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Synthesis and resolution of β^{2,2}-HBin, the first enantiomerically stable β-amino acid with chirality only due to axial dissymmetry

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Abstract—The first *gem*-disubstituted β^{2,2}-amino acid possessing only axial chirality, was synthesized by bis-alkylation of methyl or ethyl cyanoacetate with both racemic and enantiomerically pure (*R*)-2,2′-bis-(bromomethyl)-1,1′-binaphthyl, followed by $NaBH_4/CoCl_2$ reduction of the cyano group, treatment of the resulting amino esters with Boc_2O and finally saponification of the ester function, to afford the *C*- and/or *N*-protected derivatives of 2′,1′:1,2;1″,2″:3,4-dinaphthcyclohepta-1,3-diene-6-aminomethyl-6-carboxylic acid: (*RS*)- and (*R*)-X-β^{2,2}-HBin-OR (X = Boc; H) (R = Me, Et or H). For the medium-scale resolution of β^{2,2}-HBin, the racemic amino esters (*RS*)-H-β^{2,2}-HBin-OR (R = Me, Et) were treated with benzoic anhydride and the resulting derivatives (*RS*)-Bz-β^{2,2}-HBin-OR were saponified. The obtained (*RS*)-Bz-β^{2,2}-HBin-OH was coupled with L-phenylalanine cyclohexylamide by the EDC/HOBt method to afford the dipeptide diastereoisomers Bz-(*R*)-Bin-L-Phe-NH-C_6H_{11} and Bz-(*S*)-Bin-L-Phe-NH-C_6H_{11}, which were separated by chromatography. Complete hydrolysis under acidic conditions, followed by esterification of the resulting free amino acid enantiomers, *N*-protection and saponification, led to the enantiomerically pure derivatives (*R*)- and (*S*)-X-β^{2,2}-HBin-OR (X = Boc; H) (R = Me, H).

1. Introduction

The field of β-peptides has attracted considerable interest in the past few years[1,2] following the extensive studies of Seebach,[1–5] Gellman[1,6] and other groups,[1] who have shown that β-peptides may adopt stable secondary structures of an even greater variety than their α-peptide counterparts. Besides parallel and antiparallel sheet structures, two turn motifs and at least two new stable helical conformations: 3_{14} and 2.5_{12} helices,[1–6] have been discovered in oligomers of β-amino acids, different in nature from those adopted by oligomers of α-amino acids and C$^{\alpha,\alpha}$-disubstituted glycines: 3.6_{13} (α) and 3_{10} helices.[7]

In previous studies, we have shown that the C$^{\alpha,\alpha}$-disubstituted glycines Bip and Bin[8] possessing only axial chirality, behave as helix inducers in short-chain peptides.[9] In connection with this, we found it interesting to synthesize β^{2,2}-HBip and β^{2,2}-HBin (Fig. 1),[10] which are β-analogues of Bip and Bin. However, although conformational analysis of the homopeptides Boc-(β^{2,2}-HBip)$_n$-OMe suggested the concomitant occurrence of intramolecularly H-bonded forms of different ring size

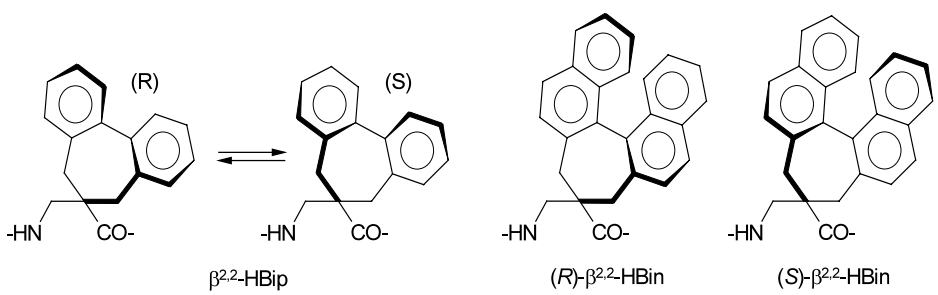

Figure 1. Structure of the axially dissymmetric β^{2,2}-HBip and β^{2,2}-HBin residues.

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in these oligomers, precise structural information could not be obtained, presumably because of the conformational lability of the β[2,2]-HBip residue.[11]

Since the folding patterns of peptides based on the corresponding axially chiral and *conformationally rigid* β[2,2]-HBin residue could probably be more easily investigated, both in the solid state (because of expected higher crystallinity) and in solution (where simpler FT-IR and ^{1}H NMR absorption spectra are expected) we targeted the synthesis of both enantiomers of β[2,2]-HBin in enantiomerically pure form. Herein, we report (i) the direct preparation of a sample of protected (*R*)-β[2,2]-HBin from the known enantiomerically pure (*R*)-2,2′-bis(bromomethyl)-1,1′-binaphthyl, allowing the determination of both its absolute configuration and its maximum specific rotation[10] and (ii) the resolution of racemic β[2,2]-HBin using L-phenylalanine cyclohexylamide as chiral auxiliary, according to the method proposed for the α-amino acids by Obrecht et al.[12] and previously applied by us in the successful resolution of the Bin residue,[13] allowing access to relatively large quantities of both enantiomers. The preparation of other enantiopure or achiral geminally disubstituted β-amino acids has been recently reviewed.[2] The β[2,2]-HBin residue may be regarded as either a 1,1′-binaphthyl-substituted 3-amino-2,2-dimethylpropanoic acid (homo-aminoisobutyric acid: β[2,2]-HAib),[14] or a dinaphtho-1-aminomethyl-cycloheptane carboxylic acid related to the 1-aminomethylcycloalkane carboxylic acid series β[2,2]-HAc$_n$c previously investigated by Seebach et al.[4] It is also the *first β-amino acid with chirality only due to axial dissymmetry*. Furthermore, in contrast to β[2,2]-HBip, it is expected to be conformationally stable even at high temperatures, according to the known very high conformational stability of 2,2′-bis(methylene)-substituted-1,1′-binaphthyls.[15]

2. Results and discussion

2.1. Direct synthesis of *C*- and *N*-protected derivatives of (*R*,*S*)-β[2,2]-HBin and (*R*)-β[2,2]-HBin

As in the previously observed bis-alkylation of benzylidene derivatives of glycine esters,[5] α,α-bis-alkylation of the active methylene of ethyl or methyl cyano-acetate in DMF/K_2CO_3 at 20°C, using both racemic (*RS*)- and enantiomerically pure (*R*)-2,2′-bis(bromomethyl)-1,1′-binaphthyl,[16] as the alkylating agent, readily furnished the cyanoesters (*RS*)-**1a** (94%), (*RS*)-**1b** (91%) and (*R*)-**1a** (79%) with $[\alpha]_{546}^{25}=-358$ (*c* 0.3; MeOH) (Fig. 2) in

