^{25}=+18$; $[\alpha]_{436}^{25}=+32$; $[\alpha]_{365}^{25}=+41$ ($c=0.20$ in MeOH); $R_f=0.30$ (A); elemental analysis calcd (%) for $C_{31}H_{34}N_2O_5\cdot0.5\,H_2O$ ($M_W=523.61$): C 71.10, H 6.74, N 5.35; found: C 71.22, H 6.91, N 5.32.

Boc-Bip-L-(αMe)Val-OMe (5L): The same experimental procedure and workup as for dipeptide **4L** was used but with Boc-Bip-OH (0.0362 g; 0.102 mmol), HCl·H-L-(αMe)Val-OMe (0.0302 g; 0.166 mmol), HOAt (0.030 g; 0.22 mmol), NMM (0.035 mL; 0.32 mmol), and EDC (0.033 g, 0.17 mmol) in CH_2Cl_2 (2 mL). The crude product was chromatographed on a 1.5×40 cm column of silica gel with eluant A and then further purified on preparative TLC plates to afford pure **5L** (0.008 g; 16%) as a solid: m.p. 155–159°C; $[\alpha]_{589}^{25}=-48$; $[\alpha]_{578}^{25}=-52$; $[\alpha]_{546}^{25}=-60$; $[\alpha]_{436}^{25}=-118$; ($c=0.23$ in MeOH); $R_f=0.45$ (A); elemental analysis calcd (%) for $C_{28}H_{36}N_2O_5$ ($M_W=480.58$): C 69.97, H 7.55; found: C 69.53, H 8.23.

Boc-Bip-L-(αMe)Leu-OMe (6L): The same experimental procedure and workup as for dipeptide **4L** was used but with Boc-Bip-OH (0.0362 g; 0.102 mmol), HCl·H-L-(αMe)Leu-OMe (0.0301 g; 0.154 mmol), HOAt (0.031 g; 0.23 mmol), NMM (0.035 mL; 0.32 mmol), and EDC (0.032 g, 0.17 mmol) in CH_2Cl_2 (2 mL). The crude product was chromatographed on a 1.5×40 cm column of silica gel with eluant A to afford pure **6L** (0.0403 g; 79%) as a glassy solid: $[\alpha]_{589}^{25}=-13$; $[\alpha]_{578}^{25}=-14$; $[\alpha]_{546}^{25}=-20$; $[\alpha]_{436}^{25}=-42$; ($c=0.23$ in MeOH); $R_f=0.55$ (A); elemental analysis calcd (%) for $C_{29}H_{38}N_2O_5\cdot0.5\,H_2O$ ($M_W=503.62$): C 69.16, H 7.81, N 5.56; found: C 68.76, H 7.81, N 5.53.

Cyclo-[Bip-L-Ala] (c1L): A solution of H-Bip-L-Ala-OMe (0.0473 g; 0.14 mmol) in acetic acid (1.5 mL) and toluene (32 mL) was magnetically stirred at 110°C for 15 h. The clear solution was evaporated in vacuo and the crude product was recrystallized from MeOH to afford pure **c1L** (0.030 g; 72%) as a solid; m.p.> 300°C; $[\alpha]_{589}^{25}=-24$; $[\alpha]_{578}^{25}=-26$; $[\alpha]_{546}^{25}=-28$; $[\alpha]_{436}^{25}=-43$; $[\alpha]_{365}^{25}=-45$ ($c=0.1$ in DMF); $R_f=0.60$ (MeOH/CH_2Cl_2, 1:9); elemental analysis calcd (%) for $C_{28}H_{35}N_3O_6$ ($M_W=509.58$): C 65.99, H 6.92, N 8.25; found: C 65.38, H 7.02, N 7.91.

Boc-Bip-(L-Ala)$_2$-OMe (1LL): The same experimental procedure and workup as for dipeptide **1D** was used but with Boc-Bip-OH (0.088 g; 0.25 mmol), HCl·H-L-Ala-L-Ala-OMe (0.107 g; 0.5 mmol), HOBt (0.068 g; 0.5 mmol), TEA (0.070 mL; 0.5 mmol), and EDC (0.058 g, 0.30 mmol) in CH_2Cl_2 (4 mL). The crude product was chromatographed on a 1.5×24 cm column of silica gel with eluant B to afford pure **1LL** (0.106 g; 97%) as a solid: m.p. 86°C; $[\alpha]_{589}^{25}=-66$; $[\alpha]_{578}^{25}=-71$; $[\alpha]_{546}^{25}=-82$; $[\alpha]_{436}^{25}=-152$; $[\alpha]_{365}^{25}=-268$ ($c=0.2$ in MeOH); $R_f=0.40$ (B); elemental analysis calcd (%) for $C_{28}H_{35}N_3O_6$ ($M_W=509.58$): C 65.99, H 6.92, N 8.25; found: C 65.38, H 7.02, N 7.91.

