Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 4, pp. 619–631, 1997

Printed in Great Britain
PII: S0957-4166(97)00009-8
0957-4166/97 $17.00 + 0.00

Novel α,α-disubstituted α-aminoacids with axial dissymmetry and their *N*- or *C*-protected derivatives

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Abstract: Racemic as well as enantiomerically pure 1,1′-binaphthyl-substituted α-aminoisobutyric acid (Bin), a new chiral atropoisomeric α,α-disubstituted glycine, and its biphenyl analogue (Bip), have been prepared with good yields by bis-alkylation of a glycine *tert*-butyl ester Schiff base with 2,2′-bis(bromomethyl)-1,1′-binaphthyl and 2,2′-bis(bromomethyl)-1,1′-biphenyl, respectively, under phase transfer conditions. The free aminoacids Bin and Bip, as well as their *N*-protected (Z, Boc, Fmoc) and/or *C*-protected (ethyl or *tert*-butyl esters) derivatives, useful for the incorporation of these new aminoacids into peptides, have been obtained. A slow interconversion between the two enantiomers of the Bip derivatives is generally observed in ^{1}H NMR at room temperature, with a rotational energy barrier of 59 kJ mol^{-1}. © 1997 Elsevier Science Ltd. All rights reserved.

Open-chain and cyclic α,α-disubstituted glycines are an important class of non-proteinogenic aminoacids. α-Aminoisobutyric acid (Aib; α-methyl alanine), the best studied member of this family, and its parent α,α-dialkylated residues, either *acyclic and achiral* such as α,α-di-benzyl-glycine, or *acyclic and chiral* such as isovaline (α-Me–α-Et–Gly), or *cyclic and achiral* such as 1-aminocycloalkane-1-carboxylic acids Ac$_n$c, have been the focus of many investigations. They are building blocks in the design of specifically folded analogues of bioactive peptides, because of their enhanced resistance to enzymatic degradation and to their inherent propensities to stabilize small peptides in rather well defined 3_{10}- or α-helical or β-turn-type conformations.[1–3] Exploitation of their homopolymers as precise molecular rulers or scaffolding blocks in the *de novo* design of protein and enzyme mimetics has also been considered.[4]

We have recently designed[5] new *cyclic, axially chiral* α,α-disubstituted α-aminoacids Bip **1** and Bin **2** (Figure 1) of the Ac$_7$c-type,[3] which are 1,1′-biphenyl- and 1,1′-binaphthyl-substituted analogs of Aib, and are expected to induce interesting conformational and optical properties when incorporated in peptides. Herein, we wish to report our detailed experimental procedure for the synthesis of the *C*- and/or *N*-protected derivatives of **1**, racemic (R,S)-**2** and enantiomerically pure (S)-**2**.

For the synthesis of both Bin and Bip, we considered the *C,C*-bis-alkylation of aldimine or ketimine derivatives of glycine esters under phase transfer conditions according to M. J. O'Donnell *et al.*[6] Solid–liquid phase transfer di-alkylation of the glycine ethyl ester Schiff base **3a** by both 2,2′-bis(bromomethyl)-1,1′-biphenyl **4** and racemic 2,2′-bis(bromomethyl)-1,1′-binaphthyl (R,S)-**5**[7a] with

Bip (1) (S)- Bin (2)

Figure 1. Novel axially dissymmetric α,α-disubstituted α-amino acids Bip (**1**) and Bin (**2**).

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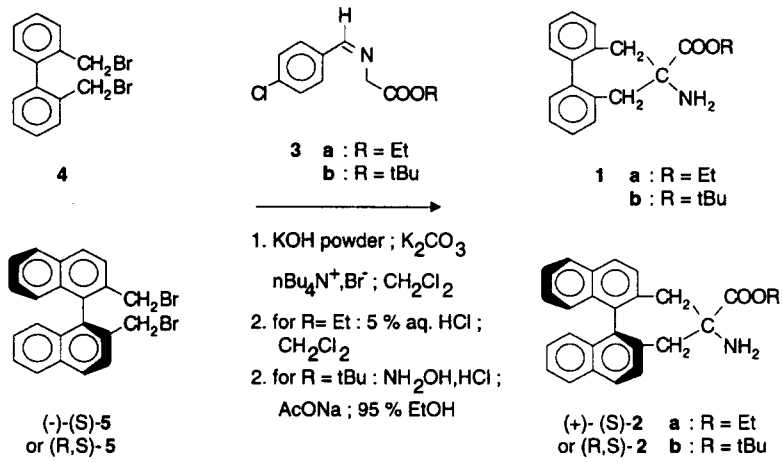

Figure 2. Synthesis of the aminoesters H-Bip-OEt (**1a**), H-Bip-OtBu (**1b**), H-Bin-OEt (**2a**) and H-Bin-OtBu (**2b**) under phase transfer conditions.

KOH powder/K_2CO_3 as base and tetrabutylammonium bromide as catalyst in dichloromethane was initially attempted (Figure 2). However, in our hands, the yields of the aminoesters H-Bip-OEt **1a** and H-Bin-OEt (R,S)-**2a** respectively obtained after acidic hydrolysis of the reaction mixtures were poor (10–42%) and moreover not reproducible, presumably because of the occurrence of a saponification side reaction. Much higher and reproducible yields were obtained in the same experimental conditions by using the *tert*-butyl ester Schiff base **3b**, which after deprotection of the amino group by transimination gave directly the aminoesters H-Bip-OtBu **1b** (85%) from **4** and H-Bin-OtBu (R,S)-**2b** (78%) from (R,S)-**5**[7a] or (S)-**2b** (81%) from enantiomerically pure (–)-(S)-**5**.[7]