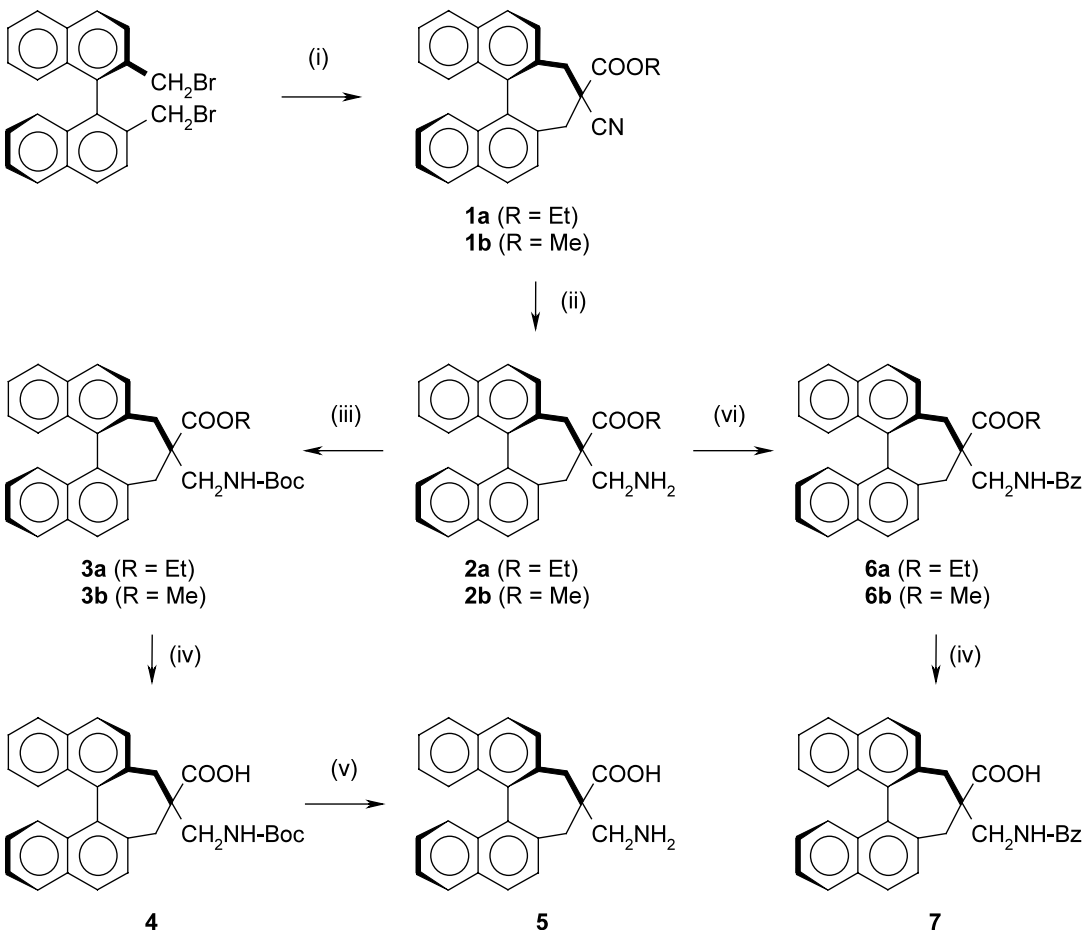

Figure 2. Synthetic scheme for the preparation of the α,α-disubstituted-β-aminoacid derivatives (*RS*)- and (*R*)-β[2,2]-HBin **2**–**7** (only the *R* configuration of the binaphthyl unit is represented). (i) EtOOC–CH_2–CN or MeOOC–CH_2–CN, DMF, K_2CO_3; (ii) $NaBH_4$, $CoCl_2$, MeOH; (iii) Boc_2O, CH_3CN; (iv) 1N NaOH, MeOH, 80°C; (v) TFA:CH_2Cl_2 1:1; (vi) Bz_2O, CH_3CN.

excellent yields. The cobalt(II)-assisted selective reduction method of nitriles in the presence of an ester function,[17] was applied to the *gem*-cyanoesters **1a** and **1b** which, upon treatment with sodium borohydride (10 equiv.) and cobalt(II) chloride (2 equiv.) in methanol at room temperature, gave the amino esters H-β^{2,2}-HBin-OEt (*R*,*S*)-**2a** (53%), (*R*)-**2a** (59%) with $[\alpha]_{546}^{25}=-297$ (*c* 0.2; MeOH) and H-β^{2,2}-HBin-OMe (*RS*)-**2b** (67%). The harshly acidic workup necessary for decomposition of the Co_2B complexes is probably responsible for the relatively low chemical yields. The alternative Raney-Ni reduction method has been reported to work efficiently for similar *gem*-cyanoesters.[4a]

The *N*-Boc-protected derivatives were synthesized in two steps from the *C*-protected derivatives **2a** and **2b**, which were first treated with di-*tert*-butyl dicarbonate in acetonitrile at room temperature[18] to give the fully protected compounds Boc-β^{2,2}-HBin-OEt (*RS*)-**3a** (89%), (*R*)-**3a** (63%) with $[\alpha]_{546}^{25}=-178$ (*c* 0.2; MeOH) and Boc-β^{2,2}-HBin-OMe (*RS*)-**3b** (93%). Saponification of the ester function of **3a** and/or **3b**, performed in aqueous 1N NaOH/MeOH at ca. 80°C, a relatively high temperature often required for α,α-disubstituted-amino esters,[4a,8b] afforded the *N*-Boc protected amino acids Boc-β^{2,2}-HBin-OH (*R*,*S*)-**4** (98%) and (*R*)-**4** (99%) with $[\alpha]_{546}^{25}=-153$ (*c* 0.2; MeOH). Finally, cleavage of the Boc group of samples of **4** in TFA/CH_2Cl_2 (1:1) at room temperature led to the free amino acid trifluoroacetates H-β^{2,2}-HBin-OH·CF_3COOH (*RS*)-**5** (62%) and (*R*)-**5** (57%) with $[\alpha]_{546}^{25}=-255$ (*c* 0.2; MeOH).

2.2. Resolution of (*RS*)-β^{2,2}-Hbin

We decided to follow Obrecht's resolution conditions[12] as closely as possible because they have previously been demonstrated to be efficient in the resolution of the corresponding α,α-disubstituted α-amino acid, Bin.[13] Therefore, a benzoyl group was chosen for protection of the amino function of the racemic amino esters (*RS*)-**2a** and (*RS*)-**2b**, which were treated with benzoic anhydride Bz_2O in acetonitrile at room temperature, to give Bz-β^{2,2}-HBin-OEt (*RS*)-**6a** (92%) and Bz-β^{2,2}-HBin-OMe (*RS*)-**6b** (86%) (Fig. 2). Saponification of the ester function of (*RS*)-**6a** and (*RS*)-**6b** in aqueous 1N NaOH/MeOH at ca. 80°C, afforded the *N*-protected amino acid Bz-β^{2,2}-HBin-OH (*RS*)-**7** (96%). This compound was coupled with L-phenylalanine cyclohexylamide, prepared as previously described,[12] by using the EDC/HOBt method in CH_2Cl_2/THF at room temperature, to give a 1:1 mixture of diastereoisomeric dipeptides Bz-(*R*)-β^{2,2}-HBin-L-Phe-NH-C_6H_{11} (*R*,*S*)-**8** and Bz-(*S*)-β^{2,2}-HBin-L-Phe-NH-C_6H_{11} (*S*,*S*)-**8** (Fig. 3) in 78% yield after chromatography. However, in contrast to the case of Bin, where the corresponding (*RS*)-dipeptide diastereoisomer could be easily separated by crystallization because of its high crystallinity from ethyl acetate,[13] attempts at the separation of (*R*,*S*)-**8** and (*S*,*S*)-**8** by crystallization were unsuccessful, as only an amorphous white solid consisting of a mixture of isomers could be obtained. Fortunately, these two diastereoisomers, which presented distinct spots of close R_f on analytical TLC, could be separated by HPLC on silica gel (conventional column chromatography or preparative TLC was only successful on very small scale), leading to pure (*R*,*S*)-**8** with $[\alpha]_{546}^{25}=-11$ (*c* 0.1;

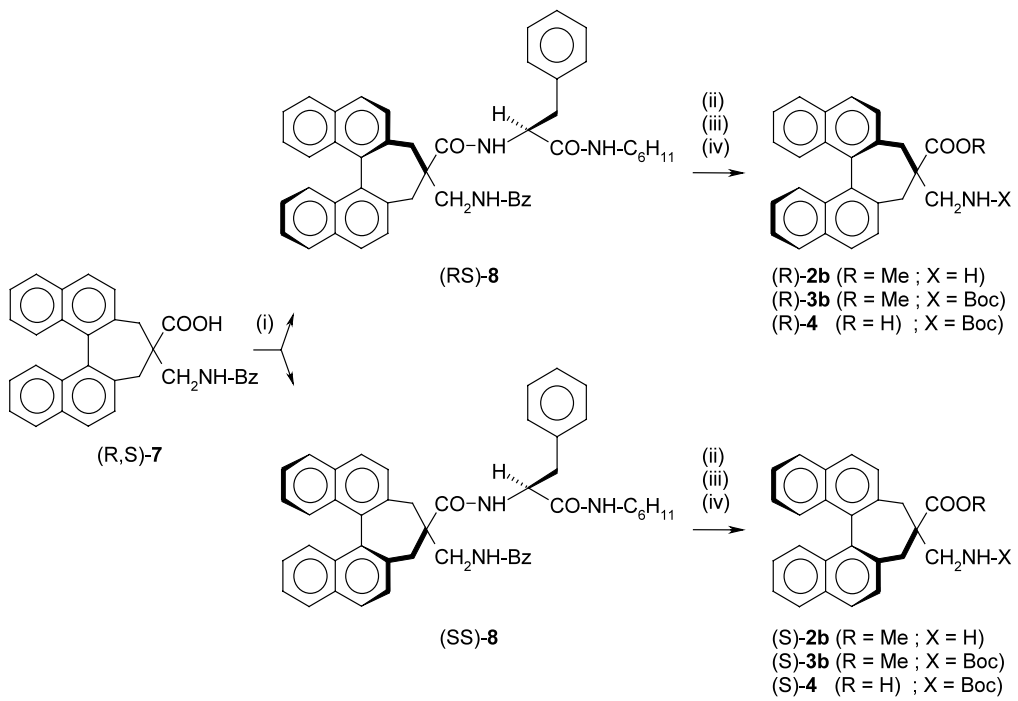

Figure 3. Resolution of (*RS*)-β^{2,2}-HBin. (i) H-L-Phe-NH-C_6H_{11}, EDC, HOBt, CH_2Cl_2/THF, rt; (ii) 1. 35% aq. HCl (10 M)/dioxane (1:1 vol./vol.), 110°C, 6–8 days. 2. MeOH/98% H_2SO_4 (cat.), reflux, 3 days; (iii) Boc_2O, CH_3CN; (iv) 1N NaOH, MeOH, 80°C.

