Pergamon

Tetrahedron 55 (1999) 12331–12348

TETRAHEDRON

Axially Chiral Bis(α-Amino Acid)s and Dioxopiperazines. Synthesis and Configurational Assignment

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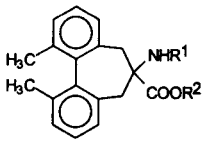
Received 21 January 1999; revised 19 July 1999; accepted 12 August 1999

Abstract: Conversion of the easily accessible racemic bis(amino acid)s *cis*- and *trans*-**2a** into the (*S*)-enantiomers *via* the corresponding Schiff bases with (1*S*,2*S*,5*S*)-2-hydroxy-3-pinanone is described. Condensation of the *N*-Boc-protected bis(amino acid)s with esters of the corresponding axially chiral amino acids (*R*)- and (*S*)-**1b** afforded tetraspiro-substituted bis(dioxopiperazine)s **7** representing a rare case of primary helical topology. Absolute configuration of the products was assigned by NMR and CD spectra and confirmed by X-ray analysis of the Schiff base (*S*)-*cis*-**3**.

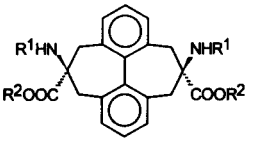
Keywords: Biaryls, amino acids and derivatives, NMR, X-ray crystal structures.

Introduction

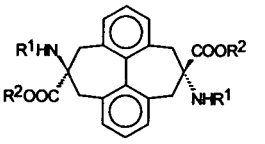
Previously, we have reported[1] the first optically active α-amino acids, (*R*)-**1a** and (*S*)-**1a** (Mebip[2]), whose chirality does not originate from the presence of a stereogenic carbon atom but from another type of molecular dissymmetry based on the biaryl axis.[4,5] Now we have prepared the corresponding axially chiral bis(α-amino acid)s,[6] *cis*- and *trans*-**2a** (Bibip[2]), in the enantiomerically pure form.



1a $R^1 = R^2 = H$
1b $R^1 = H$, $R^2 = Et$
1c $R^1 = Boc$, $R^2 = Et$
1d $R^1 = Boc$, $R^2 = H$



cis-**2a** $R^1 = R^2 = H$
cis-**2b** $R^1 = H$, $R^2 = Me$
cis-**2c** $R^1 = Boc$, $R^2 = Me$



trans-**2a** $R^1 = R^2 = H$
trans-**2b** $R^1 = H$, $R^2 = Me$
trans-**2c** $R^1 = Boc$, $R^2 = Me$

Model examination of these bis(amino acid) (Bibip) molecules suggests that they - either alone or in combination with the corresponding monoacid (Mebip) - can give rise to helical rod-like oligomers and/or polymers which are exceptional in that their axis of helicity coincides with the molecular backbone.[8,9] In this

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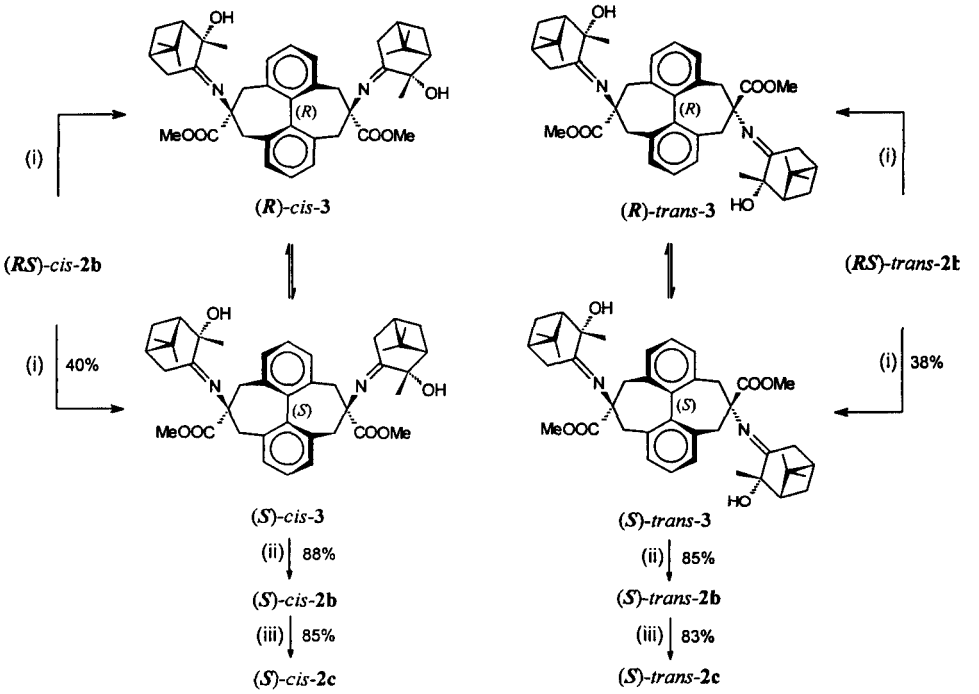
PII: S0040-4020(99)00717-6

way, the bis(amino acid)s may provide access to a very rare helical topology which is based on the primary[10,11] polymer structure. As a simple approach to such an intriguing topology we have proposed interfacial condensation of *N*- and *O*-protected amino acids **1** and/or **2** directed to the formation of rigid dioxopiperazines. Their supramolecular self-assembly controlled by the molecular helicity raises considerable interest.[12]

Results and Discussion

Synthesis of the starting enantiopure amino acids and their O- and N-protected derivatives

The racemic diesters (*RS*)-*cis*-**2b** and (*RS*)-*trans*-**2b** were obtained from the easily accessible[6] free diacids (*RS*)-*cis*-**2a** and (*RS*)-*trans*-**2a**. On reaction with the commercially available (1*S*,2*S*,5*S*)-2-hydroxy-3-pinanone[13] the diesters afforded the corresponding Schiff bases *cis*- and *trans*-**3**, each consisting of a pair of diastereoisomers ((*R*)-*cis*-**3** and (*S*)-*cis*-**3**; (*R*)-*trans*-**3** and (*S*)-*trans*-**3**, respectively).



Scheme 1. Reagents and conditions: (i) (1*S*,2*S*,5*S*)-2-hydroxy-3-pinanone, $BF_3.Et_2O$, reflux 10 h; (ii) 2M-HCl, MeOH, r.t. 16 h; (iii) di-t-Bu-dicarboxylate, CH_3CN, r.t. 24 h.

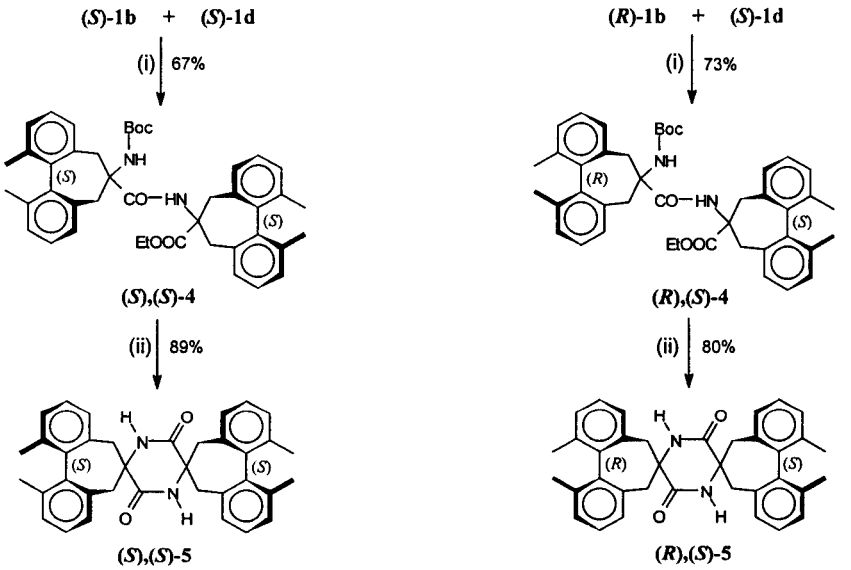
On crystallization, each diastereoisomeric pair afforded a single isomer ((*S*)-*cis*-**3** and (*S*)-*trans*-**3**, respectively). The remaining diastereoisomers, (*R*)-*cis*-**3** and (*R*)-*trans*-**3** could not be isolated from the respective mother liquors either by crystallization or by chromatography on silica gel. However, they could be

converted into the corresponding (*S*)-diastereoisomers by thermal equilibration[14-16] (Scheme 1) followed by crystallization. Hydrolysis of the separated (*S*)-diastereoisomers gave the enantiomerically pure[17] diesters (*S*)-*cis*-**2b** and (*S*)-*trans*-**2b**, which on treatment with di-t-butyl dicarboxylate afforded the corresponding *N*-Boc-protected esters (*S*)-*cis*-**2c** and (*S*)-*trans*-**2c**.

The corresponding mono(amino acid) derivatives (*R*)- and (*S*)-**1c** and **1d** were obtained similarly from the esters (*R*)-**1b** and (*S*)-**1b**. The starting esters were prepared from (*R*)- or (*S*)-2,2′-bis-(bromomethyl)--6,6′-dimethylbiphenyl by a modification of an earlier[1] procedure.