Attempt for coupling the racemic aminoester (R,S)-**2b** with Mosher's (–)-(S)-α-methoxy-α-trifluoromethyl-α-phenyl-acetic acid by the DCC/HOBt method gave no reaction. However, when the Mosher's acid was first treated with a half equivalent of DCC, acylation of (R,S)-**2b** by the resulting symmetric anhydride proceeded with an excellent yield in acetonitrile to give a *ca* 1.2:1 mixture of the diastereoisomeric amido esters $Ph(OCH_3)(CF_3)CCO$-Bin-OtBu (S,S)-**2c** and (SR)-**2c**. Such behaviour is in agreement with the known difficult acylation of Aib and others α,α-dialkylated glycines,[8] for which Yamada *et al.*[8b] have previously observed that coupling of α,α-diphenylglycine (Dph) with alanine by the EDC/HOBt method proceeded with high yields at the *C*-terminal but very low yields at the the *N*-terminal position of Dph. On the other hand, *N*-acylation of Aib derivatives by Boc anhydride has been shown to be very efficient when conducted in acetonitrile (*vide infra*). The obtained diastereoisomers (S,S)-**2c** and (SR)-**2c** had distinct signals in ^1H NMR, ^{19}F NMR and ^{13}C NMR. Furthermore, they gave two close spots on TLC (SiO_2/CH_2Cl_2) and could be separated on a TLC plate, which constitutes an initial resolution of the binaphthyl moiety. The same treatment applied to the compound (S)-**2b** gave the single amido ester (S,S)-**2c**, with 0.5–1% of the other isomer (by NMR), demonstrating that (S)-**2a** was enantiomerically pure or nearly so. The recorded absence of racemization during the alkylation process is not surprising, considering the previously demonstrated very high configurational stability of 2,2′-bis(methylene)-substituted-1,1′-binaphthyls,[9] which is also of importance in view of the further incorporation of **2** in peptides, where its chiral integrity during any step of peptide synthesis can be assumed.

Then, the free aminoacids as well as their *C*- and/or *N*-protected derivatives were prepared (Figure 3). Deprotection of the aminoesters **1b** and **2b** (and/or the *N*-Boc-aminoesters **1g** and **2g**) in TFA/CH_2Cl_2 1:1 gave H-Bip-OH **1d** (87%) and H-Bin-OH (R,S)-**2d** (90%); (S)-**2d** (95%), which were esterified in refluxing absolute EtOH with concentrated H_2SO_4 to the corresponding ethyl esters H-Bip-OEt **1a** (92%) and H-Bin-OEt (R,S)-**2a** (85%); (S)-**2a** (91%). For *N*-protection, treatment of the free

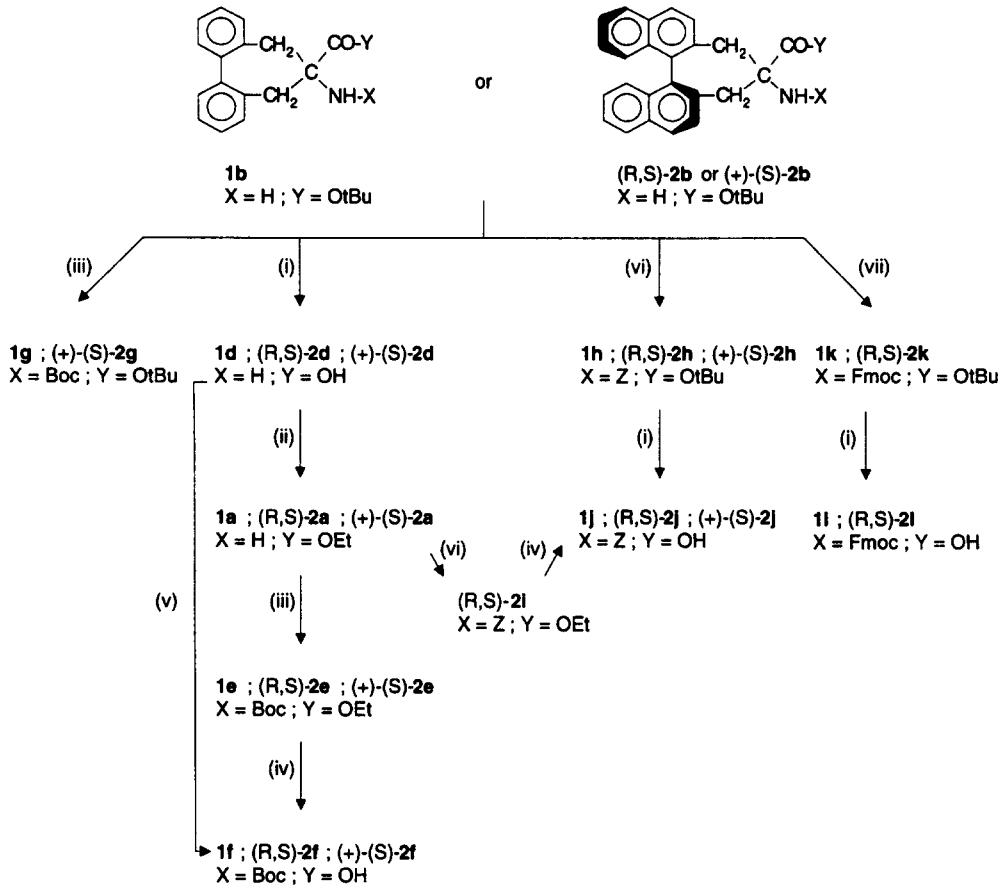

Figure 3. Synthesis of the *C*- and/or *N*-protected derivatives of Bip and Bin. *(i)* TFA/CH_2Cl_2 1:1; rt; 2 h *(ii)* abs. EtOH; H_2SO_4; reflux; 48 h *(iii)* Boc_2O; CH_3CN; rt; 24 h *(iv)* aq.N NaOH/MeOH; 75°C; 2–3 h *(v)* Boc_2O; N NaOH; dioxane; rt; 12 days or Boc_2O; Et_3N; CH_3CN; rt; 48 h *(vi)* Z–OSu; CH_3CN; rt; 24 h *(vii)* Fmoc–OSu; CH_3CN; rt; 24 h.