MeOH) in 95% yield[19] and (*S*,*S*)-**8** with $[\alpha]_{546}^{25}=+141$ (*c* 0.15; MeOH) in 56% yield.[19] The absolute configuration of the binaphthyl unit in the two diastereoisomers was established according to the further recovery of (*R*)-**2b**, (*R*)-**3b** and (*R*)-**4** from (*R*,*S*)-**8** and of (*S*)-**2b**, (*S*)-**3b** and (*S*)-**4** from the acidic hydrolysis of (*S*,*S*)-**8** (vide infra).

Acid hydrolysis of (*R*,*S*)-**8** and (*S*,*S*)-**8** was performed in a 1:1 mixture of 10N aqueous HCl and dioxane at 110°C for several days, which effected cleavage of all the amide functions in a single step. The resulting free amino acids H-β^{2,2}-HBin-OH·HCl (*R*)-**5** and (*S*)-**5**, respectively, were not purified but directly esterified in refluxing methanol/H_2SO_4 to the corresponding amino esters H-β^{2,2}-HBin-OMe (*R*)-**2b** (68%,[19] crude) and (*S*)-**2b** (75%,[19] crude). Again, it was found more convenient to complete to a chromatographic purification only after the next step of *N*-protection by a *tert*-butyloxycarbonyl (Boc) group. Therefore, these crude amino esters were treated with an excess of Boc_2O in acetonitrile at room temperature and the crude reaction products purified by column chromatography to afford the corresponding Boc-β^{2,2}-HBin-OMe (*R*)-**3b** (69%) with $[\alpha]_{546}^{25}=-180$ (*c* 0.2; MeOH) and (*S*)-**3b** (65%) with $[\alpha]_{546}^{25}=+179$ (*c* 0.2; MeOH). From these analytically pure fully protected derivatives, it was easy, when required, to either hydrolyze the Boc protecting group with TFA/CH_2Cl_2 (1:1) at room temperature back to the crude but analytically pure free amino esters H-β^{2,2}-HBin-OMe (*R*)-**2b** (98%) with $[\alpha]_{546}^{25}=-289$ (*c* 0.1; MeOH) and (*S*)-**2b** (99%) with $[\alpha]_{546}^{25}=+299$ (*c* 0.1; MeOH), or to proceed to saponification of the ester function in aqueous 1N NaOH/MeOH at ca. 80°C, to afford the analytically pure crude *N*-Boc protected amino acids Boc-β^{2,2}-HBin-OH (*R*)-**4** (94%) with $[\alpha]_{546}^{25}=-200$ (*c* 0.2; MeOH) and (*S*)-**4** (73%) with $[\alpha]_{546}^{25}=+215$ (*c* 0.2; MeOH).

As already pointed out, the absolute configuration of the β^{2,2}-HBin derivatives **2b**, **3b** and **4** resulting from resolution was readily established by comparison of the signs of their optical rotation with those of the derivatives of (*R*)-configuration resulting from direct synthesis. In the same manner, the enantiomeric purity of the (*R*)- and (*S*)-enantiomers obtained by resolution was shown to be very high, according to the observed absolute values of their specific rotations, which were similar to the ones of the corresponding enantiomerically pure samples resulting from direct synthesis. A more precise determination of the enantiomeric excess of the resolved H-β^{2,2}-HBin-OMe (*R*)-**2b** and (*S*)-**2b** enantiomers was performed, both by HPLC on β-cyclodextrin-bonded phases or after derivatization with 1-fluoro-2,4-dinitrophenyl-5-L-alanine amide,[20] and by $^1H/^{19}F$ NMR after treatment of an aliquot of both samples with (−)-(*S*)-α-methoxy-α-trifluoromethyl-α-phenyl-acetic acid anhydride, resulting from reaction of the Mosher's acid[21] with a half-equiv. of EDC,[8b] which led to the diastereoisomeric amido esters (*S*)-Ph(OCH$_3$)(CF$_3$)C-CO-(*R*)-β^{2,2}-HBin-OMe with >98% d.e. from (*R*)-**2b** and (*S*)-Ph(OCH$_3$)(CF$_3$)C-CO-(*S*)-β^{2,2}-HBin-OMe with >97% d.e. from (*S*)-**2b**. It is noteworthy that splitting of NMR signals of the two diastereoisomers occurred in spite of the β position of the chiral carbon atom of the Mosher's reagent. The very high enantiomeric purity of the recovered samples of (*R*)-**2b** and (*S*)-**2b** demonstrates the expected absence of racemization of the 2,2′-substituted-1,1′-binaphthyl unit,[15] also previously observed for the corresponding Bin derivatives,[13] under the rather drastic experimental conditions of hydrolysis of the dipeptides (*R*,*S*)-**8** and (*S*,*S*)-**8**.

In conclusion, the present medium scale resolution of the readily available racemic β^{2,2}-HBin residue to afford both of its enantiomers in enantiomerically pure form (or nearly so) and in ca. 30% overall yield,[19] has shown that the efficient method of Obrecht et al.[12] for resolution of α,α-disubstituted α-amino acids, using L-phenylalanine cyclohexylamide as resolving agent, can be extended not only to α-amino acids with axial chirality instead of stereogenicity at the α-carbon,[13] but also to axially dissymmetric α,α-disubstituted β-amino acids. As emphasized earlier, β^{2,2}-HBin is the lead of a new class of axially chiral β-amino acids, potentially useful for the synthesis of new catalysts and new conformationally constrained peptides with atropisomerism. The synthesis of β-peptides based on (*S*)- or (*R*)-β^{2,2}-HBin with a view to their conformational analysis is currently in progress. Interesting initial targets are the homopeptides (β^{2,2}-HBin)$_n$ in connection with the corresponding series of β^{2,2}-HAc$_n$c[4] and (β^{2,2}-HBip)$_n$[11] previously investigated, as well as the cyclopeptides c[β^{2,2}-HBin]$_n$ as potential inducers of new chiral tubular structures.[5,22]

3. Experimental

3.1. General

Racemic and enantiomerically pure 2,2′-bis(bromomethyl)-1,1′-binaphthyl,[16] as well as L-phenylalanine cyclohexylamide,[12] were prepared as previously described. (−)-(*S*)-α-Methoxy-α-trifluoromethyl-α-phenylacetic acid (99+%) was purchased from Aldrich. Melting points were determined with a temperature rise of 3°C/min and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 300 and 77 MHz, respectively, the solvent $CDCl_3$, DMSO-d_6, or CD_3OD being used as internal standard ($\delta=7.27$, 2.51 or 3.31 ppm, respectively, for ^1H and 77.0, 39.5 or 49.0 ppm for ^{13}C). Splitting patterns are abbreviated as follows: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet. The optical rotations were measured with an accuracy of 0.3%, in a 1 dm thermostated cell. Analytical thin-layer chromatography (TLC) and preparative column chromatography were performed on Kieselgel F 254 and on Kieselgel 60 (0.040–0.063 mm) (Merck), respectively, with the following eluent systems: CH_2Cl_2 (I); 2.5% MeOH–97.5% CH_2Cl_2 (II); 3% MeOH–97% CH_2Cl_2 (III);5% MeOH–95% CH_2Cl_2 (IV); 10% MeOH–90% CH_2Cl_2 (V); 30% Et_2O–70% pentane (VI); 15% Et_2O–85% CH_2Cl_2 (VII); 1% AcOEt–99% CH_2Cl_2 (VIII), 50% Et_2O–50% CH_2Cl_2 (IX). UV light (254 nm) allowed

visualization of the spots after TLC runs for all compounds, even at low concentration. HPLC was performed with a Gilson chromatograph equipped with a SPD-6A Shimadzu UV spectrophotometer and a C-R 5A Shimadzu integrator, using a Merck lobar column, size C (440-37), pre-packed with lichroprep Si 60, 40–63 μm.