Condensation of the O- and N-protected amino acids

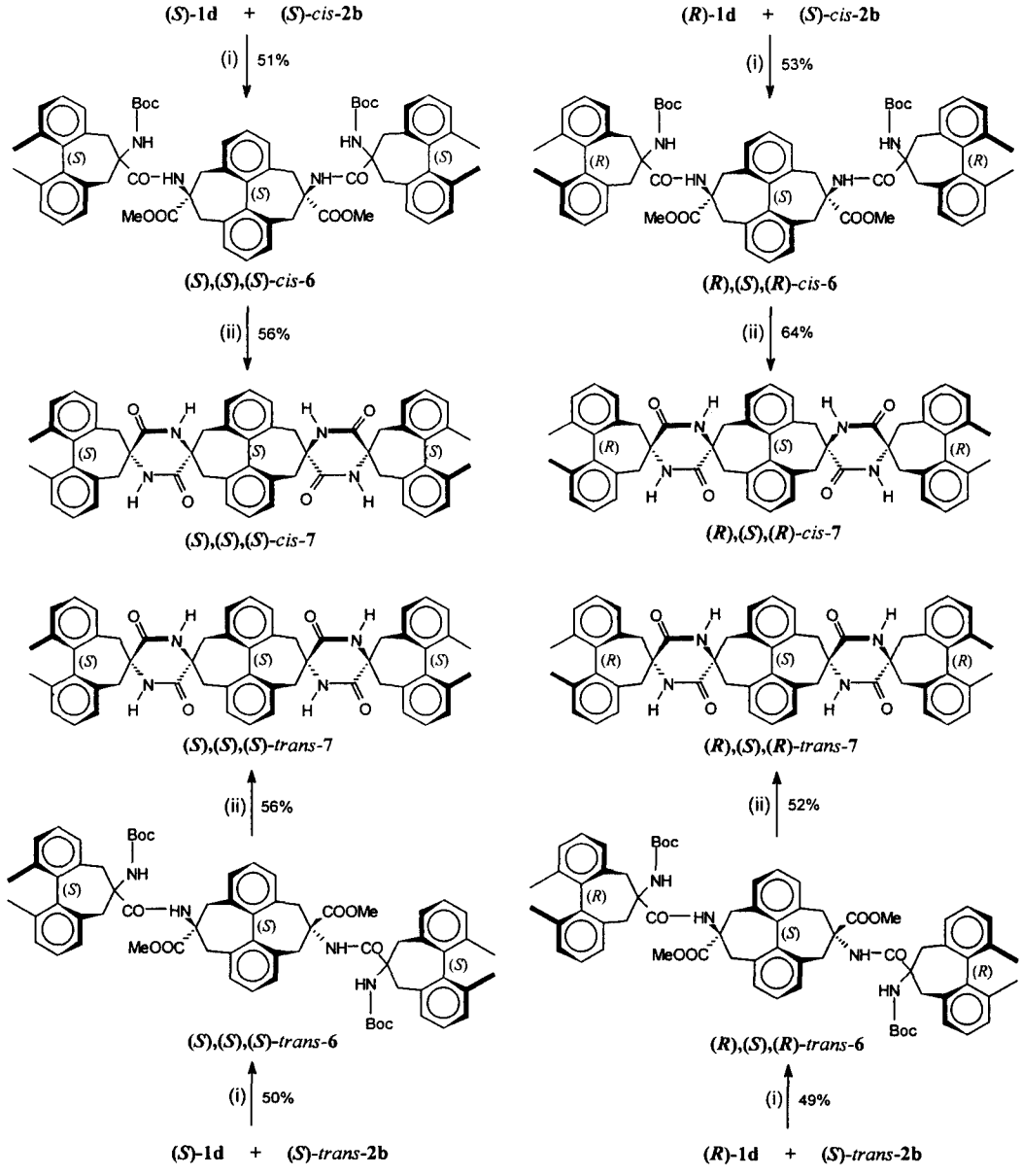
Treatment of the *N*-protected amino acid (*S*)-**1d** with the corresponding ester (*S*)-**1b** in the presence of O-benzotriazol-1-yl-N,N,N′,N′-tetramethyluronium hexafluorophosphate[18] as the condensing agent yielded the dipeptide derivative (*S*),(*S*)-**4**. Analogous condensation of (*R*)-**1d** with (*S*)-**1b** afforded the diastereoisomeric dipeptide (*R*),(*S*)-**4**. Cleavage of the *N*-Boc group in the dipeptides followed by basification gave rise to the respective spiro-substituted dioxopiperazines (*S*),(*S*)- **5** and (*R*),(*S*)-**5** (Scheme 2).



Scheme 2. Reagents and conditions: (i) O-benzotriazol-1-yl-N,N,N′,N′-tetramethyluronium hexafluorophosphate, N-methylmorpholine, CH_2Cl_2, r.t. 1 week, (ii) TFAA, r.t. 1 h.

Following the same methodology, (2:1) condensation of the monoacid *N*-Boc derivative (*S*)-**1d** and (*R*)-**1d** with the diesters (*S*)-*cis*-**2b** and (*S*)-*trans*-**2b** (or (*RS*)-*cis*-**2b** and (*RS*)-*trans*-**2b**; cf. Experimental) yielded the corresponding tripeptides (*S*),(*S*),(*S*)-*cis*-**6**, (*R*),(*S*),(*R*)-*cis*-**6**, (*S*),(*S*),(*S*)-*trans*-**6** and (*R*),(*S*),(*R*)-*trans*-**6**.

N-Deprotection of the individual tripeptides and cyclisation led to the expected stereoisomers of the spiro-substituted bis(dioxopiperazine) **7** (Scheme 3).



Scheme 3. Reagents and conditions: (i) O-benzotriazol-1-yl-N,N,N′,N′-tetramethyluronium hexafluorophosphate, N-methylmorpholine, CH_2Cl_2, r.t. 2 weeks, (ii) 1.TFAA, r.t. 2 h, 2. 2M-NaOMe, MeOH, 50 °C 6 h.

Structure of the products

The structure of all prepared compounds was confirmed by their NMR spectra (for data of compounds **1c**, **1d**, **2c**, **3**, **4** and **6** see the Experimental Part, for data of **1b**, **2b**, **5** and **7** see Tables I and II). The large number of structurally similar protons and carbon atoms in the compounds made the complete structural assignment difficult. Moreover, in the Boc-protected compounds (**1c**, **1d**, **2c**, **4** and **6**) there is a marked signal widening for atoms in the vicinity of the protecting group, obviously as the result of conformational equilibrium.

Table I Proton NMR data in $CDCl_3$

Proton	**1b**	***cis*-2b**	***trans*-2b**	**(*S*),(*S*)-5**	**(*R*),(*S*)-5**	**(*S*),(*S*),(*S*)-*cis*-7**	**(*R*),(*S*),(*R*)-*cis*-7**	**(*S*),(*S*),(*S*)-*trans*-7**	**(*R*),(*S*),(*R*)-*trans*-7**
Aromatic									
=CH-	7.05 dd 7.16 t 7.19 dd 7.10 m ~7.23 m (2H)	7.21 - 7.28 m (6H)	7.20 - 7.33 m (6H)	7.31 dd (2H) 7.26 t (2H) 7.10 dd (2H) 7.25 dd (2H) 7.18 t (2H) 6.94 dd (2H)	7.30 dd (2H) 7.28 dd (2H) 7.13 dd (2H) 7.26 dd (2H) 7.24 dd (2H) 7.10 dd (2H)	6.96 dd (2H) 7.12 dd (2H) 7.19 m (4H) 7.25 - 7.33 m (10H)	7.11 dd (2H) 7.15 dd (2H) 7.19 - 7.39 m (14H)	6.96 dd (2H) 7.11 d (2H) 7.12dd (2H) 7.19 t (2H) 7.22 dd 7.26 bd (2H) 7.28 t (2H) 7.32 dd (2H) 7.34 d (2H) 7.38 dd	7.11 dd (2H) 7.15 dd (2H) 7.25 -7..37 m (14H)
NH	1.63 b	1.69 bs	1.70 bs	5.70 s	5.45 s	5.86 s 5.72 s	5.67 s 5.56 s	5.74 s 5.88 s	5.70 s 5.58 s
Alicyclic									
$-CH_2-$ [a]	2.95 dd; 2.12 d (J = 13.2) 2.83 d 2.41 dd (J = 13.3)	3.05 dd 2.27 d (J = 13.4) 2.94 d 2.54 dd (J = 13.4)	3.04 dd 2.28 d (J = 13.3) 2.94 d 2.55 dd (J = 13.4)	3.32 d 2.49 bd (J = 13.2) 2.90 bd 2.48 d (J = 13.6)	3.26 d 2.53 bd (J = 13.2) 2.92 bd 2.34 d (J = 13.8)	3.46 d 2.62 bd (J = 13.4) 3.34 d 2.52 bd (J = 13.3) 3.04 bd 2.61 d (J = 13.6) 2.93 bd 2.51 d (J = 13.6)	3.38 d 2.67 bd (J = 13.5) 3.31 d 2.56 bd (J = 13.4) 3.07 bd 2.44 d (J = 13.9) 2.95 bd 2.40 d (J = 13.8)	3.52 d 2.64 bd (J = 13.4) 3.35 d 2.53 bd (J = 13.3) 3.01 bd 2.57 d (J = 13.7) 2.93 bd 2.51 d (J = 13.5)	3.42 d 2.67 bd (J = 13.4) 3.29 d 2.56 bd (J = 13.4) 3.04 bd 2.42 d (J = 13.9) 2.95 bd 2.40 d (J = 13.8)
CH_3-Ar	2.15 s 2.14 s	--	--	2.18 s 2.14 s	2.18 s 2.14 s	2.20 s 2.15 s	2.19 s 2.15 s	2.19 s 2.15 s	2.19 s 2.15 s
-OR	4.15 q 1.26 t	3.74 s	3.74 s	--	--	--	--	--	--

[a] Symbols dd and/or bd indicate additional splitting *ca* 1 Hz due to long-range coupling between pseudoequatorial protons of the two methylene groups of the seven-membered ring.

Table II Carbon-13 NMR chemical shifts in $CDCl_3$

Carbon	1b	*cis*-2b	*trans*-2b	(*S*),(*S*)-5	(*R*),(*S*)-5	(*S*),(*S*),(*S*)-*cis*-7	(*R*),(*S*),(*R*)-*cis*-7	(*S*),(*S*),(*S*)-*trans*-7	(*R*),(*S*),(*R*)-*trans*-7
C=O	175.27	175.88 (2)	175.91 (2)	167.92 (2)	168.32 (2)	167.86 (2)	168.44 (2)	167.86 (2)	168.33 (2)
						167.83(2)	168.17(2)	167.75(2)	168.24(2)
Aromatic:									
>C=	138.16	138.06 (2)	138.38	138.38 (2)	138.34 (2)	138.37 (2)	138.41 (2)	139.06	139.01
	137.68	136.91 (2)	137.76	137.08 (2)	137.04 (2)	137.76 (2)	137.59 (2)	138.36 (2)	138.36 (2)
	136.71	134.94 (2)	136.58 (2)	137.07 (2)	136.93 (2)	137.14 (2)	137.16 (2)	137.15 (2)	137.11 (2)
	136.14		135.31 (2)	136.00 (2)	135.87 (2)	137.07 (2)	136.96 (2)	137.02 (2)	136.97 (2)
	135.82			134.72 (2)	135.05 (2)	136.06 (2)	136.34 (2)	136.42	136.18
	135.30			133.02 (2)	132.86 (2)	135.95 (2)	135.96 (2)	136.01 (2)	135.98 (2)
						134.63 (2)	134.88 (2)	134.96 (2)	135.27 (2)
						132.90 (2)	132.80 (2)	134.58 (2)	134.89 (2)
						132.85 (2)	132.61 (2)	133.90 (2)	133.73 (2)
								132.86 (2)	132.77 (2)
-CH=	129.09	128.88 (2)	129.14 (2)	130.06 (2)	130.05 (2)	130.13 (2)	130.54 (2)	130.11 (2)	130.16 (2)
	128.87	128.80 (2)	128.50 (2)	129.81 (2)	129.66 (2)	129.98 (2)	130.16 (2)	129.85 (2)	129.94 (2)
	127.01	127.35 (2)	127.58	127.83 (2)	127.70 (2)	129.87 (2)	129.77 (2)	129.66 (2)	129.92 (2)
	126.95		127.10	127.16 (4)	127.62 (2)	129.27 (2)	129.34 (2)	129.51 (2)	129.76 (2)
	126.70			126.63 (2)	127.09 (2)	128.39 (2)	128.27 (2)	128.74	128.56
	126.68				126.83 (2)	127.87 (2)	127.77 (2)	128.02	127.94
						127.18 (2)	127.56 (2)	127.83 (2)	127.77 (2)
						127.17 (2)	127.17 (2)	127.18 (4)	127.52 (2)
						126.66 (2)	126.78 (2)	126.62 (2)	127.15 (2)
									126.81 (2)
Alicyclic:									
>C<	65.86	67.97 (2)	67.98 (2)	65.68 (2)	65.88 (2)	68.00 (2)	68.23 (2)	68.06 (2)	68.26 (2)
						65.78 (2)	65.92 (2)	65.76 (2)	65.91 (2)
$-CH_2-$	43.48	43.06 (2)	43.08 (2)	46.30 (2)	46.14 (2)	46.38 (2)	46.19 (2)	46.32 (2)	46.18 (2)
	42.42	42.51 (2)	42.45 (2)	41.76 (2)	42.85 (2)	45.96 (2)	45.72 (2)	45.89 (2)	45.69 (2)
						41.83 (2)	43.04 (2)	41.79 (4)	43.02 (2)
						41.81 (2)	42.72 (2)		42.70 (2)
CH_3-Ar	19.73	--	--	19.79 (2)	19.78 (2)	19.81 (2)	19.80 (2)	19.79 (2)	19.79 (2)
	19.72			19.67 (2)	19.69 (2)	19.69 (2)	19.70 (2)	19.68 (2)	19.70 (2)
-OR	61.03	52.25 (2)	52.23 (2)	--	--	--	--	--	--
	14.15								