aminoacids **1d** and (R,S)-**2d** by a large excess of Boc anhydride in either N NaOH/dioxane or acetonitrile/triethylamine as recommended by Kemp *et al.*[10] gave Boc-Bip-OH **1f** and Boc-Bin-OH (R,S)-**2f** with only 44% and 35% yield, respectively. However, the choice of acetonitrile as solvent proved to be excellent for acylation of the aminoesters and therefore the *N*-protected aminoacids were more efficiently prepared in two steps by *N*-protection of the corresponding aminoesters then hydrolysis of the ester function. Treatment of **1b**, **2b** and **1a**, **2a** by Boc_2O/CH_3CN[10] at room temperature gave high yields of Boc-Bip-OtBu **1g** (94%), Boc-Bin-OtBu (S)-**2g** (88%), Boc-Bip-OEt **1e** (94%) and Boc-Bin-OEt (R,S)-**2e** (90%) and (S)-**2e** (99%).[11,12] In a similar manner, reaction of **1b**, **2b** and **2a** with *N*-(benzyloxycarbonyloxy) succinimide (Z-OSu) in acetonitrile gave Z-Bip-OtBu **1h** (82%), Z-Bin-OtBu (R,S)-**2h** (97%); (S)-**2h** (93%) and Z-Bin-OEt (R,S)-**2i** (77%), while reaction of **1b** and **2b** with 9-fluorenylmethyl-succinimidyl-carbonate (Fmoc-OSu) in acetonitrile gave Fmoc-Bip-OtBu **1k** (78%) and Fmoc-Bin-OtBu (R,S)-**2k** (78%). The *C*-deprotection of the *tert*-butyl esters **1h**, **2h** and **1k**, **2k** in TFA/CH_2Cl_2 1:1 gave Z-Bip-OH **1j** (90%), Z-Bin-OH (R,S)-**2j** (91%); (S)-**2j** (94%), Fmoc-Bip-OH **1l** (94%) and Fmoc-Bin-OH (R,S)-**2l** (93%). Saponification of the *N*-protected ethyl esters **1e**, **2e** and **2i** required unusually drastic conditions (large excess of aqueous N NaOH in refluxing MeOH for several hours) but also furnished high yields of the *N*-protected aminoacids Boc-Bip-OH **1f** (95%), Boc-Bin-OH (R,S)-**2f** (96%); (S)-**2f** (96%) and Z-Bin-OH (R,S)-**2j** (83%).

The optical rotations of the (S)-Bin derivatives in methanol were generally positive at 589, 578 and

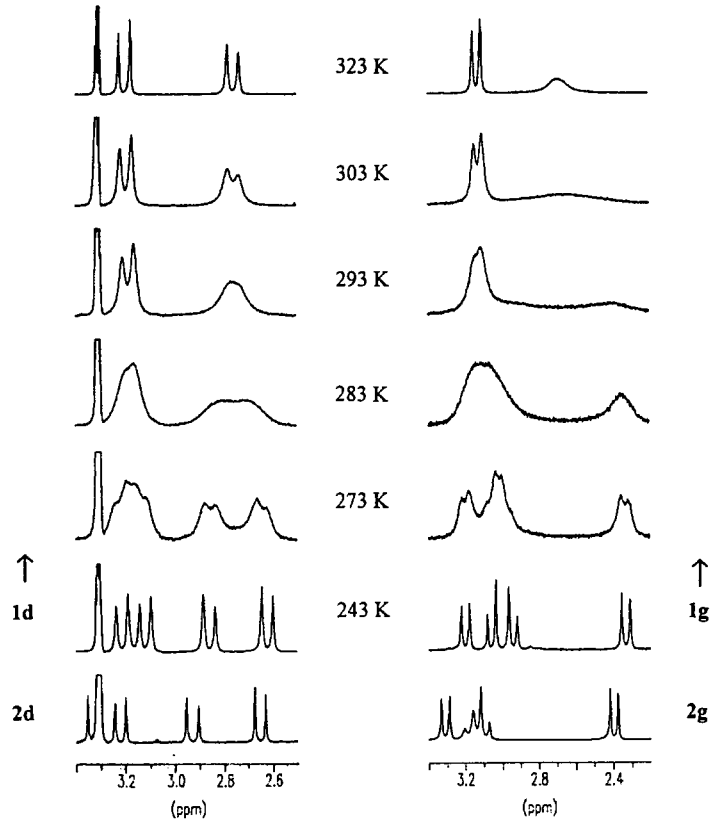

Figure 4. Temperature-dependent 300 MHz ^{1}H NMR pattern of ($ArCH_2$ β)($ArC'H_2$ β) for the compounds H-Bip-OH (**1d**) in CD_3OD and Boc-Bip-OtBu (**1g**) in $CDCl_3$ (c 20 g/l), compared to their conformationally stable analogs **2d** and **2g** at room temperature (294 K). **1d**: T_{C1}=278 K ($\Delta\nu_1$=28.3 Hz); T_{C2}=288 K ($\Delta\nu_2$=71.3 Hz). **1g**: T_{C1}=283 K ($\Delta\nu_1$=44.3 Hz); T_{C2}=303 K ($\Delta\nu_2$=184.8 Hz).

546 nm, and of either positive or negative sign at 436 and 365nm. For the conformationally labile Bip derivatives **1a–l**, broadened ^{1}H NMR signals for the ($ArCH_2$ β)($ArC'H_2$ β) protons were generally observed at room temperature, indicating a slow interconversion at the NMR time scale between the two conformers (enantiomers) resulting from rotation along the 1–1′ bond of the biphenyl moiety.[13] Indeed, as exemplified for the free aminoacid H-Bip-OH **1d** and for the fully protected derivative Boc-Bip-OtBu **1g** (Figure 4), a single pair of doublets (not completely resolved in the case of **1g**) was present in at 323 K (equivalency of the two benzylic methylene groups), while two distinct pairs of doublets were observed at 243 K, very close to the ones shown at room temperature by the corresponding conformationally stable (R,S)- or (S)-Bin derivatives **2d** and **2g**. For both compounds **1d** and **1g** the calculated[14] rotational energy barrier was 14 kcal mol^{-1}.