3.2. 2′,1′:1,2;1″,2″:3,4-Dinaphthcyclohepta-1,3-diene-6-cyano-6-carboxylic acid ethyl ester (*RS*)-1a and (*R*)-1a

A mixture of (*R*,*S*)-2,2′-bis(bromomethyl)-1,1′-binaphthyl[16] (4.40 g; 10 mmol), ethylcyanoacetate (1.28 mL; 12 mmol) and anhydrous potassium carbonate (3.31 g; 24 mmol), in DMF (20 mL) was magnetically stirred at room temperature for 16 h. The reaction mixture was then poured into water and extracted with diethyl ether (150 mL), the organic layer was washed with water (5×20 mL), dried ($MgSO_4$), filtered and evaporated in vacuo. The resulting white solid was chromatographed on a 50×3 cm column of silica gel with eluent (I) to give pure (*RS*)-**1a** as a white solid (3.70 g, 94%). Mp = 164.4°C. R_f = 0.5 (I). ^{1}H NMR ($CDCl_3$): 8.03–7.24 [m, 12H, ArH], 4.31 [m, 2H, OCH_2], 3.44 and 2.93 [d,d, J = 13.4, 2H, CH_2 β], 3.18 and 3.08 [d,d, J = 13.6, 2H, CH_2 β′], 1.37 [t, J = 7.2, 3H, CH_3]. ^{13}C NMR ($CDCl_3$): 167.5 (C=O), 134.5, 134.2, 133.5, 133.3, 132.1, 131.8, 131.6, 131.5 (CAr), 129.0, 128.4, 128.3, 128.0, 127.5, 127.1, 127.0, 126.1, 126.0, 125.7, (CHAr), 119.4 (C≡N), 63.0 (OCH_2), 52.9 (Cα), 39.3 (CH_2 β), 38.9 (CH_2 β′), 14.0 (CH_3). Anal. $C_{27}H_{21}NO_2$: calcd C 82.84, H 5.41, N 3.58; found C 83.03, H 5.61, N 3.43%.

(*R*)-**1a** was prepared in the same way as (*RS*)-**1a** from (*R*)-2,2′-bis(bromomethyl)-1,1′-binaphthyl[16] (2.20 g; 5 mmol), ethylcyanoacetate (0.64 mL; 6 mmol) and anhydrous potassium carbonate (1.65 g; 12 mmol), in DMF (10 mL) afforded, after column chromatography (SiO_2; eluent I), (*R*)-**1a** as a white solid (1.55 g, 79%). Mp = 146.7°C. $[\alpha]_{589}^{25} = -300$; $[\alpha]_{578}^{25} = -314$; $[\alpha]_{546}^{25} = -358$; $[\alpha]_{436}^{25} = -577$; $[\alpha]_{365}^{25} = -297$ (*c* 0.3; MeOH). Anal. $C_{27}H_{21}NO_2$: calcd C, 82.84; H, 5.41; N, 3.58; found C, 82.97; H, 5.51; N, 3.38%.

3.3. 2′,1′:1,2;1″,2″:3,4-Dinaphthcyclohepta-1,3-diene-6-cyano-6-carboxylic acid methyl ester (*RS*)-1b

Prepared in the same way as (*RS*)-**1a** using (*R*,*S*)-2,2′-bis(bromomethyl)-1,1′-binaphthyl (4.40 g; 10 mmol), methylcyanoacetate (1.06 mL; 12 mmol), anhydrous potassium carbonate (3.31 g; 24 mmol), and DMF (10 mL) to afford, after column chromatography (SiO_2; eluent VI), (*RS*)-**1b** as a white solid (3.43 g, 91%). Mp = 205.2°C. R_f = 0.7 (I). ^{1}H NMR ($CDCl_3$): 8.03–7.24 [m, 12H, ArH], 3.86 [s, 3H, OCH_3], 3.43 and 2.93 [d,d, J = 13.6, 2H, CH_2 β], 3.18 and 3.07 [d,d, J = 13.4, 2H, CH_2 β′]. ^{13}C NMR ($CDCl_3$): 168.0 (C=O), 134.5, 134.3, 133.5, 133.3, 131.9, 131.8, 131.6, 131.5 (CAr), 129.0, 128.51, 128.47, 128.43, 128.3, 127.9, 127.5, 127.1, 127.0, 126.1, 126.0, 125.8 (CHAr), 119.3 (C≡N), 53.7 (OCH_3), 52.9 (Cα), 39.3 (CH_2β), 39.0 (CH_2β′). Anal. $C_{26}H_{19}NO_2 \cdot 0.2H_2O$: calcd C, 81.91; H, 5.13; N, 3.67; found C, 82.09; H, 5.29; N, 3.69%.

3.4. 2′,1′:1,2;1″,2″:3,4-Dinaphthcyclohepta-1,3-diene-6-aminomethyl-6-carboxylic acid ethyl ester (*RS*)-2a and (*R*)-2a

To a solution of cyanoester (*RS*)-**1a** (8.29 g; 21.20 mmol) and cobaltous chloride hexahydrate (10.08 g; 42.40 mmol) in 99% MeOH (350 mL) and THF (120 mL), was added $NaBH_4$ (8.04 g; 212 mmol) in portions. Evolution of hydrogen gas was observed as well as the formation of a black precipitate. When the addition was complete, stirring was continued for 2 h at rt. HCl (2 M, 70 mL) was then poured in the reaction mixture in order to dissolve the black precipitate. After removal of MeOH and THF, the aqueous layer was made alkaline by addition of concentrated NH_4OH and then extracted with diethylether (4×200 mL). The combined extracts were washed with saturated sodium chloride solution, dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was chromatographed on a 4.5×30 cm column of silica gel with eluent IV to give pure (*RS*)-**2a** as a white solid (4.46 g, 53%) of. Mp = 113.7°C. R_f = 0.3 (IV). ^{1}H NMR ($CDCl_3$): 7.95–7.15 [m, 12H, ArH], 4.20 [m, 2H, OCH_2], 3.16 and 2.21 [d,d, J = 12.9, 2H, CH_2 β], 2.84 [m, 4H, CH_2 β′ and CH_2-N], 1.43 (s, 2H, NH_2), 1.28 (t, J = 7.1, 3H CH_3]. ^{13}C NMR ($CDCl_3$): 175.3 (C=O), 135.9, 135.1, 134.5, 133.9, 132.9, 132.8, 131.9, 131.7 (CAr), 128.4, 128.2, 128.1, 128.0, 127.9, 127.2, 127.1, 125.7, 125.6, 125.1, 124.9 (CHAr), 60.8 (OCH_2), 51.9 (Cα), 48.0 (CH_2N), 38.6 (CH_2 β), 36.3 (CH_2 β′), 14.4 (CH_3). Anal. $C_{27}H_{25}NO_2 \cdot 0.3H_2O$: calcd C, 80.89; H, 6.43; N, 3.49; found C, 81.04; H, 6.51; N, 3.41%.

(*R*)-**2a** was prepared in the same way as (*RS*)-**2a** starting from (*R*)-**1a** (1.44 g; 3.69 mmol), using cobaltous chloride hexahydrate (1.76 g; 7.38 mmol), $NaBH_4$ (1.39 g; 36.90 mmol) and a mixture of 99% MeOH (100 mL) and THF (30 mL) to afford (*R*)-**2a** as a white solid (0.594 g, 59%). Mp = 104.8°C. $[\alpha]_{589}^{25} = -248$; $[\alpha]_{578}^{25} = -261$; $[\alpha]_{546}^{25} = -297$; $[\alpha]_{436}^{25} = -458$; $[\alpha]_{365}^{25} = -60$ (*c* 0.205; MeOH). Anal. $C_{27}H_{21}NO_2$ calcd C, 81.99; H, 6.37; N, 3.54; found C, 81.01; H, 6.51; N, 3.41%.

3.5. 2′,1′:1,2;1″,2″:3,4-Dinaphthcyclohepta-1,3-diene-6-aminomethyl-6-carboxylic acid methyl ester (*RS*)-2b

Prepared in the same way as (*RS*)-**2a** starting from (*RS*)-**1b** (2.50 g; 6.65 mmol), cobaltous chloride hexahydrate (3.15 g; 13.30 mmol), $NaBH_4$ (2.0 g; 53 mmol) and a mixture of 99% MeOH (40 mL) and THF (10 mL) to afford after column chromatography (SiO_2; eluent IV), (*RS*)-**2b** as a white solid (1.68 g, 67%). Mp = 90.2°C. R_f = 0.15 (IV). ^{1}H NMR ($CDCl_3$): 8.05–7.15 [m, 12H, ArH], 3.71 [s, 3H, OCH_3], 3.16 and 2.21 [d,d, J = 13.2, 2H, CH_2 β], 2.85 [m, 4H, CH_2N and CH_2 β′], 1.56 (s, 2H, NH_2]. ^{13}C NMR ($CDCl_3$): 175.9 (C=O), 135.8, 135.0, 134.5, 133.8, 132.8, 132.7, 131.8, 131.7 (CAr), 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.2, 127.1, 125.8, 125.6, 125.1, 125.0 (CHAr), 61.0 (Cα), 51.9 (OCH_3), 47.9 (CH_2N), 38.7 (CH_2 β), 36.2 (CH_2 β′). Anal. $C_{26}H_{23}NO_2 \cdot 0.2H_2O$: calcd C, 81.09; H, 6.12; N, 3.63; found C, 80.99; H, 6.33; N, 3.53%.