The strategy of signal assignment is illustrated for the compound (*S*),(*S*)-**5** (Fig. 1). The signals of the individual aromatic rings were assigned on the basis of the characteristic *ortho*- and *meta*-interactions of the aromatic protons (about 7.5 and 1.5 Hz, respectively) and of long-range interactions of the methyl protons with the aromatic ones (< 1 Hz) in the 2D-COSY spectrum. The slightly different values of geminal interactions (13.6 and 13.2 Hz, respectively), and particularly their detection in the 2D-COSY spectrum, allowed us to distinguish the signals of both the methylene groups. Further important information was obtained from the 2D-ROESY spectrum. On the basis of the methyl ROE-crosspeaks it was possible to assign the protons (δ 7.31 and

7.25) in the *ortho*-positions relative to the methyl groups. As follows from the approximate interatomic distances on models, the observed contacts of the NH proton (δ 5.70) with one methylene (δ 2.48) and one aromatic proton (δ 7.10), and further the contacts between the aromatic and methylene protons (δ 7.10 to δ 2.49; δ 6.94 to δ 2.90), determine unequivocally the mutual spacial relations between the hydrogen atoms in the molecule (see Fig. 1). The wide doublets of methylene protons at δ 2.49 and 2.90 are in accord with their pseudoequatorial orientation and their non-zero mutual long-range interaction in the approximately planar "zig-zag" arrangement. The completely assigned hydrogen atoms were then utilized for the structural assignment of all the carbon atoms (Fig. 1) using the heterocorrelated 2D-HMQC and 2D-HMBC spectra.

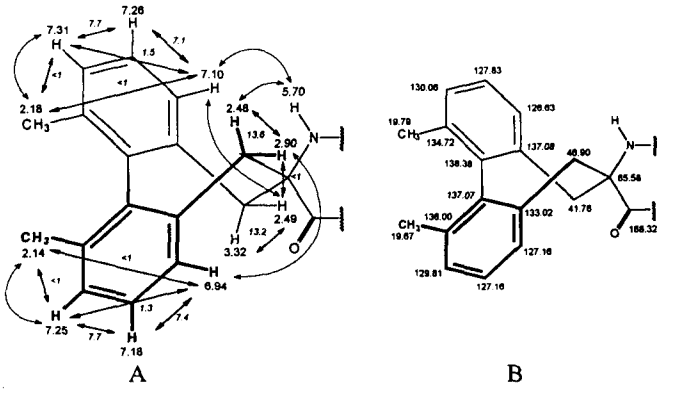


Fig. 1 The structural assignment of proton and carbon NMR signals in the biphenyl part of (*S*),(*S*)-**5** (A: straight-line arrows indicate couplings (from 2D-COSY) and curved-line arrows represent NOE contacts (from 2D-ROESY); proton chemical shifts and coupling constants (in italics) are given; B: structural assignment of carbon-13 signals from 2D-HMQC and HMBC spectra).

NMR assignment of cis- *and* trans-*configuration to compounds* ***2b, 3, 6 and 7***

The *cis*- or *trans*-relationship of the amino (or carbonyl) groups with respect to the hypothetical plane defined in compounds **2, 3, 6** and **7** by the central tetracyclic part of the molecule, correlates with the different orientation of the twofold symmetry axis in these compounds. Whereas in the *cis*-isomers this axis is perpendicular to this "main" average plane and bisects the biaryl bond, in the *trans*-isomers the twofold axis lies in this plane and passes through four carbon atoms of the biphenyl system (1,1′,4,4′). This difference results in different spin systems of the aromatic protons and carbon atoms in the *cis*- and *trans*-isomers. The aromatic protons in the *cis*-isomers form two identical ABC-systems and the aromatic carbon atoms give rise to two identical ABCDEF-systems (6 signals each of which corresponds to two carbon atoms). On the other hand, the aromatic protons in the *trans*-isomers afford two different three-spin systems, AA′B and EE′F, and the aromatic carbon atoms form two distinct six-spin systems A_2BC_2D and E_2FG_2H (8 signals, 4 of which correspond to two and another 4 to one carbon atom). Whereas in the ^1H NMR spectra application of the mentioned criteria is rendered difficult due to 2nd-order effects or overlap with aromatic protons of other biphenyl fragments present in the molecule, in the ^{13}C NMR spectra this distinction was unequivocal for all the compounds studied.

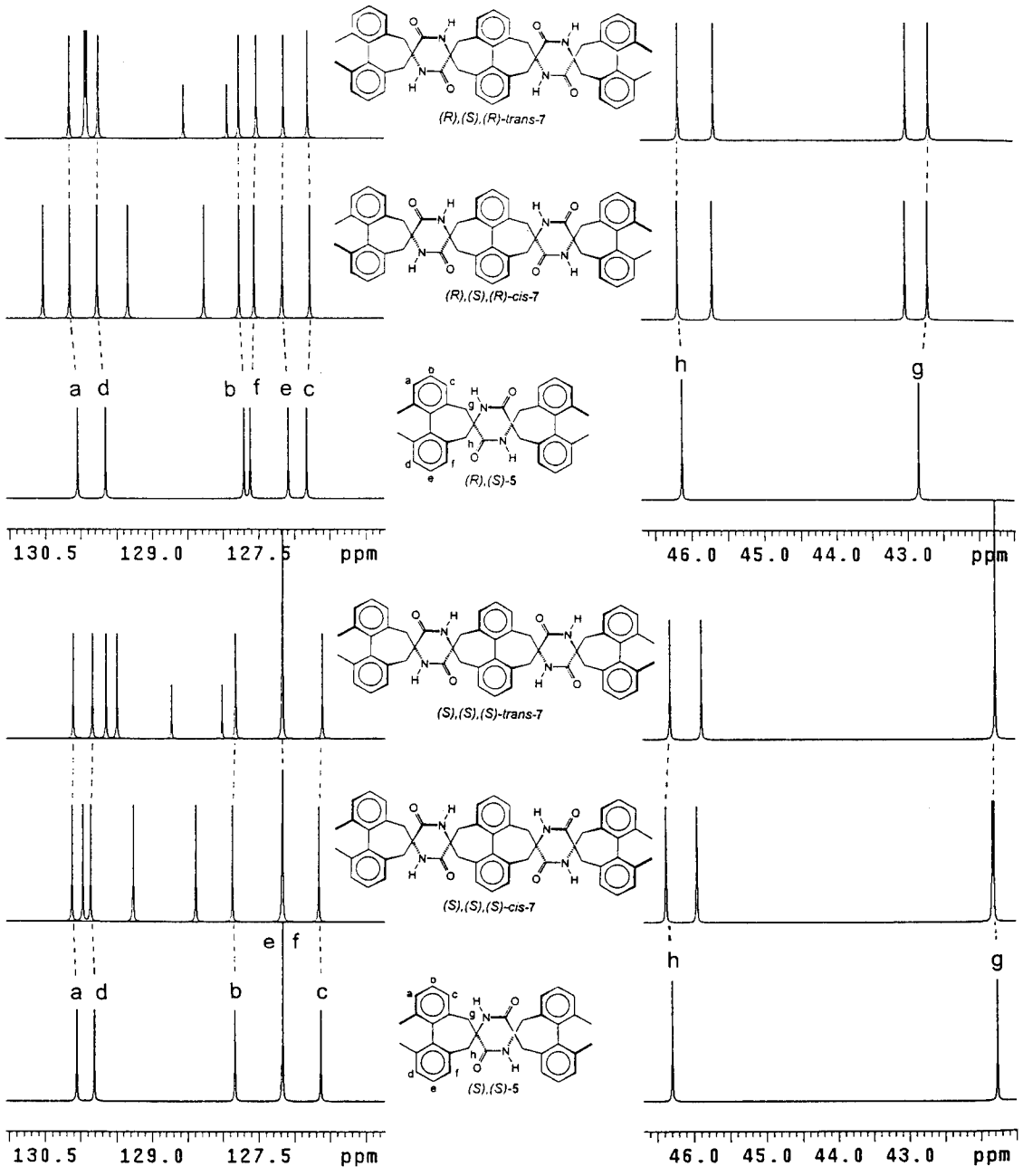


Fig. 2 Comparison of ^{13}C NMR spectra of "model" compounds *(S),(S)*-**5** and *(R),(S)*-**5** with bis(dioxopiperazines) *(S),(S),(S)-cis*-**7**, *(S),(S),(S)-trans*-**7**, *(R),(S),(R)-cis*-**7** and *(R),(S),(R)-trans*-**7** (only regions containing aromatic =CH- and alicyclic CH_2 carbons are shown).

Assignment of absolute configuration of cis- *and* trans-*isomers of compound 7 by NMR*

The sense of the twist (absolute configuration) of the central biphenyl moiety in the isomers **7** was determined using the isomeric pair (*S*),(*S*)-**5** and (*R*),(*S*)-**5** of known absolute configuration as models. The reasoning is based on the asssumption that the chemical shifts of protons and carbon atoms of the outer tricyclic fragments in bis(dioxopiperazines) **7** are influenced by the configuration on the central biphenyl moiety. As shown by comparison of the aromatic -CH= and alicyclic -CH_2- signals in the ^{13}C NMR spectra (Fig. 2), for each of the bis(dioxopiperazines) **7** one can find a marked similarity of signals of the outer tricyclic fragments with those in one of the model compounds **5**. This "pattern analysis", together with the known absolute configuration of the outer biphenyls, assigned the absolute configuration to the central biphenyl part of the molecule.