Boc-D-Ala-Bip-L-Ala-OMe (D1L): TFA (2.5 mL) was added to a solution of dipeptide **1L** (0.0628 g; 0.143 mmol) in CH_2Cl_2 (2.5 mL). The solution was stirred at room temperature for 3 h and evaporated in vacuo. The residue was dissolved in EtOAc (100 mL). The solution was washed with 5% $NaHCO_3$ (50 mL) and then with H_2O (100 mL), dried over $MgSO_4$, and evaporated in vacuo. The obtained crude H-Bip-L-Ala-OMe was dissolved in CH_3CN (1 mL) and CH_2Cl_2 (1 mL). By using the same experimental procedure and workup as for the synthesis of dipeptide **D1**, this solution was treated with the symmetrical anhydride $[Boc\text{-}D\text{-}Ala]_2O$, prepared in situ from Boc-D-Ala-OH (0.109 g; 0.57 mmol) and EDC (0.055 g, 0.28 mmol), in CH_3CN (2 mL). The crude product was chromatographed on a 1.5×40 cm column of silica gel with eluant A to afford pure **D1L** (0.0588 g; 97% overall) as a solid, which was crystallized from CH_2Cl_2: m.p. 224°C; $[\alpha]_{589}^{25}=-73$; $[\alpha]_{578}^{25}=-78$; $[\alpha]_{546}^{25}=-90$; $[\alpha]_{436}^{25}=-183$; $[\alpha]_{365}^{25}=-367$ ($c=0.24$ in MeOH); $R_f=0.15$ (A); elemental analysis calcd (%) for $C_{28}H_{35}N_3O_6\cdot CH_2Cl_2\cdot1.5\,H_2O$ ($M_W=621.55$): C 56.04; H 6.49; N 6.76; found: C 55.74, H 6.01; N 6.51.

Boc-L-Val-Bip-D-Val-OMe (L2D): The same experimental procedure and workup as for the synthesis of tripeptide **D1L** was used. *N*-deprotection of the dipeptide **2D** (0.0236 g; 0.05 mmol) in CH_2Cl_2 (2.5 mL) and TFA (2.5 mL) led to H-Bip-D-Val-OMe (crude), which was treated with the symmetrical anhydride $[Boc\text{-}L\text{-}Val]_2O$, prepared in situ from Boc-L-Val-OH (0.044 g; 0.20 mmol) and EDC (0.019 g, 0.10 mmol), in CH_3CN (2 mL). The crude product was chromatographed on a preparative TLC plate of silica gel. Repeated elutions with MeOH/CH_2Cl_2 (99:1) afforded pure **L2D** (0.0119 g; 42% overall) as a glassy solid: $[\alpha]_{589}^{25}=+53$; $[\alpha]_{578}^{25}=+54$; $[\alpha]_{546}^{25}=+63$; $[\alpha]_{436}^{25}=+126$; $[\alpha]_{365}^{25}=+256$ ($c=0.22$ in MeOH); $R_f=0.40$ (A); elemental analysis calcd (%) for $C_{32}H_{43}N_3O_6$ ($M_W=565.69$): C 67.94, H 7.66; found: C 67.95, H 8.13.

Circular dichroism: The CD spectra were obtained on a Jasco J-710 dichrograph. Cylindrical, fused quartz cells of 10, 1, 0.2, and 0.1 mm pathlengths (Hellma) were used. The values are expressed in terms of $[\Theta]_T$, the total molar ellipticity [deg cm^2 dmol^{-1}]. Spectrograde MeOH and acetonitrile (Acros Organics) were used as solvents. The peptide concentration was 1×10^{-3} M.

X-ray diffraction: Crystals of Boc-(*R*)-Bip-D-Ala-OMe were grown by vapor diffusion from ethyl acetate/petroleum ether. Diffraction data were collected on a Philips PW1100 diffractometer. Crystallographic data are summarized in Table 2. The structure was solved by direct methods with the SHELXS 97[39] program. Refinement was carried out on F^2 by full-matrix block least-squares, with the use of all data, by application of the SHELXL 97[40] program, with all non-hydrogen atoms anisotropic and by allowing the positional parameters and the anisotropic displacement pa-

Table 2. Crystallographic data and structure refinement for Boc-(*R*)-Bip-D-Ala-OMe (**1D**).

formula	$C_{25}H_{30}N_2O_5$	$F(000)$	936
M_r	438.5	crystal size [mm]	3.00×0.10×0.10
T [K]	293(2)	θ range [°]	4.23–60.03
λ [Å]	1.54178	index ranges	$-11\le h\le10$
crystal system	monoclinic		$-1\le k\le23$
space group	$P2_1$		$0\le l\le13$
a [Å]	9.807(2)	reflections collected	4151
b [Å]	20.907(5)	independent reflections	3951 (R(int) = 0.035)
c [Å]	12.120(2)	data/restraints/parameters	3951/1/529
β [°]	100.19(5)	goodness-of-fit (on F^2)	1.08
V [Å^3]	2445(1)	final R indices ($I>2\sigma(I)$)	$R_1=0.053$, $wR_2=0.147$
Z	4	R indices (all data)	$R_1=0.063$, $wR_2=0.166$
ρ_{calcd} [Mg m^{-3}]	1.19	largest diff. peak/hole [e Å^{-3}]	0.340/−0.270
μ [mm^{-1}]	0.68		

rameters of the non-hydrogen atoms to refine at alternate cycles. The aromatic rings were constrained to the idealized geometry. Hydrogen atoms were calculated at idealized positions and refined as riding, with U_{iso} set equal to 1.2 (or 1.5 for methyl groups) times the U_{eq} of the parent atom.

CCDC-262534 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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