3.6. 2′,1′:1,2;1″,2″:3,4-Dinaphthcyclohepta-1,3-diene-6-*N*-*tert*-butyloxycarbonylaminomethyl-6-carboxylic acid ethyl ester (*RS*)-3a and (*R*)-3a

To a solution of (*R*,*S*)-**2a** (0.395 g; 1.0 mmol) in acetonitrile (10 mL) was added di-*tert*-butyl dicarbonate (0.436 g; 2.0 mmol). The solution was stirred at rt overnight and evaporated in vacuo. The residue was directly chromatographed on a 4.5×35 cm column of silica gel with eluent I to afford pure (*RS*)-**3a** as a white solid (0.442 g, 89%). Mp = 105.1°C. R_f = 0.1 (I). ^{1}H NMR ($CDCl_3$): 7.96–7.21 [m, 12H, ArH], 4.86 (m, 1H, NH) 4.16 [dq, *J* = 1.7 and 7.2, 2H, OCH_2], 3.31 [m, 2H, CH_2N], 3.08 and 2.31 [d,d, *J* = 13.2, 2H, CH_2 β], 2.86 and 2.76 [d,d, *J* = 13.60, 2H, CH_2 β′], 1.45 [s, 9H, CH_3 Boc], 1.28 (t, *J* = 7, 2H CH_3]. ^{13}C NMR ($CDCl_3$): 175.0 (C=O), 155.8 (N-C=O), 135.4, 134.4, 133.9, 132.9, 132.8, 131.7, (CAr), 128.6, 128.2, 128.1, 127.8, 127.2, 127.1, 125.7, 125.6, 125.1, 125.0 (CHAr), 79.4 (O-C), 61.2 (OCH_2), 59.1 (Cα), 45.6 (CH_2N), 38.5 (CH_2 β), 36.5 (CH_2 β′), 28.3 (CH_3 Boc), 14.2 (CH_3). Anal. $C_{32}H_{33}NO_4$: calcd C, 77.55; H, 6.71; N, 2.83; found C, 77.42; H, 6.78,; N, 2.67%.

(*R*)-**3a** was prepared in the same way as (*RS*)-**3a** starting from (*R*)-**2a** (0.500 g; 1.26 mmol) and di-*tert*-butyl dicarbonate (0.550 g; 2.52 mmol) in acetonitrile (13 mL) to afford, after column chromatography (SiO_2; eluent I), as a white solid (0.435 g, 63%). Mp = 120.0°C. $[\alpha]^{25}_{589} = -148$; $[\alpha]^{25}_{578} = -155$; $[\alpha]^{25}_{546} = -178$; $[\alpha]^{25}_{436} = -255$; $[\alpha]^{25}_{365} = +135$ (*c* 0.2; MeOH). Anal. $C_{32}H_{33}NO_4$: calcd C, 77.55; H, 6.71; N, 2.83; found C, 77.02; H, 6.91; N, 2.71%.

3.7. 2′,1′:1,2;1″,2″:3,4-Dinaphthcyclohepta-1,3-diene-6-*N*-*tert*-butyloxycarbonylaminomethyl-6-carboxylic acid methyl ester (*RS*)-3b

Prepared in the same way as (*R*,*S*)-**3a** from the aminoester (*R*,*S*)-**2b** (0.250 g; 0.65 mmol) and di-*tert*-butyl dicarbonate (0.287 g; 1.31 mmol) in acetonitrile (7 mL). Yield 0.293 g (93%) after column chromatography (SiO_2; eluent I), as a white solid. Mp = 187.3°C. R_f = 0.22 (I). ^{1}H NMR ($CDCl_3$): 7.92–7.12 [m, 12H, ArH], 4.83 (m, 1H, NH), 3.62 (s, 3H, OCH_3), 3.25 [m, 2H, CH_2N], 3.03 and 2.24 [d,d, *J* = 13.2, 2H, CH_2 β], 2.80 and 2.72 [d,d, *J* = 13.60, 2H, CH_2 β′], 1.39 [s, 9H, CH_3 Boc]. ^{13}C NMR ($CDCl_3$): 175.4 (C=O), 155.7 (N-C=O), 135.3, 134.3, 133.9, 132.9, 132.8, 131.7, 131.6 (CAr), 128.5, 128.2, 128.1, 127.9, 127.1, 127.0, 125.6, 125.5, 125.1, 125.0 (CHAr), 79.4 (O-C), 59.2 (Cα), 52.1 (OCH_3), 45.6 (CH_2N), 38.5 (CH_2 β), 36.4 (CH_2 β′), 27.3 (CH_3 Boc). Anal. $C_{31}H_{31}NO_4 \cdot 0.5H_2O$: calcd C, 75.89; H, 6.57; N, 2.82; found C, 75.77; H, 6.54; N, 2.69%.

3.8. 2′,1′:1,2;1″,2″:3,4-Dinaphthcyclohepta-1,3-diene-6-*N*-benzoylaminomethyl-6-carboxylic acid ethyl ester (*RS*)-6a

To a solution of (*RS*)-**2a** (5.64 g; 14.29 mmol) in acetonitrile (140 mL) was added benzoic anhydride (6.46 g; 28.58 mmol). The solution was stirred at rt overnight and evaporated in vacuo. The residue was solubilized in ethyl acetate, the organic solution was washed with 5% $NaHCO_3$ then with water, dried ($MgSO_4$), filtered and evaporated in vacuo. The residue was chromatographed on a 4.5×35 cm column of silica gel with eluent II to give 6.57 g (92%) of pure (*R*,*S*)-**6a** as a white solid. Mp = 181.0°C. R_f = 0.7 (II). ^{1}H NMR ($CDCl_3$): 8.05–7.15 [m, 17H, ArH], 6.72 (m, 1H, NH) 4.22 [q, *J* = 7.2, 2H, OCH_2], 3.79 [dd, *J* = 6.8 and 13.6, 1H, CHN], 3.52 [dd, *J* = 5.3 and 13.6, 1H, CHN], 3.12 and 2.44 [d,d, *J* = 13.2, 2H, CH_2 β], 2.94 and 2.85 [d,d, *J* = 13.60, 2H, CH_2 β′], 1.27 [t, *J* = 7.2, 3H, CH_3]. ^{13}C NMR ($CDCl_3$): 175.5 (C=O), 167.3 (N-C=O), 135.1, 134.4 134.2, 134.0, 133.0, 131.7, 131.6, 131.5, (CAr), 128.6, 128.4, 128.3, 128.1, 127.8,127.2, 127.1, 125.7, 125.6, 125.2, 125.1 (CHAr), 61.2 (OCH_2), 58.7 (Cα), 44.4 (CH_2N), 38.8 (CH_2 β), 36.7 (CH_2 β′), 14.2 (CH_3). Anal. $C_{34}H_{29}NO_3 \cdot 0.5H_2O$: calcd C, 80.29; H, 5.95; N, 2.75; found C, 80.52; H, 6.08; N, 2.83%.

3.9. 2′,1′:1,2;1″,2″:3,4-Dinaphthcyclohepta-1,3-diene-6-*N*-benzoylaminomethyl-6-carboxylic acid methyl ester (*RS*)-6b

Prepared in the same way as (*RS*)-**6a** from the amino ester (*RS*)-**2b** (0.768 g; 2.02 mmol) and benzoic anhydride (0.910 g; 4.04 mmol) in acetonitrile (20 mL) to afford, after column chromatography (SiO_2; eluent I), (*RS*)-**6b** as a white solid (0.840 g, 86%). Mp = 90.3°C. R_f = 0.21 (I). ^{1}H NMR ($CDCl_3$): 8.38–7.22 [m, 17H, ArH], 6.84 (m, 1H, NH), 3.86 [dd, *J* = 6.8 and 13.6, 1H, CHN], 3.75 [s, 3H, OCH_3], 3.56 [dd, *J* = 5.3 and 13.6, 1H, CHN], 3.17 and 2.47 [d,d, *J* = 13.2, 2H, CH_2 β], 2.98 and 2.90 [d,d, *J* = 13.60, 2H, CH_2 β′]. ^{13}C NMR ($CDCl_3$): 175.9 (C=O), 167.7 (N-C=O), 135.1, 134.3 134.2, 134.0, 133.4, 132.9, 132.8, 131.65, 131.64, 131.5, (CAr), 128.55, 128.52, 128.3, 128.2, 128.1, 127.9, 127.8, 127.1, 127.0, 126.9, 125.7, 125.6, 125.1, 125.0 (CHAr), 58.8 (Cα), 52.3 (OCH_3), 44.5 (CH_2N), 38.7 (CH_2 β), 36.6 (CH_2 β′). Anal. $C_{33}H_{27}NO_3 \cdot 1.2H_2O$: calcd C, 78.14; H, 5.84; N, 2.76; found C, 78.02; H, 5.52; N, 2.26%.