Assignment of absolute configuration of compounds 7 by CD

Data on absolute configuration of the central biphenyl unit in the stereoisomeric compounds **7** may also be obtained by comparison of their CD spectra. Whereas their UV absorption spectra show practically no differences either due to the *cis-trans* configuration of the central biphenyl moiety or the configuration of the biphenyl parts (three absorption regions: short-wavelength shoulder at 222 nm ($\varepsilon \sim 143000$), broad maximum at 247 nm ($\varepsilon \sim 30000$), and a shoulder around 270 nm ($\varepsilon \sim 11000$)), the signs and magnitudes of the CD spectra are very sensitive to structural changes. Whereas the *cis-trans* isomerism results only in a moderate intensity difference (compounds (*S*),(*S*),(*S*)-*cis*-**7** and (*S*),(*S*),(*S*)-*trans*-**7**; Fig. 3, curves **c** and **d**, respectively), partial reversal of configuration of the peripheral biphenyl systems (compound (*R*),(*S*),(*R*)-*cis*-**7**, curve **e**) results in a profound change of the curve character.

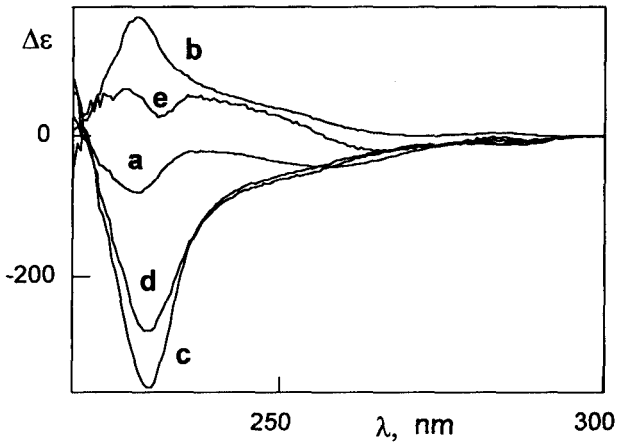


Fig. 3. CD spectra of: (*S*)-*cis*-**2c** (curve **a**), (*R*),(*R*)-**5** (curve **b**), (*S*),(*S*),(*S*)-*cis* –**7** (curve **c**), (*S*),(*S*),(*S*)-*trans*-**7** (curve **d**) and (*R*),(*S*),(*R*)-*cis*-**7** (curve **e**).

The spectra of both the *cis*- and *trans*-isomers of (*S*),(*S*),(*S*)-**7** retain the character of those of the related simpler derivatives (only with increased intensities; cf spectra of *cis*-**2c** and **5**; Fig.3, curves **a** and **b**, respectively) while the isomer (*R*),(*S*),(*R*)-**7** exhibits a curve giving evidence of an ample mutual compensation of dichroic bands corresponding to biphenyl subsystems of different absolute configuration. As the absolute configuration of both the peripheral biphenyl systems is known, one can, with high reliability, assign the absolute configuration to the central biphenyl system. The derived results are in accord with those deduced from the NMR studies (*vide supra*).

Determination of absolute configuration of (S)-cis-3 by single crystal X-ray analysis

To determine the absolute configuration of the central biphenyl moiety in the whole *cis*-series, the intermediate *(S)-cis*-**3** was subjected to X-ray analysis. Since the absolute configuration of the pinane residues is known, determination of the relative configuration of the compound was sufficient. The result of the X-ray analysis is depicted in Figure 4. There is nothing unusual on bond lengths and angles which lie within normal ranges. The two phenyl rings are planar within ± 0.015 Å and their least-squares planes subtend the dihedral angle of 45.08(8)°. While the conformation of the two seven-membered rings is almost identical, the disposition of the substituents at the quaternary carbon atoms differs slightly from one ring to another. The major difference is in the orientation of the carboxymethyl groups since the carbonyl oxygen O1 is *syn*-clinal to N1 but O4 is *anti*-periplanar to N2. The hydroxyl groups of the pinane fragments form long and strongly bent intramolecular hydrogen bonds to the imine nitrogens. In the crystal, there are no short intramolecular contacts except those at the normal van der Waals level.

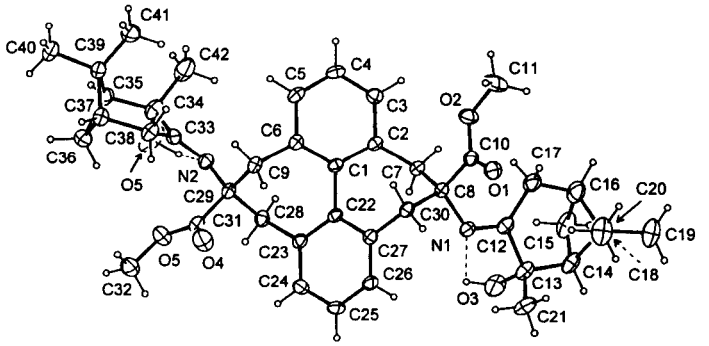


Fig. 4. ORTEP view of *cis-(S)*-**3** with 50% probability ellipsoids and hydrogen atoms as circles of arbitrary size. Hydrogen bonds drawn as dotted lines.

Thus, on the basis of the X-ray evidence the above NMR and CD spectral assignment of the absolute configuration of the diastereoisomers of **7** has been fully confirmed.

Experimental

Note on the nomenclature:

To avoid cumbersome names, we use three-letter amino acid symbols (as defined above[2]) and, where necessary, with arrows indicating direction of the peptide -CO-NR- bond (compounds **4** - **7**). Thus, e.g., the peptide (*R*),(*S*),(*R*)-*cis*-**6** is described as (*R*)-N-Boc-Mebip→(*S*)-*cis*-Bibip-$(OMe)_2$←(*R*)-N-Boc-Mebip whereas its full chemical name is diethyl 5,11-*bis*[(*R*)-6-(*tert*-butyloxycarbonylamino)-1,11-dimethyl-6,7-dihydro-*5H*-dibenzo[*a,c*]cycloheptene-6-carbonylamino]-(*S*)-*cis*-5,6,11,12-tetrahydro-*4H,10H*-dibenzo[*ef,kl*]heptalene-5,11-dicarboxylate. Analogously, for the spiro dioxopiperazines **5** and **7** we use the common "cyclo"-notation; as an example may serve the tetraspiro compound (*R*),(*S*),(*R*)-*trans*-**7**, denoted as cyclo-(*R*)-Mebip-[cyclo-(*S*)-*trans*-Bibip-(*R*)-Mebip], which in full can be named tetraspiro[(*R*)-1,11-dimethyl-6,7-dihydro-*5H*-dibenzo[*a,c*]cycloheptene-6,1′-(2,5-dioxo-3,6-diazacyclohexane)-4′,5′′-((*S*)-*trans*-5,6,11,12-tetrahydro*4H,10H*-dibenzo[*ef,kl*]heptalene)-11′′,1′′′-(2,5-dioxo-3,6-diazacyclohexane)-4′′′,6′′′′-((*R*)-1,11-dimethyl-6,7-dihydro-*5H*-dibenzo[*a,c*]cycloheptene)].

The NMR spectra were measured on FT Varian UNITY-500 (^{1}H at 500 MHz and ^{13}C at 125.7 MHz) and UNITY-200 spectrometers (^{1}H at 200 MHz) in $CDCl_3$ at r.t. (about 20 °C) and are referenced to tetramethylsilane as internal standard (^{1}H NMR) or to the solvent signal (^{13}C NMR; $\delta(CDCl_3)$ = 77.0 ppm). IR spectra were taken on an FTIR Bruker IFS-88 spectrometer using KBr technique. CD spectra in chloroform were obtained in quarz cells (0.1 and 0.01 cm) with a Jobin-Yvon CD 6 instrument at concentrations 5.10^{-4}- 2.10^{-3} M. The spectra were referenced to pure solvent scans and further processed using Spectracalc and Gramms (Galaxy Industries) software packages. Optical rotations were measured on a Perkin-Elmer 241 automatic polarimeter.

(*R*)-2,2'-Bis(bromomethyl)-6,6'-dimethylbiphenyl[19] ($[\alpha]_D^{20}$ –54.7; c 0.5, benzene), (*S*)-2,2'-bis(bromomethyl)-6,6'-dimethylbiphenyl[19] ($[\alpha]_D^{20}$ +54.9; c 0.5, benzene) and racemic amino acids (*RS*)-*cis*-**2a** and (*RS*)-*trans*-**2a** (ref. 16b) were obtained according to the published procedures.

*Ethyl (*R)- *and (*S)-*6-amino-1,11-dimethyl-6,7-dihydro-5H-dibenzo[*a,c*]cycloheptene-6-carboxylate (*R*)-**1b** and (*S*)-**1b***

A solution of tetra-n-butylammonium hydrogen sulfate (3.40 g; 10 mmol) was neutralized with 4M aqueous sodium hydroxide (2.5 ml; 10 mmol). To this solution was added a solution of (*R*)-2,2'-bis(bromomethyl)-6,6'-dimethylbiphenyl (1.85 g; 5 mmol) and ethyl *p*-chlorobenzylideneglycinate[20] (1.70 g; 7.5 mmol) in dichloromethane (15 ml). The mixture was vigorously stirred and 4M aqueous NaOH (2.75 ml; 11 mmol) was added during 20 min. After the addition, another portion of ethyl *p*-chlorobenzylideneglycinate (0.56 g; 2.5 mmol) in dichloromethane (1 ml) was added, followed by dropwise addition (10 min) of 4M aqueous NaOH (0.9 ml; 3.6 mmol). The mixture was stirred at r.t. for 1 h, the organic layer was separated and the aqueous one washed twice with dichloromethane. The combined organic portions were stripped of the solvent, the dry residue was mixed with 20% citric acid solution (30 ml) and ether (20 ml) and the mixture was stirred at r.t. overnight. The aqueous layer was separated and washed with ether (2 × 10 ml), then made alkaline with saturated solution of Na_2CO_3 and the free amino ester was taken up in ether (4 × 10 ml). Chromatography on silica gel in ether with 1% TFA afforded 0.85 g (55%) of (*R*)-**1b** as a yellowish oil, $[\alpha]_D^{20}$ –19.1 (c 0.5, chloroform). For ^{1}H and ^{13}C NMR data see Tables I and II. MS (FAB): m/z 310 [M^+ + 1] (100). Anal. Calcd for $C_{20}H_{23}NO_2$ (309.4): C, 77.64; H, 7.49; N, 4.53. Found: C, 77.65; H, 7.62; N, 4.27.

(*S*)-**1b** was prepared by the same procedure from (*S*)-2,2'-bis(bromomethyl)-6,6'-dimethylbiphenyl[19] in 58% yield; yellowish oil, $[\alpha]_D^{20}$ +18.7 (c 0.5, chloroform). Its ^{1}H NMR and mass spectra were identical with those of (*R*)-**1b**.