The crystal structures of H-Bip-OtBu **1b** and H-(S)Bin-OH **2d** were pseudo-symmetrical with a non crystallographic C_2 axis passing through Cα and the middle of the opposite bond.[5] The torsion angle along the 1–1′ bond was 46.5° for **1b** and 53.8° for **2d**, in agreement with the greater steric hindrance brought by the extra phenyl rings present in Bin.

The axially chiral pseudo C_2-symmetric α,α-symmetrically disubstituted glycines Bin and Bip should have interesting applications in the design of protein mimetics. Their *N*- and *C*-protected derivatives are building blocks for peptide synthesis: (i) the rapidly synthesized *tert*-butyl esters H-Bip-OtBu **1b**, H-Bin-OtBu (S) or (R,S)-**2b** have an acido-labile carboxy protecting group, whereas the corresponding ethyl ester function of H-Bip-OEt **1a** and H-Bin-OEt (R,S)-**2a** can be cleaved by

saponification, after coupling; (ii) the *N*-protected derivatives Boc-Bip-OH **1f**, Boc-Bin-OH **2f**, Z-Bip-OH **1j**, Z-(S)-Bin-OH **2j**, Fmoc-Bip-OH **1l** and Fmoc-(R,S)-Bin-OH **2l** possess protecting groups cleavable in strong (Z) or moderate (Boc) acidic media, or by treatment with a secondary amine (Fmoc), or by hydrogenolysis (Z and Fmoc).[15]

We are currently investigating the conformational and optical properties of the homopolymers and peptide derivatives of these new aminoacids.

Experimental

2,2′-Bis(bromomethyl)-1,1′-biphenyl **4** was purchased from Aldrich. Racemic and enantiomerically pure 2,2′-bis(bromomethyl)-1,1′-binaphthyl (RS)-**5** and (−)-(S)-**5** were prepared as previously described.[7] 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); 5% MeOH–95% CH_2Cl_2 (III); 10% MeOH–90% CH_2Cl_2 (IV); Petroleum ether (40–60°C)/AcOEt (10:2) (V).

2′,1′:1,2;1″,2″:3,4-Dibenzcyclohepta-1,3-diene-6-amino-6-carboxylic acid ethyl ester ***1a***

By bis-alkylation of the glycine ethyl ester Schiff base: A mixture of a large excess (the use of a stoichiometric amount gave only unidentified products) of the Schiff base **3a** (2.48 g; 11 mmol), 2,2′-bis(bromomethyl)-1,1′-biphenyl **4** (1.70 g; 5 mmol), tetrabutylammonium bromide (0.064 g; 0.2 mmol), anhydrous potassium carbonate (6.9 g; 50 mmol) and finely ground KOH pellets (2.8 g; 50 mmol) in dichloromethane (100 ml) was magnetically stirred at room temperature for 12 h and then filtered on glass wool. Aqueous 2 N HCl (100 ml) was added to the filtrate and the mixture was stirred at room temperature for 5 h. The decanted organic layer was extracted with 100 ml of a solution of 2 N NaOH containing 2 g of hydroxylamine hydrochloride, then washed with 0.5 M HCl and brine, dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residue was chromatographed on a column of silicagel with eluent (II) to give 0.255 g (18%) of almost pure **1a** as an orange glassy oil. Further purification by preparative TLC (SiO_2; eluent II) gave an analytically pure sample as a pale orange solid foam. Yield 0.148 g (11%). *By esterification of the free aminoacid*: A solution of H-Bip-OH hydrochloride **1c** (*vide infra*) (0.220 g; 0.76 mmol) in abs. EtOH (50 ml) containing 98% H_2SO_4 (2 ml) was refluxed for 48 h. After cooling, the solution was dropped on crushed ice and made basic by addition of portions of $NaHCO_3$ with stirring. The resulting turbid solution was extracted with diethyl ether. The decanted ethereal phase was washed with water, dried ($MgSO_4$), filtered and evaporated *in vacuo*, to give 0.197 g (92%) of pure **1a** as a white solid foam. Rf=0.40 (II). ^{1}H NMR ($CDCl_3$): 7.47–7.31, m, 8 H (Ar–H); 4.23, q (7.1), 2H (OEt); 3.06, d (13.3), 2H and 2.48, s (broad), 2H (CH_2 β coalescing); 1.83, s (broad), 2H (NH_2); 1.31, t (7.1), 3H (OEt). ^{13}C NMR ($CDCl_3$): 175.25 (CO); 140.29–125.26 (CAr); 67.70 (Cα); 60.91 (OEt); 42 64 (Cβ); 13.95 (OEt). Anal.($C_{18}H_{19}NO_2$) calcd. C: 76.84; H: 6.81; N: 4.98; found C: 76.74; H: 6.72; N: 5.17.

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

By bis-alkylation of the glycine ethyl ester Schiff base: Obtained in the same way as above from the Schiff base **3a** (0.586 g; 2.6 mmol) and racemic 2,2′-bis(bromomethyl)-1,1′-binaphthyl (R,S)-**5**[7a] (0.440 g; 1 mmol). Yield 0.160 g (42%) after column chromatography (SiO_2; eluent II), as an orange solid foam. Other runs in similar experimental conditions gave 17%, 29% and 10% yield. *By esterification of the free aminoacid*: Obtained in the same way as above from H-Bin-OH hydrochloride (R,S)-**1c** (*vide infra*) (0.266 g; 0.68 mmol). Yield 0.202 g (85%). Mp=80°C. Rf=0.40 (II). ^{1}H NMR ($CDCl_3$): 7.97–7.21, m, 12H (Ar–H); 4.18, m, 2H (OEt); 3.16, d (13.3) and 2.67, d (13.4), 2H (CH_2 β); 3.05, d (13.2) and 2.39, d (13.2), 2H (C′H_2 β); 1.63, s (broad), 2H (NH_2); 1.27, t (7.1), 3H (OEt). ^{13}C NMR ($CDCl_3$): 175.48 (CO); 135.95–125.06 (CAr); 68.62 (Cα); 61.19 (OEt); 43.42 (Cβ); 43.12

(C′β); 14.14 (OEt). FAB$^+$ MS *m/z* (relative intensity): 382 (MH^+) (52); 308 (MH^+ – HCOOEt) (100). Anal.($C_{26}H_{23}NO_2$, 0.35 H_2O) calcd. C: 80.53; H: 6.16; N: 3.61; found C: 80.51; H: 6.25; N: 3.53.