3.10. 2′,1′:1,2;1″,2″:3,4-Dinaphthcyclohepta-1,3-diene-6-*N*-*tert*-butyloxycarbonylaminomethyl-6-carboxylic acid (*RS*)-4 and (*R*)-4

A suspension of (*RS*)-**3a** (0.360 g, 0.73 mmol) in MeOH (40 mL) and 1N NaOH (20 mL) was stirred at 80°C for 4 h. The resulting clear solution was allowed to cool to rt, acidified by addition of an excess of 0.5 M HCl and extracted with diethylether. The ethereal solution was washed twice with water, dried ($MgSO_4$), filtered and evaporated in vacuo to give pure (*RS*)-**4** as a white solid (0.335 g, 98%). Mp = 172.2°C. R_f = 0.11 (IV). ^{1}H NMR ($CDCl_3$): 8.02–7.21 [m, 12H, ArH], 6.34 [s broad, 1H, OH], 4.97 [m, 1H, NH], 3.37 [m, 2H, CH_2N], 3.10 and 2.35 [d,d, *J* = 13.6, 2H, CH_2 β], 2.88 and 2.80 [d,d, *J* = 13.8, 2H, CH_2 β′], 1.43 [s, 9H, CH_3 Boc]. ^{13}C NMR ($CDCl_3$): 180.9 (C=O), 156.1 (N-C=O), 135.5, 134.4, 133.9, 132.9, 132.8, 131.7, 131.6 (CAr), 128.6, 128.2, 127.9, 127.1, 125.6, 125.5, 125.1, 124.9 (CHAr), 79.9 (O-C), 59.2 (Cα), 45.9 (CH_2N), 38.3 (CH_2 β), 36.6 (CH_2 β′), 28.3 (CH_3 Boc). Anal. $C_{30}H_{29}NO_4$·

0.25H_2O: calcd C, 76.31; H, 6.29; N, 2.96; found C, 76.35; H, 6.56; N, 2.76%.

(*R*)-**4** was prepared in the same way as (*RS*)-**4** by saponification of (*R*)-**3a** (0.22 g, 0.44 mmol) in MeOH (20 mL) and 1 M NaOH (16 mL) at 80°C for 5 h to afford (*R*)-**4** as a white solid (0.206 g, 99%). Mp = 250–270°C (decomp. at solid state before melting). $[\alpha]_{589}^{25} = -129$; $[\alpha]_{578}^{25} = -134$; $[\alpha]_{546}^{25} = -153$; $[\alpha]_{436}^{25} = -225$; $[\alpha]_{365}^{25} = +71$ (*c* 0.2; MeOH). Anal. $C_{30}H_{29}NO_4 \cdot 1.6\ H_2O$: calcd C, 72.59; H, 6.54; N, 2.82; found C, 72.59; H, 6.51; N, 2.73%.

3.11. 2′,1′:1,2;1″,2″:3,4-Dinaphthcyclohepta-1,3-diene-6-*N*-benzoylaminomethyl-6-carboxylic acid (*RS*)-7

(*RS*)-**7** was prepared in the same way as (*RS*)-**4**: by saponification of (*RS*)-**6b** (6.50 g, 13 mmol) in MeOH (350 mL) and 1 M NaOH (150 mL) at 80°C for 4 h. Yield 5.89 g (96%) as a white solid. Mp = 181°C. $R_f = 0.3$ (IV). ^{1}H NMR ($CDCl_3$): 8.05–7.19 [m, 17H, ArH], 7.02 (t, *J* = 6.2, 1H, NH), 6.75 [s broad, 1H, OH], 3.84 [dd, *J* = 6.2 and 13.6, 1H, CHN], 3.46 [dd, *J* = 6.2 and 13.6, 1H, CHN], 3.19 and 2.36 [d,d, *J* = 13.2, 2H, CH_2 β], 2.86 [s, 2H, CH_2 β′]. ^{13}C NMR (DMSO-d_6): 175.5 (C=O), 166.9 (N-C=O), 135.9, 135.6, 134.7, 133.6, 133.2, 132.5, 132.4, 131.2, 131.1, 131.0, (CAr), 128.9, 128.4, 128.2, 127.8, 127.4, 126.3, 125.9, 125.1 (CHAr), 58.9 (Cα), 44.5 (CH_2N), 37.9 (CH_2 β), 36.4 (CH_2 β′). Anal. $C_{33}H_{27}NO_3 \cdot 1.4H_2O$: calcd C, 77.37; H, 5.64; N, 2.82; found C, 77.32; H, 5.61; N, 2.09%.

3.12. 2′,1′:1,2;1″,2″:3,4-Dinaphthcyclohepta-1,3-diene-6-aminomethyl-6-carboxylic acid, trifluoroacetate (*RS*)-5 and (*R*)-5

To a cold solution of (*RS*)-**4** (0.056 g, 0.12 mmol) in CH_2Cl_2 (0.5 mL) was added TFA (0.5 mL). The solution was stirred at rt for 2 h and evaporated in vacuo. The resulting solid was repeatedly triturated with diethylether and the mixture evaporated in vacuo, to afford pure (*RS*)-**5** as a white solid (0.36 g, 62%). Mp = 196.4°C. R_f = 0.1 (I). ^{1}H NMR (CD_3OD): 8.01–7.21 [m, 12H, ArH], 3.31 [m, 2H, CH_2N], 3.15 and 2.33 [m,7H, CH_2 β, CH_2 β′ and NH_3^+]. ^{13}C NMR (CD_3OD): 174.7 (C=O), 136.1, 135.9, 135.0, 134.7, 133.3, 133.0, (CAr), 129.7, 129.6, 129.5, 129.3, 129.1, 128.1, 127.9, 127.2, 126.9, 126.7, 126.5 (CHAr), 54.9 (Cα), 45.6 (CH_2N), 39.9 (CH_2 β), 39.1 (CH_2 β′). Anal. $C_{27}H_{22}F_3NO_4 \cdot 1.1H_2O$: calcd C, 64.69; H, 4.87; N, 2.79; found C, 64.76; H, 4.88; N, 2.81%.

(*R*)-**5** was obtained in the same way as (*RS*)-**5** starting from (*R*)-**4** (0.034 g, 0.0.73 mmol) and TFA (0.5 mL) in CH_2Cl_2 (0.5 mL) to afford (*R*)-**5** as a white solid (0.020 g, 57%). Mp = 209.3°C. R_f = 0 (I). $[\alpha]_{589}^{25} = -212$; $[\alpha]_{578}^{25} = -221$; $[\alpha]_{546}^{25} = -255$; $[\alpha]_{436}^{25} = -401$; $[\alpha]_{365}^{25} = -146$ (*c* 0.2; MeOH). Anal. $C_{27}H_{22}F_3NO_4 \cdot 1.2H_2O$: calcd C, 64.46; H, 4.88; N, 2.78; found C, 64.34; H, 4.77; N, 2.81%.

3.13. Coupling of (*RS*)-7 with L-phenylalanine cyclohexylamide

To a solution of (*RS*)-**7** (7.6 g; 16.1 mmol), H-L-Phe-NHC_6H_{11}[12] (5.63 g; 22.9 mmol) and HOBt (*N*-hydroxybenzotriazole) (3.09 g; 22.9 mmol) in CH_2Cl_2 (160 mL) and THF (160 mL) was added dropwise at 0°C, a solution of EDC (*N*-ethyl-*N*′-dimethylaminopropylcarbodiimide hydrochloride) (3.76 g; 19.6 mmol) in CH_2Cl_2 (80 mL). The solution was allowed to warm to rt and stirred overnight. The solvents were evaporated in vacuo and the residue was dissolved in EtOAc (900 mL). The solution was successively extracted with 0.5N HCl (3×200 mL), H_2O (2×200 mL), 5% $NaHCO_3$ (3×250 mL), H_2O (3×250 mL), then dried ($MgSO_4$), filtered and evaporated in vacuo. The residue was chromatographed on a 4.5×40 cm column of silica gel with eluent (V) to give 8.77 g (78%) of a 1:1 mixture of diastereomers (*R*,*S*)-**8** and (*S*,*S*)-**8**. Attempts for crystallization of this mixture in EtOAc was unsuccessful: no crystals deposited even from highly concentrated solutions and evaporation to dryness led to an amorphous white solid. 7.5 g of the mixture of diastereomers (*R*,*S*)-**8** and (*S*,*S*)-**8** were separated by HPLC using eluent (VII) for (*R*,*S*)-**8** and eluent (IX) for (*S*,*S*)-**8** to give pure (*R*,*S*)-**8** (3.62 g, 95%) and pure (*S*,*S*)-**8** (2.12 g, 56%).