*Ethyl (*R)- and *(*S)-*6-(*tert*-butyloxycarbonylamino)-1,11-dimethyl-6,7-dihydro-5H-dibenzo-[*a,c*]cycloheptene-6-carboxylate (*R*)-**1c** and (*S*)-**1c***

A solution of amino ester (*R*)-**1b** (0.62 g; 2 mmol) and di-tert-butyl dicarboxylate (0.65 g; 3 mmol) in acetonitrile (3 ml) was set aside at r.t. for 16 h. Evaporation of the solvent and chromatography on silica gel in light petroleum - ether (3:1) gave 0.75 g (92%) of (*R*)-**1c** as solid oil, $[\alpha]_D^{20}$ +96.9 (c 0.5, chloroform). ^{1}H NMR

($CDCl_3$, 200 MHz) δ 7.26-7.00 (6 H, m, Ar-H), 4.66 (1 H, bs, NH), 4.20 (2 H, q, J =7.0 Hz, CH_2O), 3.07, 2.14 (2x 1 H, 2x d, J =12.8 Hz, Ar-CH_2), 2.93, 2.84 (2x 1 H, 2x d, J =13.1 Hz, Ar-CH_2), 2.15 (3 H, s, Ar-CH_3), 2.14 (3 H, s, Ar-CH_3), 1.45 (9 H, s, t-Bu), 1.25 (3 H, t, J =7.0 Hz, C$\underline{H}_3$$CH_2O$). MS (FAB): m/z 410 [$M^+$ + 1] (30), 354 (35), 310 (100). IR: ν_{max} (cm^{-1}) 3377 (NH), 1742, 1716 (C=O), 3064, 1595, 782, 745 (arom.). HRMS (FAB) calcd for $C_{25}H_{32}NO_4$: 410.2331. Found: 410.2339.

(*S*)-**1c** was prepared by the same procedure from (*S*)-**1b** in 90% yield; yellowish oil, $[\alpha]_D^{20}$ –96.8 (c 0.5, chloroform). Its ^1H NMR, IR and mass spectra were identical with those of (*R*)-**1c**.

*(R)- and (S)-6-(*tert*-Butyloxycarbonylamino)-1,11-dimethyl-6,7-dihydro-5H-dibenzo[a,c]cycloheptene-6-carboxylic acid* (*R*)-***1d*** and (*S*)-***1d***

A solution of the amino ester (*R*)-**1c** (0.61 g; 1.5 mmol) in ethanol (6 ml) and 4M NaOH (3 ml) was refluxed for 5 h. After cooling, the solution was diluted with water (10 ml) and washed with ether (2 × 5 ml). The aqueous layer was acidified with 1M HCl (13 ml) and the product was taken up in ether (3 × 10 ml). The combined organic portions were washed with water, brine, dried over Na_2SO_4, and the solvent was evaporated to give 0.55 g (96%) of (*R*)-**1d**, mp 180-182 °C (ether-light petroleum), $[\alpha]_D^{20}$ +96.3 (c 0.5, chloroform). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.26-7.21 (3 H, m, Ar-H), 7.18 (1 H, t, Ar-H), 7.11 (1 H, bd, Ar-H), 7.02 (1 H, bdd, Ar-H), 4.75 (1H, bs, NH), 3.16, 2.17 (2x 1 H, 2x d, J =12.7 Hz, Ar-CH_2), 2.98, 2.84 (2x 1H, 2x d, J =13.6 Hz, Ar-CH_2), 2.14 (3 H, s, Ar-CH_3), 2.16 (3 H, s, Ar-CH_3), 1.46 (9 H, s, *t*-Bu). IR: ν_{max} (cm^{-1}) 3262 (NH), 1720, 1707, (C=O), 3000br (C-O), 3065, 1596, 782, 737 (arom.). MS (FAB): m/z 382 [M^+ + 1] (20), 326 (55), 282 (100). Anal. Calcd for $C_{23}H_{47}NO_4$ (381.5): C, 72.42; H, 7.13; N, 3.67. Found: C, 72.71; H, 7.39; N, 3.47.

(*S*)-**1d** was prepared by the same procedure from (*S*)-**1c** in 94% yield; mp 180-182 °C (ether-light petroleum), $[\alpha]_D^{20}$ –99.1 (c 0.5, chloroform). Its ^1H NMR, IR and mass spectra were identical with those of (*R*)-**1d**.

Dimethyl (RS)- and (S)-cis-*5,11-diamino-5,6,11,12-tetrahydro-4H,10H-dibenzo[ef,kl]heptalene-5,11-dicarboxylate* (RS)-cis-***2b*** *and (S)-cis-**2b***

Trihydrate[6] of amino acid (*RS*)-*cis*-**2a** (0.81 g; 2.0 mmol), *p*-toluenesulfonic acid (0.76 g; 4.0 mmol), *p*-toluenesulfonyl chloride[21] (1.14 g; 6.0 mmol) and methanol (10 ml) were refluxed for 24 h. After cooling, the mixture was made alkaline with saturated solution of Na_2CO_3 and the free amino ester was extracted with dichloromethane (4 × 20 ml). The combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated. Chromatography on silica gel (1%TEA/DCM) gave the product which crystallized on mixing with dry ether in a refrigerator. Yield 0.59 g (78%) of (*RS*)-*cis*-**2b**, mp 154-156 °C. For ^1H and ^{13}C NMR data see Tables I and II. IR: ν_{max} (cm^{-1}) 3377, 3505 (NH), 1728, (C=O), 1203 (C-O), 3060, 1596, 788, 737 (arom.). MS (FAB): m/z 381 [M^+ + 1] (100). Anal. Calcd for $C_{22}H_{24}N_2O_4$ (380.4): C, 69.46; H, 6.36; N, 7.36. Found: C, 69.24; H, 6.41; N, 7.39.

The enantiomer (*S*)-*cis*-**2b** was obtained by the following procedure. A solution of amino ester (*RS*)-*cis*-**2b** (0.95 g; 2.5 mmol), (1*S*,2*S*,5*S*)-2-hydroxy-3-pinanone[13] (1.26 g; 7.5 mmol) and $BF_3{\cdot}Et_2O$ (75 µl) in dry benzene (15 ml) was refluxed for 10h. The resulting diastereoisomeric mixture of (*S*)-*cis*-**3** and (*R*)-*cis*-**3** was chromatographed on silica gel in dichloromethane-light petroleum (1:1) containing 1 % of TEA. Crystallization from ether-hexane and then from dichloromethane-ether afforded 0.39 g (23%) of pure (*S*)-*cis*-**3**. The mother liquors, containing (*S*)-*cis*-**3** and (*R*)-*cis*-**3** in the ratio about 1:3, were dissolved in toluene (5 ml) containing TEA (0.1 ml), mixed with $MgSO_4$ (100 mg) and the mixture was equilibrated at 150 °C for 2 h under nitrogen. Chromatography of the resulting mixture ((*S*)-*cis*-**3** : (*R*)-*cis*-**3** ≈ 1:1) and subsequent crystallization gave further amount of (*S*)-*cis*-**3**. The mother liquors were again equilibrated, chromatographed and crystallized as described, furnishing still another crop of the product. Total yield of (*S*)-*cis*-**3** (from (*RS*)-*cis*-**2b**) was 0.68 g (40%); mp 260-263 °C (dichloromethane-ether), $[\alpha]_D^{20}$ –131 (c 0.5, chloroform). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.38 (2 H, m, Ar-H), 7.26 (4 H, m, Ar-H), 3.72 (6H, s, 2 x COOMe), 3.31, 2.36 (2 x 2 H, 2x d, J = 13.3 Hz, 2 x Ar-CH_2), 2.95, 2.86 (2 x 2 H, 2x d, J = 12.8 Hz, 2 x Ar-CH_2), pinanol residues: 2.48 (2 H, dd, J = 17.8, 3.2 Hz), 2.41 (2 H, ddd, J=17.8, 3.0, 2.2 Hz), 2.28 (2 H, m, J =10.6, 5.8, 5.8, 2.2 Hz), 2.07 (2 H, t, J = 5.8 Hz), 1.98 (2 H, m, J = 5.8, 5.8, 3.2, 3.0 Hz), 1.45 (2 H, d, J = 10.6 Hz), 1.51 (6 H, s), 1.32 (6 H, s), 0.93 (6 H, s). ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 175.13 (2 x C=O), 138.44 (2), 135.65 (2) and 135.64 (2) (6 x Ar: =C<), 129.74 (2), 129.32 (2) and 126.89 (2) (6 x Ar: -CH=), 74.93 (2 x >C<), 38.46 (2) and 38.42 (2) (4 x –CH_2-),

51.98 (2 x OCH_3), pinanol residue: 175.69 (2), 77.12 (2), 49.90 (2), 42.87 (2), 38.59 (2), 34.14 (2), 29.08 (2), 28.11 (2), 27.33 (2), 22.87 (2). MS (FAB): m/z 681 [M^+ + 1] (80), 229 (100). Anal. Calcd for $C_{42}H_{52}N_2O_6$ (680.9): C, 74.09; H, 7.70; N, 4.11. Found: C, 74.16; H, 7.91; N, 4.03. Its diastereoisomeric purity was checked by HPLC on silica gel in dichloromethane-light petroleum (30 : 70), containing 0.8 % TEA.

A solution of (*S*)-*cis*-**3** (0.51 g, 0.75 mmol) in dichloromethane (5 ml) was mixed with 2M HCl (1.5 ml) and methanol (5 ml). After standing at r.t. for 16 h, the organic solvents were evaporated in vacuo and the residue was diluted with water (20 ml) and washed with ether (3 × 5 ml). The product was liberated by an excess of 10% Na_2CO_3 and taken up in dichloromethane (5 × 10 ml). Evaporation gave 0.25 g (88%) of (*S*)-*cis*-**2b** as an oil, $[\alpha]_D^{20}$ –175 (c 0.5, chloroform). ^1H NMR, ^{13}C NMR and IR data were identical with those of the racemate.

*Dimethyl (*S*)-*cis*-5,11-di(tert-butoxyamino)-5,6,11,12-tetrahydro-4H,10H-dibenzo[ef,kl]heptalene-5,11-dicarboxylate (*S*)-*cis*-**2c***

A solution of amino ester (*S*)-*cis*-**2b** (76 mg; 0.2 mmol) and di-tert-butyl dicarboxylate (65 mg; 0.3 mmol) in acetonitrile (1 ml) was set aside at r.t. for 24 h. Evaporation of the solvent and chromatography on silica gel in light petroleum - ether (1:1) gave 99 mg (85%) of (*S*)-*cis*-**2c**, mp 221-223 °C, $[\alpha]_D^{20}$ –258 (c 0.5, chloroform). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.25 – 7.29 (4 H, m, Ar-H), 7.18 (2 H, m, Ar-H), 4.90 (2 H, bs, 2 x NH), 3.76 (6 H, s, 2 x COOMe), 3.31, 2.30 (2 x 2 H, 2 x d, J = 13.3 Hz, 2 x Ar-CH_2), 2.96, 2.94 (2 x 2 H, 2 x bd, J ~ 13 Hz, 2 x Ar-CH_2), 1.45 (18 H, s, 2 x t-Bu). ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 173.23 (2 x C(=O)-O), 154.60 (2 x O-CO-NH), 138.37 (2), 135.55 (2), 134.87 (2) (6 x Ar: =C<), 129.21 (2), 128.97 (2), 127.75 (2) (6 x Ar:–CH=), 68.92 (2 x >C<), 52.45 (2 x OCH_3), 41.25 (2), 38.52 (2) (4 x –CH_2-), 28.26 (6 x CH_3). MS (FAB): m/z 581 [M^+ + 1] (2), 481 (5), 57 (100). Anal. Calcd for $C_{32}H_{40}N_2O_8 \cdot 1.5H_2O$: C, 63.25; H, 7.13; N, 4.61. Found: C, 63.25; H, 6.76; N, 4.66. The enantiomeric purity was checked by chiral HPLC (Whelk, Merck; 10% 2-propanol in heptane).