(+)-(S)-2a was prepared in the same way as above by esterification of the aminoacid trifluoroacetate (+)-(S)-**2c** (*vide infra*) (1.036 g; 2.22 mmol). Yield 0.770 g (91%). Mp=75°C. Anal. ($C_{26}H_{23}NO_2$, 0.5 H_2O) calcd. C: 79.97; H: 6.19; N: 3.59; found C: 80.15; H: 6.04; N: 3.55. $[\alpha]^{25}_{589}$=+316.6, $[\alpha]^{25}_{578}$=+331.1, $[\alpha]^{25}_{546}$=+376.8, $[\alpha]^{25}_{436}$=+603.3, $[\alpha]^{25}_{365}$=+306.2 (c 0.5; MeOH).

2′,1′:1,2;1″,2″:3,4-Dibenzcyclohepta-1,3-diene-6-amino-6-carboxylic acid tert*-butyl ester* ***1b***

A mixture of glycine *tert*-butyl ester Schiff base **3b** (6.97 g; 27.5 mmol), the dibromide **4** (8.50 g; 25 mmol), tetrabutyl ammonium bromide (1.61 g; 5 mmol), anhydrous potassium carbonate (34.5 g; 250 mmol) and finely grounded KOH pellets (14 g; 250 mmol) in dichloromethane (300 ml) was magnetically stirred at room temperature for 24 h. The reaction mixture was then evaporated *in vacuo* and the residue solubilized in water–diethyl ether. The ethereal solution was washed with water and brine, dried ($MgSO_4$), filtered and evaporated. To the resulting orange solid foam was added hydroxylamine hydrochloride (3.82 g; 55 mmol), sodium acetate (4.51 g; 55 mmol) and 95% EtOH (250 ml).[16] The mixture was magnetically stirred at room temperature for 48 h and then evaporated *in vacuo*. The residue was solubilized in aqueous 5% $NaHCO_3$ and Et_2O. The separated ethereal solution was washed with water and brine, dried ($MgSO_4$), filtered and evaporated. The resulting orange solid foam was chromatographed on a 4.5×40 cm column of silicagel with eluents (I) (removal of impurities of higher Rf and of the Schiff base of hydroxylamine) then (II) to give 6.61 g (85%) of **1b** as an orange solid foam, which contained a few impurities by TLC but was pure by ^1H NMR and could be used in the next steps without further purification (another run gave 75% yield). Preparative TLC of an aliquot (SiO_2; eluent II) furnished an analytical sample as a pale orange solid foam. Mp=88°C. Rf=0.40 (II). ^1H NMR ($CDCl_3$): 7.6–7.4, m, 8 H (Ar–H); 3.16, d (13.3), 2H and 2.57, d (broad), 2H (CH_2 β coalescing); 1.94, s (broad), 2H (NH_2); 1.63, s, 9H (OtBu). ^{13}C NMR ($CDCl_3$): 174.39 (CO); 140.24–127.01 (CAr); 80.97 (OtBu); 68.05 (Cα); 42 79 (Cβ); 27.69 (OtBu). Anal.($C_{20}H_{23}NO_2$, 0.5 H_2O) calcd. C: 75.44; H: 7.60; N: 4.40; found C: 75.74; H: 7.27; N: 4.43.

(RS)-2′,1′:1,2;1″,2″:3,4-Dinaphthcyclohepta-1,3-diene-6-amino-6-carboxylic acid tert*-butyl ester* ***2b***

Obtained in the same way as **1b** from the Schiff base **3b** (2.79 g; 11 mmol) and the dibromide (R,S)-**5**[7a] (4.40 g; 10 mmol). Yield 3.21 g (78%) of almost pure compound after column chromatography (another run gave 76%). Pale orange solid foam. Mp=94°C. Rf=0.40 (II); 0.60 (III). ^1H NMR ($CDCl_3$): 8.05–7.30, m, 12H (Ar–H); 3.27, d (13.3) and 2.54, d (13.3), 2H (CH_2 β); 3.24, d (13.1) and 2.80, d (13.1), 2H (C′H_2 β); 1.85, s (broad), 2H (NH_2); 1.61, s, 9H (OtBu). ^{13}C NMR ($CDCl_3$): 174.37 (CO); 135.96–124.76 (CAr); 81.08 (OtBu); 68.80 (Cα); 43.35 (Cβ); 42.99 (C′β); 27.72 (OtBu). Anal. ($C_{28}H_{27}NO_2$, 0.5 H_2O) calcd. C: 80.35; H: 6.75; N: 3.35; found C: 80.37; H: 6.72; N: 3.31.

(+)-(S)-2b was prepared in the same way from the Schiff base **3b** (2.79 g; 11 mmol) and optically pure (−)-(S)-**5**, $[\alpha]^{22}_{546}$=−201 (c 1; benzene)[7] (4.40 g; 10 mmol). Yield 3.318 g (81%) of almost pure compound after column chromatography as an orange solid foam. Preparative TLC of an aliquot (SiO_2; eluent II) furnished an analytical sample as a pale orange solid foam. Mp=98°C. Anal.($C_{28}H_{27}NO_2$, 0.5 H_2O) calcd. C: 80.35; H: 6.75; N: 3.35; found C: 80.44; H: 6.58; N: 3.32. $[\alpha]^{25}_{589}$=+309.8, $[\alpha]^{25}_{578}$=+324.0, $[\alpha]^{25}_{546}$=+368.4, $[\alpha]^{25}_{436}$=+590.4 (c 0.5; MeOH).