Bz-(R)-β^{2,2}-HBin-L-Phe-NH-C_6H_{11} (*R*,*S*)-8: white solid. Mp = 169–171°C. R_f = 0.34 (VII). ^{1}H NMR ($CDCl_3$): 8.01–7.82 [m, 6H, ArH], 7.70 [m (D-like), 1H, ArH], 7.48–7.04 [m, 14H, ArH and NH β^{2,2}-HBin], 6.95 [m (D-like), 2H, ArH], 6.26 [d, *J* = 7.7, 1H, NH Phe], 6.07 [d, *J* = 8.1, 1H, NHC_6H_{11}], 4.54 [m, 1H, CHα Phe], 3.77 [dd, *J* = 7.2 and 13.8, 1H, NCHβ β^{2,2}-HBin], 3.67 [m, 1H, $CH_{cyclohexyl}$], 3.45 [dd, *J* = 5.1 and 13.8, 1H, NCHβ β^{2,2}-HBin], 2.99 [dd, *J* = 6.6 and 13.6, 1H, CHβ Phe], 2.85 [dd, *J* = 8.8 and 13.6, 1H, CHβ Phe], 2.83 and 2.49 [d,d, *J* = 13.6, 2H, CH_2β β^{2,2}-HBin], 2.70 and 2.64 [d,d, *J* = 13.2, 2H, CH_2β′ β^{2,2}-HBin], 1.86–0.89 [m, 10H, 5 $CH_{2cyclohexyl}$]. ^{13}C NMR ($CDCl_3$): 175.9, 170.0, 167.4 (C=O Phe, C=O β^{2,2}-HBin, C=O Bz), 136.2, 134.5, 134.3, 134.2, 133.9, 132.9, 132.8, 131.8, 131.6, 131.4, 128.9, 128.8, 128.6, 128.4, 128.37, 128.31, 128.2, 127.3, 127.25, 127.2, 127.0, 126.9, 125.8, 125.6, 125.3, 125.1 (CAr and CHAr), 58.8 (Cα β^{2,2}-HBin), 54.9 (Cα Phe), 48.5 ($CH_{cyclohexyl}$), 44.9 (NCH_2β β^{2,2}-HBin), 39.2 (CH_2β β^{2,2}-HBin), 38.0 (CH_2β Phe), 36.7 (CH_2β′ β^{2,2}-HBin), 32.8, 32.6, 25.3, 24.7 ($CH_{2cyclohexyl}$). $[\alpha]_{589}^{25} = -9$; $[\alpha]_{578}^{25} = -11$; $[\alpha]_{546}^{25} = -11$; $[\alpha]_{436}^{25} = -70$; $[\alpha]_{365}^{25} = +705$ (*c* 0.10; MeOH). Anal. $C_{47}H_{45}N_3O_3 \cdot 0.5H_2O$: calcd C, 79.63; H, 6.54; N, 5.93; found C, 79.71; H, 6.62; N, 5.84%.

Bz-(S)-β^{2,2}-HBin-L-Phe-NH-C_6H_{11} (*S*,*S*)-8: White solid. Mp = 176–178°C°C. R_f = 0.24 (VII). ^{1}H NMR ($CDCl_3$): 8.05–7.85 [m, 6H, ArH], 7.71 [m (D-like), 1H, ArH], 7.51–7.20 [m, 11H, ArH and NH β^{2,2}-HBin], 7.09–6.90 [m, 5H, ArH], 6.23 [d, *J* = 7.2, 1H, NH Phe], 5.56 [d, *J* = 8.1, 1H, NHC_6H_{11}], 4.56 [m, 1H, Hα Phe], 3.83 [dd, *J* = 7.1 and 13.5, 1H, NCHβ β^{2,2}-HBin], 3.63 [m, 1H, $CH_{cyclohexyl}$], 3.43 [dd, *J* = 4.8 and 13.5, 1H, NCHβ β^{2,2}-HBin], 3.45 and 2.96 [d,d, *J* = 13.2, 2H, CH_2β β^{2,2}-HBin], 3.06 [dd, *J* = 5.5 and 13.5, 1H, CHβ Phe], 2.85 [dd, *J* = 8.1 and 13.5, 1H, CHβ Phe], 2.81 and 2.62 [d,d, *J* = 12.7, 2H, CH_2β′ β^{2,2}-HBin], 1.86–0.78 [m, 10H, 5 $CH_{2cyclohexyl}$]. ^{13}C NMR ($CDCl_3$): 175.1, 169.3, 167.5 (C=O Phe, C=O β^{2,2}-HBin, C=O Bz), 135.8, 135.7, 135.0, 134.3, 134.2, 134.1, 133.6, 133.0, 132.9, 131.7, 131.6, 131.4, 129.0, 128.6, 128.44, 128.4, 128.3, 128.26, 128.2, 127.8, 127.2, 127.1, 127.0,

125.8, 125.7, 125.3, 125.2 (CAr and CHAr), 58.9 (Cα β^{2,2}-HBin), 54.8 (Cα Phe), 48.5 (CHC_5H_{10}), 45.0 (NCH_2β β^{2,2}-HBin), 38.5 (CH_2β β^{2,2}-HBin), 38.2 (CH_2β Phe), 36.4 (CH_2β′ β^{2,2}-HBin), 32.8, 32.6, 25.3, 24.7 (CH_2 C_5H_{10}). $[\alpha]_{589}^{25}=+122$; $[\alpha]_{578}^{25}=+128$; $[\alpha]_{546}^{25}=+141$; $[\alpha]_{436}^{25}=+211$; $[\alpha]_{365}^{25}=-20$ (*c* 0.15; MeOH). Anal. $C_{47}H_{45}N_3O_3$: calcd C, 80.65; H, 6.48; N, 6.00; found C, 80.08; H, 6.62; N, 5.75%.

3.14. Acidic hydrolysis of (*R*,*S*)-8 and (*S*,*S*)-8. 2′,1′:1,2;1″,2″:3,4-dinaphthcyclohepta-1,3-diene-6-*N*-*tert*-butyloxycarbonylaminomethyl-6-carboxylic acid methyl ester (*R*)-3b and (*S*)-3b

To a solution of (*R*,*S*)-**8** (3.55 g; 5.07 mmol) in dioxane (40 mL) was added 35% (10N) HCl (40 mL), resulting in the formation of a strong white precipitate. The mixture was magnetically stirred at 110°C and the precipitate gradually disappeared to give a clear pale yellow solution after ca. 20 h. The solution was stirred at 110°C for 6 days, then evaporated to dryness in vacuo at 80°C. Water (ca. 20 mL) was added to the residue and the mixture was evaporated again in vacuo, this operation being repeated several times, to give crude (*R*)-H-β^{2,2}-HBin-OH·HCl as a solid. The crude solid was esterified in refluxing MeOH (100 mL) containing 98% H_2SO_4 (2 mL) for 4 days. the solution was then concentrated in vacuo at 30°C to ca. 10 mL and crushed ice (100 mL) then water (50 mL) were added to the stirred mixture, followed by small portions of solid $NaHCO_3$ up to a large excess. The basic aqueous phase was extracted with ether (150 mL), the organic phase was washed with water (3×20 mL), dried ($MgSO_4$), filtered and evaporated in vacuo to give 1.32 g (68.0%) of crude H-β^{2,2}-HBin-OMe (*R*)-**2b** which was used in the next step without further purification. This crude amino ester (1.29 g; 3.4 mmol) was treated with di-*tert*-butyl dicarbonate (1.63 g; 7.48 mmol) in acetonitrile (75 mL) in the same experimental conditions of reaction and work-up as for the synthesis of (*R*,*S*)-**3a**, to give 1.214 g (69%) of pure Boc-β^{2,2}-HBin-OMe (*R*)-**3b** after column chromatography (SiO_2; eluent VIII), as a white solid. Mp = 114–116°C. $[\alpha]_{589}^{25}=-151$; $[\alpha]_{578}^{25}=-159$; $[\alpha]_{546}^{25}=-180$; $[\alpha]_{436}^{25}=-266$; $[\alpha]_{365}^{25}=-123$ (*c* 0.21; MeOH). Anal. $C_{31}H_{31}NO_4\cdot 1.5H_2O$: calcd C, 74.84; H, 6.89; N, 2.81; found C, 74.58; H, 6.35; N, 2.47%.

In the same manner, to a solution of (*S*,*S*)-**8** (2.06 g; 2.94 mmol) in dioxane (24 mL) was added HCl (35%, 10 N, 24 mL). The mixture was magnetically stirred at 110°C, resulting in the slow disparition of the initially formed white precipitate to give a clear pale yellow solution. After 6 days at 110°C, the solution was evaporated to dryness in vacuo, to give crude (*S*)-H-β^{2,2}-HBin-OH·HCl as a solid. The crude solid was treated exactly as above: esterification in refluxing MeOH with 98% H_2SO_4 led after work-up to crude H-β^{2,2}-HBin-OMe (*S*)-**2b** (0.845 g, 75%), which was directly treated with di-*tert*-butyl dicarbonate (1.08 g; 4.94 mmol) in acetonitrile (45 mL), to give pure Boc-β^{2,2}-HBin-OMe (*S*)-**3b** after column chromatography (SiO_2; eluent VIII), as a white solid (0.888 g, 65%). Mp = 116–119°C. $[\alpha]_{589}^{25}=+155$; $[\alpha]_{578}^{25}=+159$; $[\alpha]_{546}^{25}=+179$; $[\alpha]_{436}^{25}=+261$; $[\alpha]_{365}^{25}=-126$ (*c* 0.2; MeOH). Anal. $C_{31}H_{31}NO_4\cdot 0.3H_2O$: calcd C, 76.45; H, 6.54; N, 2.87; found C, 76.54; H, 6.51; N, 2.58%.