*Dimethyl (RS)- and (S)-trans-5,11-diamino-5,6,11,12-tetrahydro-4H,10H-dibenzo[ef,kl]heptalene-5,11-dicarboxylate (RS)-trans-**2b** and (S)-trans-**2b***

Amino esters (*RS*)-*trans*-**2b** and (*S*)-*trans*-**2b** were prepared from (*RS*)-*trans*-**2a** (2.0 mmol) analogously as described above for (*RS*)-*cis*-**2b** and (*S*)-*cis*-**2b**.

(*RS*)-*trans*-**2b**. Yield 0.55 g (73%), mp 200-202 °C. For ^1H and ^{13}C NMR data see Tables I and II. IR: ν_{max} (cm^{-1}) 3370, 3302 (NH), 1728 (C=O), 3064, 1594, 795, 740 (arom.). MS (FAB): m/z 381 M^+ + 1 (100). Anal. Calcd for $C_{22}H_{24}N_2O_4$ (380.4): C, 69.46; H, 6.36; N, 7.36. Found: C, 69.18; H, 6.25; N, 7.35.

(*S*)-*trans*-**3**. Total yield 0.64 g (38%), mp 260-263 °C, $[\alpha]_D^{20}$ –121 (c 0.5, chloroform). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.39 (2 H, m, Ar-H), 7.25 (4 H, m, Ar-H), 3.72 (6 H, s, 2 x COOMe), 3.31, 2.38 (2 x 2 H, 2 x d, J = 13.2 Hz, 2 x Ar-CH_2), 2.96, 2.83 (2 x 2 H, 2 x d, J = 12.8 Hz, 2 x Ar-CH_2), pinanol residue: 2.48 (2 H, dd, J = 18.3, 3.3 Hz), 2.41 (2 H, ddd, J = 18.3, 3.0, 2.2 Hz), 2.28 (2 H, m, J = 10.6, 5.8, 5.8, 2.2 Hz), 2.07 (2 H, t, J = 5.8 Hz), 1.98 (2 H, m, J =5.8, 5.8, 3.3, 3.0 Hz), 1.44 (2 H, d, J = 10.6 Hz), 1.51 (6 H, s), 1.32 (6 H, s), 0.91 (6 H, s). ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 175.14 (2 x C=O), 138.78, 138.08, 135.73 (2), 135.54 (2) (6 x Ar: =C<), 129.74 (2), 129.34 (2), 127.00, 126.76 (6 x Ar: -CH=), 74.93 (2 x >C<), 38.45 (2), 38.38 (2) (4 x -CH_2), 51.98 (2 x OCH_3), pinanol residue: 175.64 (2), 77.12 (2), 49.89 (2), 42.86 (2), 38.58 (2), 34.12 (2), 29.06 (2), 28.10 (2), 27.32 (2), 22.84 (2). MS (FAB): m/z 681 [M^+ + 1] (100), 229 (85). Anal. Calcd for $C_{42}H_{52}N_2O_6$ (680.9): C, 74.09; H, 7.70; N, 4.11. Found: C, 73.84; H, 7.76; N, 3.98. Its diastereoisomeric purity was checked by HPLC on silica gel in dichloromethane-light petroleum (30 : 70), containing 0.8 % TEA.

(*S*)-*trans*-**2b**. Yield 0.24 g (85%), oil, $[\alpha]_D^{20}$ –181° (c 0.5, chloroform). Its ^1H NMR, ^{13}C NMR and IR data were identical with those of the racemate.

*Dimethyl (*S*)-trans-5,11-di(tert-butoxyamino)-5,6,11,12-tetrahydro-4H,10H-dibenzo[ef,kl]heptalene-5,11-dicarboxylate (*S*)-trans-**2c***

The title compound was prepared from (*S*)-*trans*-**2b** in the same manner as described above for the (*S*)-*cis*-**2c** isomer. Yield 96 mg (83%), mp 141-143 °C. $[\alpha]_D^{20}$ –269 (c 0.5, chloroform). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.31 (1 H, m, Ar-H), 7.17 – 7.23 (5 H, m, Ar-H), 4.88 (2 H, bs, 2 x NH), 3.75(6 H, s, 2 x $COOCH_3$), 3.20, 2.29 (2 x 2 H, d, J = 13.3 Hz, 2 x Ar-CH_2), 3.03, 2.97 (2 x 2 H, 2 x bd, J = 13.6 Hz, 2 x Ar-CH_2), 1.46 (18 H, s,

2 x t-Bu). ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 173.14 (2 x C(=O)-O), 154.59 (2 x O-CO-NH), 138.70, 138.09 (2), 135.48, 134.85 (2) (6 x Ar: =C<), 129.06 (2), 129.02 (2), 127.87, 127.60 (6 x Ar: -CH=), 69.00 (2 x >C<), 52.45 (2 x OCH_3), 41.34 (2), 38.07 (2) (4 x $-CH_2-$), 28.28 (6 x CH_3). IR: ν_{max} (cm^{-1}) 3380, (NH), 1743, 1720 (C=O), 3066, 1597, 791, 775, 739 (arom.). MS (FAB): m/z 581 [M^+ + 1] (3), 481 (23), 57 (100). Anal. Calcd for $C_{32}H_{40}N_2O_8 \cdot H_2O$: C, 64.20; H, 7.07; N, 4.68. Found: C, 64.49; H, 7.05; N, 4.45. The enantiomeric purity was checked by chiral HPLC (Whelk column, Merck; 10% 2-propanol in heptane).

(R)-N-Boc-Mebip-(S)-Mebip-OEt (R),(S)-4

A mixture of amino acid (*R*)-**1d** (210 mg; 0.55 mmol), amino ester (*S*)-**1b** (155 mg; 0.50 mmol), O-benzotriazol-1-yl-N,N,N′,N′-tetramethyluronium hexafluorophosphate[18] (208 mg; 0.55 mmol), N-methylmorpholine (165 μl; 1.5 mmol) and dichloromethane (1 ml) was stirred at r.t. for 1 week. Chromatography of the crude mixture on silica gel (3%EtOH/DCM) afforded 245 mg (73%) of dipeptide (*R*),(*S*)-**4** that slowly crystallized in a refrigerator. Mp at about 135 °C with resolidification, then at 190-192 °C, $[\alpha]_D^{20}$ +23.8 (c 0.5, chloroform). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.25-7.02 (10 H, m, Ar-H), 7.00 (1 H, bd, Ar-H), 6.86 (1 H, bd, Ar-H), 6.84 (1 H, bs, NH), 4.75 (1 H, bs, NH), 4.18, 4.13 (2 x 1 H, 2 x dq, *J* = 10.7, 7.1 Hz, O**CH$_2$**CH_3), 3.30, 2.07 (2 x 1 H, 2 x d, *J* = 13.0 Hz, Ar-CH_2), 3.13, 2.22 (2 x 1H, 2 x d, *J* = 12.8 Hz, Ar-CH_2), 3.10, 2.69 (2 x 1 H, 2 x bd, *J* = 13.5 Hz, Ar-CH_2), 2.88, 2.82 (2 x 1 H, 2 x d, *J* = 13.5 Hz, Ar-CH_2), 2.159, 2.155, 2.146, 2.137 (4 x 3 H, 4 x s, 4 x Ar-CH_3), 1.42 (9 H, bs, t-Bu), 1.20 (3 H, t, *J* = 7.1 Hz, OCH_2**CH_3**). IR: ν_{max} (cm^{-1}) 3409, 3357 (NH), 1729, 1717, 1677 (C=O), 1160 (C-O), 3063, 1594, 783, 743 (arom.). MS (FAB): m/z 673 [M^+ + 1] (15), 573 (35), 236 (100). Anal. Calcd for $C_{43}H_{48}N_2O_5 \cdot 0.5H_2O$: C, 75.74; H, 7.24; N, 4.11. Found: C, 75.55; H, 7.21; N, 4.07.

(S)-N-Boc-Mebip-(S)-Mebip-OEt (S),(S)-4

Prepared in the same manner as above from (*S*)-**1b** and (*S*)-**1d** in 67% yield; glass, $[\alpha]_D^{20}$ –75.2 (c 0.5, chloroform). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.24-7.10 (11 H, m, Ar-H), 6.96 (1 H, bd, Ar-H), 6.90 (1H, bs, NH), 4.50 (1 H, bs, NH), 4.17 (???), 4.17 (2 x 1 H, 2 x dq, *J* = 10.6, 7 Hz, O**CH$_2$**CH_3), 3.29, 2.17 (2 x 1 H, 2 x d, *J* = 12.8 Hz, Ar-CH_2), 3.19, 2.05 (2 x 1 H, 2 x d, *J* ~ 13 Hz, Ar-CH_2), 3.09, 2.67 (2 x 1 H, 2 x bd, *J* ~ 13 Hz, Ar-CH_2), 2.87, 2.84 (2 x 1 H, 2 x bd, *J* ~ 13 Hz, Ar-CH_2), 2.155, 2.130, 2.127, 2.120 (4 x 3H, 4 x s, 4 x Ar-CH_3), 1.37 (9 H, bs, t-Bu), 1.18 (3 H, bt, *J* ~ 7 Hz, OCH_2**CH_3**). MS (FAB): m/z 673 [M^+ + 1] (8), 573 (32), 310 (100), 236 (80). Anal. Calcd for $C_{43}H_{48}N_2O_5 \cdot 0.5H_2O$: C, 75.74; H, 7.24; N, 4.11. Found: C, 75.52; H, 7.52; N, 3.83.

cyclo-(R)-Mebip-(S)-Mebip (R),(S)-5

A solution of dipeptide (*R*),(*S*)-**4** (101 mg; 0.15 mmol) in trifluoroacetic acid (500 μl) was set aside at r.t. for 1 h. The acid was evaporated, the obtained dry dipeptide trifluoroacetate was dissolved in dry methanol (400 μl) and then 2M methanolic sodium methoxide (200 μl) was added. After standing at r.t. for 1 day, the deposited product was collected, washed with methanol and dried; yield 63 mg (80%) of (*R*),(*S*)-**5**, mp at about 250 °C with resolidification, then at 310-312 °C (ethanol). $[\alpha]_D^{20}$ 0 (c 0.5, chloroform). For ^{1}H and ^{13}C NMR data see Tables I and II. IR: ν_{max} (cm^{-1}) 3361, 3200 (NH), 1681, 1664 (C=O), 3064, 3018, 1594, 1573, 781, 742 (arom.). MS (FAB): m/z 527 [M^+ + 1] (100), 236 (30). Anal. Calcd for $C_{36}H_{34}N_2O_2 \cdot 0.25H_2O$: C, 81.40; H, 6.55; N, 5.27. Found: C, 81.66; H, 6.83; N, 4.98.

cyclo-(S)-Mebip-(S)-Mebip (S),(S)-5

A solution of dipeptide (*S*),(*S*)-**4** (101 mg; 0.15 mmol) in trifluoroacetic acid (500 μl) was set aside at r.t. for 1 h. The acid was evaporated, the obtained dry dipeptide trifluoroacetate was dissolved in dry methanol (400 μl) and then 2M methanolic sodium methoxide (200 μl) was added. After standing at r.t. for 1 day, the solution was diluted with water (5 ml) and the crude product was taken up in dichloromethane (3 × 3 ml). Purification by chromatography on silica gel in DCM with 3% EtOH afforded 70 mg (89%) of (*S*),(*S*)-**5**, mp at about 188 °C with resolidification, then at 194-196 °C (toluene-ether), $[\alpha]_D^{20}$ –98.5 (c 0.5, chloroform). For ^{1}H and ^{13}C NMR data see Tables I and II. IR: ν_{max} (cm^{-1}) 3359, 3197 (NH), 1678 (C=O), 3063, 1595, 779, 739 (arom.).