Coupling of (RS)-2b and (+)-(S)-2b with (−)-(S)-α-methoxy-α-trifluoromethyl-α-phenyl-acetic acid.

To a solution of (−)-(S)-α-methoxy-α-trifluoromethyl-α-phenyl-acetic acid (Aldrich, 99+ %)(0.024 g; 0.1 mmol) in acetonitrile (0.5 ml) was added DCC (0.010 g; 0.05 mmol), which immediately resulted in the formation of a white precipitate of DCU. After stirring at room temperature for 15 min, the solution of the resulting anhydride was filtered through a pipet capped with cotton wool and directly transferred into a solution of (R,S)-**2b** (0.0083 g; 0.2 mmol) in acetonitrile (0.2 ml). The resulting clear colorless solution was strirred at room temperature overnight (analytical TLC of an aliquot showed only traces of starting aminoester after 1 h) and then diluted with diethyl ether (100

ml) in a separatory funnel. The organic phase was extracted with two portions of 50 ml 5% $NaHCO_3$ then two portions of 100 ml water, dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residue was chromatographed on a 1.5×35 cm column of silicagel with eluent (I). The fractions containing the desired product were pooled, care being taken not to exercise a mechanical separation of one of the diastereoisomers over the other, and the solution evaporated *in vacuo* to give 0.0106 g (83.6%) of a mixture of pure amido esters (S,S)-**2c** and (S,R)-**2c** in the ratio of *ca* 1.2 to 1 by NMR. Preparative TLC (SiO_2; eluent I) allowed the separation of these two compounds (yet both contaminated by *ca* 10% of the other isomer). Identical experimental conditions and work up applied to the aminoester (+)-(S)-**2b** (0.0172 g; 0.042 mmol) and the anhydride resulting from the treatment of (−)-(S)-MTPA (0.049 g; 0.21 mmol) with DCC (0.021 g; 0.1 mmol) in acetonitrile (1 ml) gave (S,S)-**2c** and (S,R)-**2c** in the ratio of *ca* 99.5 to 0.5 by NMR. (S,S)-**2c**: Rf=0.48 (I). ^{1}H NMR ($CDCl_3$): 7.98–7.23, m, 17H (Ar–H); 7.11, s, 1H (NH); 3.38, m, 3H (OMe); 3.36, d (12.9) and 2.53, d (12.9), 2H (CH_2 β); 3.25, d (13.8) and 3.14, d (13.8), 2H (C′H_2 β); 1.42, s, 9H (OtBu). ^{19}F NMR ($CDCl_3$): −68.73, s (CF_3). ^{13}C NMR ($CDCl_3$): 170.11 (COOtBu); 165.20 (CONH); 134.77–125.29 (CAr); 83.86, q (26), (CF_3); 82.00 (OtBu); 69.84 (Cα); 54.77 (OMe); 41.93 (Cβ); 37.70 (C′β); 27.82 (OtBu). (S,R)-**2c**: Rf=0.52 (I). ^{1}H NMR ($CDCl_3$): 7.98–6.97, m, 17H (Ar–H); 6.74, s, 1H (NH); 3.47, m, 3H (OMe); 3.30, d (12.7) and 2.48, d (12.7), 2H (CH_2 β); 3.13, d (13.8) and 3.07, d (13.8), 2H (C′H_2 β); 1.51, s, 9H (OtBu). ^{19}F NMR ($CDCl_3$): −68.39, s (CF_3). ^{13}C NMR ($CDCl_3$): 169.80 (COOtBu); 165.20 (CONH); 134.77–125.29 (CAr); 82.01 (OtBu); 69.59 (Cα); 55.05 (OMe); 41.85 (Cβ); 37.28 (C′β); 27.82 (OtBu).

2′,1′:1,2;1″,2″:3,4-Dibenzcyclohepta-1,3-diene-6-amino-6-carboxylic acid ***1d***

The aminoester **1b** (0.865 g; 2.80 mmol) was solubilized in CH_2Cl_2 (10 ml) and TFA (10 ml) was added. The solution was stirred at room temperature overnight and evaporated *in vacuo*. The residue was dissolved in aqueous N NaOH and the orange brown solution acidified by addition of an excess of concentrated HCl, then evaporated to dryness. The residue was dissolved in 150 ml of boiling water and activated charcoal was added. The mixture was filtered when hot, the resulting clear colorless solution was concentrated *in vacuo* to *ca* 25 ml and left at room temperature overnight. The resulting crystals were collected by filtration, abundently washed with water and air dried to yield 0.249 g (31%) of H-Bip-OH hydrochloride **1d** as a white crystalline powder. More compound (0.456 g; 56%) was obtained, also as a white powder, after evaporation of the filtrate. Mp>300°C (decomp. at solid state before melting). ^{1}H NMR (CD_3OD): 7.7–7.3, m, 8 H (Ar–H); 3.18, d (broad, 11.9), 2H and 2.70, d (broad, 11.9), 2H (CH_2 β coalescing). ^{1}H NMR (243 K; CD_3OD): 3.22, d (14.5) and 2.86, d (14.5), 2H (CH_2 β); 3.12, d (13.6) and 2.62, d (13.6), 2H (C′H_2 β). ^{1}H NMR (323 K; CD_3OD): 3.20, d (14.0), 2H and 2.76, d (14.0), 2H (CH_2 β). ^{13}C NMR (CD_3OD): 174.28 (CO); 14170–129.10 (CAr); 71.02 (Cα); 40.08 (Cβ). Anal.($C_{16}H_{15}NO_2$, 0.75 HCl) calcd. C: 68.47; H: 5.66; N: 4.99; found C: 68.41; H: 5.84; N: 4.87.