3.15. 2′,1′:1,2;1″,2″:3,4-Dinaphthcyclohepta-1,3-diene-6-aminomethyl-6-carboxylic acid methyl ester (*R*)-2b and (*S*)-2b

To a cold (0°C) solution of (*R*)-**3b** (0.24 g; 0.5 mmol) in CH_2Cl_2 (0.5 mL) was added TFA (0.5 mL). The solution was stirred at rt for 3 h and evaporated in vacuo. The residue was solubilized in EtOAc (100 mL) and 5% $NaHCO_3$ (10 mL). the organic layer was extracted with $NaHCO_3$ (2×10 mL), dried ($MgSO_4$), filtered and evaporated in vacuo to give pure (*R*)-**2b** as a white solid (0.188 g; 98%). Mp = 97.7°C. $[\alpha]_{589}^{25}=-236$; $[\alpha]_{578}^{25}=-253$; $[\alpha]_{546}^{25}=-289$; $[\alpha]_{436}^{25}=-448$; $[\alpha]_{365}^{25}=-13$ (*c* 0.1; MeOH). Anal. $C_{26}H_{23}NO_2\cdot 0.3H_2O$: calcd C, 80.72; H, 6.15; N, 3.62; found C, 80.85; H, 6.34; N, 3.39.

Treatment of (*S*)-**3b** (0.241 g; 0.5 mmol) in exactly the same manner gave pure (*S*)-**2b** as a white solid (0.190 g; 99%). Mp = 101.1°C. $[\alpha]_{589}^{25}=+258$; $[\alpha]_{578}^{25}=+265$; $[\alpha]_{546}^{25}=+299$; $[\alpha]_{436}^{25}=+462$; $[\alpha]_{365}^{25}=+68$ (*c* 0.1; MeOH). Anal. $C_{26}H_{23}NO_2\cdot 0.2H_2O$: calcd C, 81.00; H, 6.11; N, 3.63; found C, 81.07; H, 6.21; N, 3.35%.

3.16. Coupling of (*R*)-2b and (*S*)-2b with (−)-(*S*)-α-methoxy-α-trifluoromethyl-α-phenylacetic acid

To a solution of (−)-(*S*)-α-methoxy-α-trifluoromethyl-α-phenyl-acetic acid (0.019 g; 0.08 mmol) in acetonitrile (2 mL) was added EDC (0.0078 g; 0.04 mmol). After stirring at rt for 1 h the clear colorless solution of the resulting MTPA anhydride was divided in two portions of 1 mL each, which were respectively added to samples of (*S*)-**2b** (0.0031 g; 0.008 mmol) and (*R*)-**2b** (0.0030 g; 0.008 mmol). The resulting clear colorless solutions were stirred at rt overnight and the solvent was removed in vacuo. After addition of ether (10 mL) the organic phases were successively extracted with 5% $NaHCO_3$ (2×2 mL), then water (2×2 mL), dried ($MgSO_4$), filtered and evaporated in vacuo. The residues were chromatographed on preparative TLC plates of silica gel with eluent (I), care being taken not to exercise a mechanical separation of one of the diastereoisomers over the other. From (*R*)-**2b** was obtained amido ester (*S*)-Ph(OCH_3)(CF_3)C-CO-(*R*)-β^{2,2}-HBin-OMe with >98% d.e.: ^{1}H NMR ($CDCl_3$): 7.95–7.20 [m, 18H, ArH and NH], 3.74 [dd, *J* = 7.7 and 13.5, 1H, NCHβ], 3.67 [s (99.3%), 3H, OCH_3 β^{2,2}-HBin], 3.63 [s (0.7%), OCH_3 β^{2,2}-HBin of the (*S*,*S*)-isomer], 3.43 [m, 3H, OCH_3 MTPA], 3.32 [dd, *J* = 5.3 and 13.5, 1H, NCHβ], 3.99 and 2.39 [d,d, *J* = 13.1, 2H, CH_2β], 2.90 and 2.77 [dd, *J* = 13.7, 2H, CH_2β′]. ^{19}F NMR ($CDCl_3$): −69.24 [s (99%), CF_3], −69.29 [s (1%), CF_3 of the (*S*,*S*) isomer]. ^{13}C NMR ($CDCl_3$): 175.4, 166.4 (C=O β^{2,2}-HBin, C=O MTPA), 134.9, 134.3, 134.0, 133.0, 132.9, 132.3, 131.7, 131.6, 129.4, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.2, 127.0, 125.7, 125.2 (CAr and CHAr, 83.5 (CF_3), 59.0 (Cα), 55.0 (OCH_3 MTPA), 52.6 (OCH_3 β^{2,2}-HBin), 44.0 (CH_2N), 38.9 (CH_2β), 36.3 (CH_2β′). The amido ester

was obtained from (*S*)-**2b** (*S*)-Ph(OCH_3)(CF_3)C-CO-(*S*)-$\beta^{2,2}$-HBin-OMe with >97% de: ^{1}H NMR ($CDCl_3$): 7.93–7.21 [m, 18H, ArH and NH], 3.73 [dd, $J=7.6$ and 13.5, 1H, NCHβ], 3.67 [s (1.4%), OCH_3 $\beta^{2,2}$-HBin of the (*S*,*R*) isomer], 3.63 [s (98.6%), 3H, OCH_3 $\beta^{2,2}$-HBin], 3.42 [m, 3H, OCH_3 MTPA], 3.37 [dd, $J=5.5$ and 13.5, 1H, NCHβ], 3.06 and 2.36 [d,d, $J=13.2$, 2H, $CH_2\beta$], 2.88 and 2.70 [d,d, $J=13.4$, 2H, $CH_2\beta'$]. ^{19}F NMR ($CDCl_3$): −69.24 [s (>98%), CF_3], −69.29 [s (< 2%), CF_3 of the (*S*,*R*) isomer]. ^{13}C NMR ($CDCl_3$): 175.3, 166.5 (C=O $\beta^{2,2}$-HBin, C=O MTPA), 134.9, 134.3, 134.0, 133.9, 132.9, 132.8, 132.3, 131.7, 129.4, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.5, 127.1, 127.0, 125.8, 128.7, 125.2, 125.1 (CAr and CHAr), 83.9 (CF_3), 59.1 (Cα), 55.0 (OCH_3 MTPA), 52.3 (OCH_3 $\beta^{2,2}$-HBin), 38.6 ($CH_2\beta$), 36.7 ($CH_2\beta'$).

3.17. 2′,1′:1,2;1″,2″:3,4-Dinaphthcyclohepta-1,3-diene-6-*N*-*tert*-butyloxycarbony-L-aminomethyl-6-carboxylic acid (*R*)-4 and (*S*)-4

Saponification of (*R*)-**3b** (1.19 g; 2.49 mmol) in MeOH (50 mL) and 1 M NaOH (25 mL) at 80°C for 4 h, in the same experimental conditions of reaction and work-up as for the synthesis of (*R*,*S*)-**4**, gave pure (*R*)-**4** as a white solid (1.09 g, 94%). Mp = 270–290°C (decomp. at solid state before melting). $[\alpha]_{589}^{25}=-168$; $[\alpha]_{578}^{25}=-173$; $[\alpha]_{546}^{25}=-200$; $[\alpha]_{436}^{25}=-299$; $[\alpha]_{365}^{25}=+62$ (*c* 0.2; MeOH). Anal. $C_{30}H_{29}NO_4\cdot H_2O$: calcd C, 74.20; H, 6.43; N, 2.88; found C, 74.16; H, 6.01; N, 2.59%.

(*S*)-**4** was also prepared in the same way as (*R*,*S*)-**4**, by saponification of (*S*)-**3b** (0.87 g, 1.80 mmol) in MeOH (50 mL) and 1 M NaOH (25 mL) at 80°C for 4 h to afford (*S*)-**4** as a white solid (0.62 g, 73%). Mp = 290–310°C (decomp. at solid state before melting). $[\alpha]_{589}^{25}=+183$; $[\alpha]_{578}^{25}=+188$; $[\alpha]_{546}^{25}=+215$; $[\alpha]_{436}^{25}=+321$; $[\alpha]_{365}^{25}=-68$ (*c* 0.2; MeOH). Anal. $C_{30}H_{29}NO_4\cdot H_2O$: calcd C, 76.18; H, 6.31; N, 2.96; found C, 76.21; H, 6.37; N, 2.69%.

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