MS (FAB): m/z 527 [M^+ + 1] (100), 236 (35). Anal. Calcd for $C_{36}H_{34}N_2O_2 \cdot 0.25H_2O$: C, 81.40; H, 6.55; N, 5.27. Found: C, 81.56; H, 6.63; N, 5.11.

(R)-N-Boc-Mebip → (S)-cis-*Bibip-(OMe)$_2$ ← (R)-N-Boc-Mebip* *(R),(S),(R)*-cis-***6***

Procedure A: A mixture of amino ester (*S*)-*cis*-**2b** (95 mg; 0.25 mmol), amino acid (*R*)-**1d** (210 mg; 0.55 mmol), O-benzotriazol-1-yl-N,N,N′,N′-tetramethyluronium hexafluorophosphate[18] (209 mg; 0.55 mmol), N-methylmorpholine (165 μl; 1.5 mmol) and dichloromethane (1 ml) was stirred at r.t. for 2 weeks. Chromatography on silica gel (2%EtOH/DCM) afforded 146 mg (53%) of (*R*),(*S*),(*R*)-*cis*-**6**, mp 219-221 °C, $[\alpha]_D^{20}$ –36.5 (c 0.5, chloroform). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.25-7.19 (8 H, m, Ar-H), 7.16 (2 H, t, Ar-H), 7.13 (2 H, t, Ar-H), 7.06 (4 H, bdd, Ar-H), 7.00 (2 H, bdd, Ar-H), 4.55 (2 H, s, 2 × NH), 3.70 (6 H, s, 2 × $COOCH_3$), 3.24, 2.35 (2 x 1 H, 2 x d, J = 13.4 Hz, Ar-CH_2), 3.30, 2.07 (2 x 1 H, 2 x d, J = 12.9 Hz, Ar-CH_2), 3.05, 2.75 (2 x 1 H, 2 x d, J = 14.0 Hz, Ar-CH_2), 2.94 (2 H, bs, Ar-CH_2), 2.15 (12 H, s, 4 × Ar-CH_3), 1.39 (18 H, s, 2 x t-Bu). IR: ν_{max} (cm^{-1}) 3433, 3404, 3361 (NH), 1729, 1716, 1688, (C=O), 1160 (C-O), 3064, 1596, 784, 744 (arom.). MS (FAB): m/z 1108 [M^+ + 1] (20), 1008 (5), 908 (100). Anal. Calcd for $C_{68}H_{74}N_4O_{10}$ (1107.4): C, 73.76; H, 6.74; N, 5.06. Found: C, 73.77; H, 6.83; N, 4.98.

Procedure B: A mixture of amino ester (*RS*)-*cis*-**2b** (190 mg; 0.50 mmol), amino acid (*R*)-**1d** (419 mg; 1.1 mmol), O-benzotriazol-1-yl-N,N,N′,N′-tetramethyluronium hexafluorophosphate[18] (417 mg; 1.1 mmol), N-methylmorpholine (329 μl; 3.0 mmol) and dichloromethane (2 ml) was stirred at r.t. for 2 weeks. Chromatography on silica gel (2%EtOH/DCM) afforded 280 mg (51%) of a mixture of two diastereoisomeric tripeptides, (*R*),(*S*),(*R*)-*cis*-**6** and (*R*),(*R*),(*R*)-*cis*-**6**, which were separated by crystallization. The former isomer crystallized from ethanol. Yield 120 mg (22%).

(R)-N-Boc-Mebip→(R)-cis-*Bibip-(OMe)$_2$←(R)-N-Boc-Mebip* *(R),(R),(R)*-cis-***6***

Prepared from the mother liquors from Procedure B (see the preceding experiment), consisting of an 8:1 mixture of (*R*),(*R*),(*R*)-*cis*-**6** and (*R*),(*S*),(*R*)-*cis*-**6**, by crystallization from toluene-heptane. Yield 115 mg (21%), mp 181-183 °C, $[\alpha]_D^{20}$ +199 (c 0.5, chloroform). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42 (2 H, t, Ar-H), 7.27-7.05 (14 H, m, Ar-H), 6.92 (2 H, bd, Ar-H), 4.46 (2 H, bs, 2 × NH), 3.73 (6 H, s, 2 × $COOCH_3$), 3.61, 2.24 (2 x 1 H, 2 x d, J = 13.4 Hz, Ar-CH_2), 3.11, 2.08 (2 x 1 H, 2 x d, J = 12.7 Hz, Ar-CH_2), 3.00, 2.78 (2 x 1 H, 2 x d, J ~ 14.5 Hz, Ar-CH_2), 2.86 (2 H, bs, Ar-CH_2), 2.15 (6H, s, 2 × Ar-CH_3), 2.12 (6H, s, 2 × Ar-CH_3), 1.27 (18 H, s, 2 × t-Bu). IR: ν_{max} (cm^{-1}) 3408, (NH), 1745, 1725, 1698, (C=O), 3064, 1596, 784, 744 (arom.). MS (FAB): m/z 1108 [M^+ + 1] (28), 1008 (9), 908 (100). Anal. Calcd for $C_{68}H_{74}N_4O_{10}$ (1107.4): C, 73.76; H, 6.74; N, 5.06. Found: C, 74.01; H, 7.01; N, 4.80.

(S)-N-Boc-Mebip→(S)-cis-*Bibip-(OMe)$_2$←(S)-N-Boc-Mebip* *(S),(S),(S)*-cis-***6***

A mixture of amino ester (*S*)-*cis*-**2b** (95 mg; 0.25 mmol), amino acid (*S*)-**1d** (210 mg; 0.55 mmol), O-benzotriazol-1-yl-N,N,N′,N′-tetramethyluronium hexafluorophosphate[18] (209 mg; 0.55 mmol), N-methylmorpholine (165 μl; 1.5 mmol) and dichloromethane (1 ml) was stirred at r.t. for 2 weeks. Chromatography on silica gel in dichloromethane with 2% EtOH afforded 141 mg (51%) of tripeptide (*S*),(*S*),(*S*)-*cis*-**6**, mp 177-179 °C, $[\alpha]_D^{20}$ –184 (c 0.5, chloroform). Its ^{1}H NMR, IR and mass spectra were identical with those of (*R*),(*R*),(*R*)-*cis*-**6**. For ^{1}H NMR and ^{13}C NMR data see Tables I and II.

(S)-N-Boc-Mebip→(S)-trans-*Bibip-(OMe)$_2$←(S)-N-Boc-Mebip* *(S),(S),(S)*-trans-***6***

Prepared from (*S*)-*trans*-**2b** and (*S*)-**1d** by the procedure described above for (*S*),(*S*),(*S*)-*cis*-**6**. Yield 138 mg (50%), mp 192-194 °C, $[\alpha]_D^{20}$ –218 (c 0.5, chloroform). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.15 - 7.34 (14 H, m, Ar-H), 7.06 (2 H, m, Ar-H), 6.96 (2 H, bd, Ar-H), 4.54 (2 H, bs, 2 x NH), 3.72 (6 H, s, 2 x $COOCH_3$), 3.43, 2.27 (2 x 2 H, 2 x d, J = 13.4 Hz, 2 x Ar-CH_2), 3.20, 2.08 (2 x 2H, 2 x d, J = 12.8 Hz, 2 x Ar-CH_2), 3.05, 2.72 (2 x 2 H, 2 x d, J = 13.6 Hz, 2 x Ar-CH_2), 2.94 (4H, bs, 2 x Ar-CH_2), 2.16 (6 H, s, 2 x CH_3), 2.13 (6 H, s, 2 x CH_3), 1.32 (18 H, s, 2 x t-Bu). IR: ν_{max} (cm^{-1}) 3408, (NH), 1743, 1725, 1696 (C=O), 1162 (C-O), 3064, 1596, 784, 742 (arom.). MS(FAB): m/z 1108 [M^+ + 1](12), 1008 (100), 908 (7). HRMS (FAB) calcd for $C_{68}H_{74}N_4O_{10}$: 1107.5483. Found: 1107.5477.