*(RS)-2′,1′:1,2;1″,2″:3,4-Dinaphthcyclohepta-1,3-diene-6-amino-6-carboxylic acid (***2d***)*

Obtained in the same way as **1d** from the aminoester (R,S)-**2b** (0.541 g; 1.32 mmol). Yield 0.464 g (90%) after crystallization from water. Pale yellow crystalline powder. Mp=270°C (decomp). ^{1}H NMR (CD_3OD): 8.07–7.14, m, 12H (Ar–H); 3.35, d (14.5) and 2.91, d (14.5), 2H (CH_2 β); 3.20, d (13.0) and 2.63, d (12.9), 2H (C′H_2 β). Anal.($C_{24}H_{19}NO_2$, 0.8 HCl) calcd. C: 75.34; H: 5.22; N: 3.66; found C: 75.27; H: 5.54; N: 3.55.

(+)-(S)-2d was prepared in the same way from the *N*-Boc-aminoester (+)-(S)-**2g** (*vide infra*) (1.327 g; 2.61 mmol), except that the obtained TFA salt was triturated in diethyl ether, decanted and dried. Yield 1.213 g (95.4%). Pale yellow crystalline powder. Crystallization of an aliquot (0.100 g) from methanol gave 0.037 g of analytically pure white crystals. Mp=282°C. ^{1}H NMR (CD_3OD): 8.08–7.16, m, 12 H (Ar–H); 3.33, d (14.5) and 2.92, d (14.5), 2H (CH_2 β); 3.22, d (13.1) and 2.65, d (13.1), 2H (C′H_2 β). ^{13}C NMR (CD_3OD): 173.82 (CO); 162.77 (weak, CF_3COO^-); 135.98–116.29 (CAr);

120.17, 116.29 (CF_3); 71.01 (Cα); 40.83 (Cβ); 39.90 (C′β). Anal.($C_{24}H_{19}NO_2$, 0.7 CF_3COOH) calcd. C: 70.41; H: 4.58; N: 3.23; found C: 70.18; H: 5.02; N: 3.21. The zwitterionic form of the free aminoacid, with CF_3COOH absent, was observed by X-Ray analysis of the crystals.[5] $[\alpha]^{25}_{589}$=+314.3, $[\alpha]^{25}_{578}$=+327.9, $[\alpha]^{25}_{546}$=+375.0, $[\alpha]^{25}_{436}$=+616.7, $[\alpha]^{25}_{365}$=+423.3 (c 0.6; MeOH).

*2′,1′:1,2;1″,2″:3,4-Dibenzcyclohepta-1,3-diene-6-*tert*-butyloxycarbonylamino-6-carboxylic acid ethyl ester* ***1e***

To a mixture of the aminoester **1a** (0.331 g; 1.18 mmol) and Boc_2O (0.514 g; 2.36 mmol) was added acetonitrile (25 ml). The resulting clear solution was stirred at room temperature for 48 h and evaporated *in vacuo*. The residue was chromatographed on a 2.3×55 cm column of silicagel with eluent (I) to give 0.422 g (94%) of pure **1e** as a pale yellow viscous oil. Crystallization from hexane (dissolution in ether, addition of hexane and evaporation of ether) gave 0.293 g of analytically pure white crystals. Mp=143°C. Rf=0.35 (I). ^{1}H NMR ($CDCl_3$): 7.46–7.26, m, 8 H (Ar–H); 4.96, s (broad), 1H (NH); 4.26, q (7.1), 2H (OEt); 3.4–2.9, m (broad) and 3.3–2, m (broad), 4H (CH_2 β coalescing); 1.48, s, 9H (Boc); 1.30, t (7.1), 3H (OEt). ^{13}C NMR ($CDCl_3$): 172.65 (COOEt); 154.51 (OCONH); 140.62–127.59 (CAr); 80.12 (Boc); 68.93 (Cα); 61.35 (OEt); 41–38 (broad) (Cβ coalescing); 28.26 (Boc); 14.23 (OEt). Anal.($C_{23}H_{27}NO_4$, 0.25 H_2O) calcd. C: 71.57; H: 7.18; N: 3.63; found C: 71.51; H: 6.94; N: 3.67.

*(RS)-2′,1′:1,2;1″,2″:3,4-Dinaphthcyclohepta-1,3-diene-6-*tert*-butyloxycarbonylamino-6-carboxylic acid ethyl ester* ***2e***

Prepared in the same way as **1e** from the aminoester (RS)-**2a** (0.068 g; 0.018 mmol) and Boc_2O (0.080 g; 0.36 mmol) in acetonitrile (5 ml). Yield 0.077 g (89.7%) after column chromatography (SiO_2; eluent I), as a white solid foam. Analytically pure white crystals were obtained from methanol. Mp=210°C. Rf=0.33 (I). ^{1}H NMR ($CDCl_3$): 8.00–7.25, m, 12H (Ar–H); 4.98, s (broad), 1H (NH); 4.31, q (broad, 6.9), 2H (OEt); 3.40, d (13.1) and 2.47, d (13.1), 2H (CH_2 β); 3.26, d (broad, 13.6) and 3.17, d (13.6), 2H (C′H_2 β); 1.56, s, 9H (Boc); 1.35, t (broad, 7.1), 3H (OEt). ^{13}C NMR ($CDCl_3$): 172.77 (COOEt); 154.65 (OCONH); 134.53–125.39 (CAr); 80.13 (Boc); 69.63 (Cα); 61.50 (OEt); 41.96 (Cβ); 38.70 (C′β); 28.39 (Boc); 14.37 (OEt). Anal.($C_{31}H_{31}NO_4$, 0.5 H_2O) calcd. C: 75.89; H: 6.57; N: 2.85; found C: 75.88; H: 6.41; N: 2.82.