(R)-N-Boc-Mebip→(S)-trans-*Bibip-(OMe)$_2$←(R)-N-Boc-Mebip* *(R),(S),(R)*-trans-***6***

Prepared from (*S*)-*trans*-**2b** and (*R*)-**1d** by the procedure described above for (*S*),(*S*),(*S*)-*cis*-**6**. Yield 135 mg (49%), mp 209-211 °C, $[\alpha]_D^{20}$ –9.4 (c 0.5, chloroform). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.25-6.95 (18 H, m, Ar-H), 4.56 (2 H, s, 2 × NH), 3.73 (6 H, s, 2 × $COOCH_3$), 3.30, 2.39 (2 x 1 H, 2 x d, *J* = 13.4 Hz, Ar-CH_2), 3.28, 2.09 (2 x 1 H, 2 x d, *J* = 12.9 Hz, Ar-CH_2), 3.08, 2.75 (2 x 1 H, 2 x d, *J* = 14.0 Hz, Ar-CH_2), 3.00 (2 H, bs, Ar-CH_2), 2.16 (6 H, s, 2 × Ar-CH_3), 2.15 (6 H, s, 2 × Ar-CH_3), 1.40 (18 H, s, 2 × t-Bu). MS (FAB): m/z 1108 [M^+ + 1] (25), 1008 (100), 908 (7). HRMS (FAB) calcd for $C_{68}H_{74}N_4O_{10}$: 1107.5483. Found: 1107.5475.

cyclo-(R)-Mebip-[cyclo-(S)-cis-*Bibip-(R)-Mebip]* *(R),(S),(R)*-cis-***7**

A solution of tripeptide (*R*),(*S*),(*R*)-*cis*-**6** (111 mg; 0.1 mmol) in trifluoroacetic acid (600 μl) was set aside at r.t. for 2 h. The acid was evaporated, the obtained dry dipeptide trifluoroacetate was dissolved in dry methanol (5 ml) and then 2M methanolic sodium methoxide (200 μl) was added. After heating at 50 °C for 6 h and standing at r.t. for 18 h, the solution was diluted with water (5 ml) and the crude product was taken up in dichloromethane (3 × 3 ml). Purification by chromatography on silica gel in DCM with 2% EtOH afforded the desired product (*R*),(*S*),(*R*)-*cis*-**7**. Yield 54 mg (64%), mp >360 °C (dichloromethane-methanol), $[\alpha]_D^{20}$ –23.8 (c 0.5, chloroform). For ^{1}H and ^{13}C NMR data see Tables I and II. MS (FAB): m/z 843 [M^+ + 1] (100). HRMS (FAB) calcd for $C_{56}H_{51}N_4O_4$: 843.3910. Found: 843.3917.

cyclo-(S)-Mebip-[cyclo-(S)-cis-*Bibip-(S)-Mebip]* (S),(S),(S)-cis-***7**

Prepared from (*S*),(*S*),(*S*)-*cis*-**6** analogously as described for (*R*),(*S*),(*R*)-*cis*-**7**. Yield 47 mg (56%), mp >360 °C (dichloromethane-methanol), $[\alpha]_D^{20}$ –269 (c 0.5, chloroform). For ^{1}H and ^{13}C NMR data see Tables I and II. IR: ν_{max} (cm^{-1}) 3363, 3192 (NH), 1680 (C=O), 3063, 3020, 1596, 784, 740 (arom.). MS (FAB): m/z 843 M^+ + 1 (100). Anal. Calcd for $C_{32}H_{40}N_2O_8 \cdot 1.5H_2O$: C, 77.31; H, 6.14; N, 6.44. Found: C, 77.19; H, 6.15; N, 6.52.

cyclo-(R)-Mebip-[cyclo-(R)-cis-*Bibip-(R)-Mebip]* *(R),(R),(R)*-cis-***7**

Prepared from (*R*),(*R*),(*R*)-*cis*-**6** analogously as described for (*R*),(*S*),(*R*)-*cis*-**7**. Yield 49 mg (58%), mp >360 °C (dichloromethane-methanol), $[\alpha]_D^{20}$ +248 (c 0.5, chloroform). The ^{1}H NMR, ^{13}C NMR and IR spectra were identical with those of (*S*),(*S*),(*S*)-*cis*-**7** (see Tables I and II). MS (FAB): m/z 843 [M^+ + 1] (100). HRMS (FAB) calcd for $C_{56}H_{51}N_4O_4$: 843.3910. Found: 843.3905.

cyclo-(R)-Mebip-[cyclo-(S)-trans-*Bibip-(R)-Mebip]* *(R),(S),(R)*-trans-***7**

Prepared from (*R*),(*S*),(*R*)-*trans*-**6** as described for the compounds of the *cis*-**7** series. Yield 44 mg (52%), mp >360 °C (dichloromethane-methanol), $[\alpha]_D^{20}$ +2.7 (c 0.5, chloroform). For ^{1}H and ^{13}C NMR data see Tables I and II. MS (FAB): m/z 843 M^+ + 1 (100). HRMS (FAB) calcd for $C_{56}H_{51}N_4O_4$: 843.3910. Found: 843.3919.

cyclo-(S)-Mebip-[cyclo-(S)-trans-*Bibip-(S)-Mebip]* *(S),(S),(S)*-trans-***7**

Prepared from (*S*),(*S*),(*S*)-*trans*-**6** as described for the compounds of the *cis*-**7** series. Yield 47 mg (56%), mp >360 °C (dichloromethane-methanol), $[\alpha]_D^{20}$ –282 (c 0.5, chloroform). For ^{1}H and ^{13}C NMR data see Tables I and II. IR: ν_{max} (cm^{-1}) 3363, 3254, 3212 (NH), 1686 (C=O), 3063, 3018, 1596, 784, 735 (arom.). MS (FAB): m/z 843 [M^+ + 1] (100). Anal. Calcd for $C_{32}H_{40}N_2O_8 \cdot 2.5H_2O$: C, 75.83; H, 6.11; N, 6.43. Found: C, 75.74; H, 6.24; N, 6.31.

Single crystal X-ray of (S)-cis-***3***

(S)-cis-**3**, $C_{42}H_{52}N_2O_6$, M = 680.86, orthorhombic, space group $P2_12_12_1$ (No. 19), *a* = 10.472(2), *b* = 14.139(2), *c* = 24.599(3) Å, *V* = 3642(1) Å^3, *Z* = 4, D_c = 1.242 g/cm^3. A colourless parallelepiped of the dimensions 0.24 x 0.43 x 0.80 mm was measured at 150(2) K on a CAD4 diffractometer (MoK_α radiation, λ = 0.71069 Å). Using the θ-2θ scan, 4425 independent reflections were collected in the range *h* = 0 to 13, *k* = 0 to 18, *l* = 0 to 31; 3824 reflections were regarded as observed according to the $I > 2\sigma(I)$ criterion. Three standard reflections measured every hour displayed 3.1 % intensity decrease. Absorption was neglected (μ = 0.082 mm^{-1}). The structure was solved by direct methods (SIR[22]) and refined by full-matrix least squares based on F^2 (SHELXL97[23]). The tertiary and hydroxyl hydrogen atoms were refined isotropically, the other were fixed in

calculated positions and assigned temperature parameters 1.2 of those of their bonding partners. The refinement for 475 parameters converged to $R = 0.0358$, $wR = 0.1284$, $GOF = 1.075$. The final difference map displayed no peaks of chemical significance. Full crystallographic data are available by e-mail from J. P. on request and have been also deposited (except structure factors) by Cambridge Crystallographic Data Centre.

Acknowledgement

The financial support by the Grant Agency of the Academy of Sciences of the Czech Republic (grant No. A40550) and by the Grant Agency of the Czech Republic (grants No. 203/97/0025 and 203/97/0242) is gratefully acknowledged.

References and Notes

1. Ridvan L., Abdallah N., Holakovský R., Tichý M., Závada J. *Tetrahedron: Asymmetry* **1996**, *7*, 231-236.
2. In accord with the established practice of the "stenographic" notation of amino acids, symbol Bip has been coined for the non-methylated analogue of the amino acid **1a**; ref. 3. As an extension, we now propose the symbol Mebip and Bibip for the homologous structures **1a** and **2a**.
3. Mazaleyrat J.-P., Gaucher A., Wakselman M., Tchertanov L., Guilhem J. *Tetrahedron Lett.* **1996**, *37*, 2971-2974.
4. This is the nineth of the series of papers dealing with axially chiral biaryl amino acids, their derivatives and analogues; for previous papers see ref. 5.
5. Tichý M., Holanová J., Závada J. *Tetrahedron: Asymmetry* **1998**, *9*, 3497-3504.
6. Synthesis of the racemic bis(amino acid)s has been already reported elsewhere; ref. 7.
7. Tichý M., Ridvan L., Buděšínský M., Závada J., Podlaha J., Císařová I. *Collect .Czech. Chem. Commun.* **1998**, *63*, 211-221.
8. In common helical polymers such as poly(amino acid)s, polymethacrylates or polyisocyanates, the stereochemistry is different since the polymeric backbone does not coincide with the axis of helicity but, instead, winds up around it; ref. 9.
9. Okamoto Y., Nakato T. *Chem. Rev.* **1994**, *94*, 349-372.
10. Customarily, the helical topology of common polymers and biopolymers is based on the secondary and/or tertiary structure. To our best knowledge, no authentic polymer with primary helical structure has been reported so far. Synthetic approaches to such structures ("helixates") never exceeded the level of the lowest oligomers; cf.,e.g., ref. 11.
11. (a) Gange D., Magnus P., Bass L., Arnold E.V., Clardy J. *J. Am. Chem. Soc.* **1980**, *102*, 2134-2135; (b) Bělohradský M., Buděšínský M., Günterová J., Hodačová J., Holý P., Závada J. *J. Org. Chem.* **1996**, *61*, 1205-1210; (c) Bělohradský M., Buděšínský M., Günterová J., Hodačová J., Holý P., Závada J. *Tetrahedron* **1996**, *52*, 11013-11024.
12. Palacin S., Chin D.N., Simanek E.E., MacDonald J.C., Whitesides G.M., McBride M.T., Palmore G.T.R. *J. Am. Chem. Soc.* **1997**, *119*, 11807-11816.
13. Bajgrowicz J.A., Cossec B., Pigiere Ch., Jacquier R., Viallefont Ph. *Tetrahedron Lett.* **1984**, *17*, 1789-1792.
14. The relatively low inversion barriers in the tetracyclic tetrahydroheptalene derivatives (in contrast to tricyclic 6,7-dihydro-5*H*-dibenzo[*a,c*]cycloheptene systems) have been already discussed by Mislow (ref. 15), and also observed by us (ref. 16a) in aza-bridged systems of analogous structure.
15. Mislow K., Glass M.A.W., Hopps H.B., Simon E., Wahl G.H., Jr. *J.Am.Chem.Soc.* **1964**, *86*, 1710-1733.
16. (a) Tichý M., Günterová J., Závada J. *Collect. Czech. Chem. Commun.* **1997**, *62*, 1080-1088; (b) Tichý M., Ridvan L., Holý P., Závada J., Císařová I., Podlaha J. *Tetrahedron: Asymmetry* **1998**, *9*, 227-234.
17. The opposite stereoisomers *cis*-(*R*)-**2d** and *trans*-(*R*)-**2d** (not required in the present study) are accessible from the racemic precursors *cis*-(*RS*)-**2b** and *trans*-(*RS*)-**2b** by an analogous reaction sequence involving (1*R*,2*R*,5*R*)-2-hydroxy-3-pinanone which is also commercially available (Aldrich).
18. Knorr R., Trzeciak A., Bannwarth W., Gillessen D. *Tetrahedron Lett.* **1989**, *30*, 1927-1930.
19. Wittig G., Zimmermann H. *Chem. Ber.* **1953**, *86*, 629-640.
20. O'Donnell M.J., Bennett W.D., Bruder W.A., Jacobsen W.N., Knuth K., LeClef B., Polt R.L., Bordwell F.G., Mrozack S.R., Cripe T.A. *J. Am. Chem. Soc.* **1988**, *110*, 8520-8525.

21. Arai I., Muramatsu I. *J. Org. Chem.* **1983**, *48*, 121-123.
22. Altomare A., Burla M. C., Camalli M., Cascarano G., Giacovazzo C., Guagliardi A., Polidori G. *J. Appl. Crystallogr.* **1994**, *27*, 435.
23. Sheldrick G.M. *SHELXL97. Program for Crystal Structure Refinement from Diffraction Data.* University of Göttingen, Göttingen, Germany 1997.