(+)-(S)-2e was prepared in the same way from (+)-(S)-**2a** (1.114 g; 2.92 mmol) and Boc_2O (1.275 g; 5.84 mmol) in acetonitrile (75 ml). Yield 1.400 g (99.6%) after column chromatography (SiO_2; eluent I), as a white solid foam. Mp=129°C. Anal.($C_{31}H_{31}NO_4$, 0.5 H_2O) calcd. C: 75.89; H: 6.57; N: 2.85; found C: 75.87; H: 6.45; N: 2.87. $[\alpha]^{25}_{589}$=+38.5, $[\alpha]^{25}_{578}$=+39.3, $[\alpha]^{25}_{546}$=+41.0, $[\alpha]^{25}_{436}$=−0.1°, $[\alpha]^{25}_{365}$=−599.7 (c 0.6; MeOH).

*2′,1′:1,2;1″,2″:3,4-Dibenzcyclohepta-1,3-diene-6-*tert*-butyloxycarbonylamino-6-carboxylic acid* tert*-butyl ester* ***1g***

Prepared in the same way as **1e** from the aminoester **1b** (4.104 g; 13.3 mmol) and Boc_2O (5.79 g; 26.6 mmol) in acetonitrile (125 ml). Yield 5.10 g (93.9%) after column chromatography (SiO_2; eluent I), as a white solid foam. Analytically pure white crystals were obtained from ether (off)–hexane. Mp=166°C. Rf=0.48 (I). ^{1}H NMR ($CDCl_3$): 7.45–7.23, m, 8 H (Ar–H); 4.87, s (broad), 1H (NH); 3.11, d (broad), 2H and 3.3–2, m (broad), 2H (CH_2 β coalescing); 1.51, s, 9H (OtBu); 1.49, s, 9H (Boc). ^{1}H NMR (243 K; $CDCl_3$): 3.20, d (13.1) and 2.33, d (13.1), 2H (CH_2 β); 3.05, d (13.8) and 2.95, d (13.8), 2H (C′H_2 β). ^{1}H NMR (323 K; $CDCl_3$): 3.13, d (13.5), 2H and 2.68, s (broad), 2H (CH_2 β). ^{13}C NMR ($CDCl_3$): 171.46 (COOtBu); 154.49 (OCONH); 140.63–127.53 (CAr); 81.24 (OtBu); 79.75 (Boc); 69.37 (Cα); 41–38 (broad) (Cβ coalescing); 28.31 (OtBu); 27.92 (Boc). ^{13}C NMR (243 K; $CDCl_3$): 171.44 (COOtBu); 154.22 (OCONH); 140.51–127.47 (CAr); 81.21 (OtBu); 79.86 (Boc); 69.02 (Cα); 41.01 (Cβ); 37.87 (C′β); 28.11 (OtBu); 27.71 (Boc). Anal.($C_{25}H_{31}NO_4$) calcd. C: 73.32; H: 7.63; N: 3.42; found C: 73.22; H: 7.42; N: 3.35.

*(+)-(S)-2′,1′:1,2;1″,2″:3,4-Dinaphthcyclohepta-1,3-diene-6-*tert*-butyloxycarbonylamino-6-carboxylic acid* tert*-butyl ester (2g)*

Prepared in the same way as **1g** from the aminoester (+)-(S)-**2b** (2.007 g; 4.91 mmol) and Boc_2O (2.14 g; 9.8 mmol) in acetonitrile (125 ml). Yield 2.188 g (87.6%) after column chromatography (SiO_2; eluent I), as a pale yellow solid foam. Mp=136°C. Rf=0.45 (I). ^1H NMR ($CDCl_3$): 7.97–7.23, m, 12H (Ar–H); 4.77, s (broad), 1H (NH); 3.31, d (13.0) and 2.40, d (13.0), 2H (CH_2 β); 3.18, d (broad, 13.7) and 3.09, d (13.7), 2H (C′H_2 β); 1.52, s, 9H (OtBu); 1.51, s, 9H (Boc). ^{13}C NMR ($CDCl_3$): 171.39 (COOtBu); 154.45 (OCONH); 134.90–125.18 (CAr); 81.28 (OtBu); 79.75 (Boc); 69.92 (Cα); 41.94 (Cβ); 38.40 (C′β); 28.29 (OtBu); 27.90 (Boc). Anal.($C_{33}H_{35}NO_4$, 0.5 H_2O) calcd. C: 76.52; H: 6.99; N: 2.70; found C: 76. 74; H: 6.78; N: 2.73. $[\alpha]^{25}_{589}$=+38.7, $[\alpha]^{25}_{578}$=+39.0, $[\alpha]^{25}_{546}$=+41.0, $[\alpha]^{25}_{436}$=−2.8, $[\alpha]^{25}_{365}$=−601.5 (c 0.5; MeOH).

2′,1′:1,2;1″,2″:3,4-Dibenzcyclohepta-1,3-diene-6-benzyloxycarbonylamino-6-carboxylic acid tert*-butyl ester **1h***

To a mixture of the aminoester **1b** (0.278 g; 0.90 mmol) and Z-OSu (0.269 g; 1.08 mmol) was added acetonitrile (10 ml). The resulting clear solution was stirred at room temperature for 48 h and evaporated *in vacuo*. The residue was chromatographed on a 2.3×33 cm column of silicagel with eluent (I) to give 0.326 g (82%) of pure **1h** as a white solid foam. Analytically pure white crystals were obtained from ether (off)–hexane. Mp=112°C. Rf=0.45 (I). ^1H NMR ($CDCl_3$): 7.45–7.22, m, 13 H (Ar–H); 5.14, s (broad), 2H (Z); 5.07, s (broad), 1H (NH); 3.3–3, m (broad) and 3.2–2.2, m (broad), 4H (CH_2 β coalescing); 1.44, s, 9H (OtBu). ^{13}C NMR ($CDCl_3$): 171.18 (COOtBu); 154.96 (OCONH); 140.59–127.51 (CAr); 81.61 (OtBu); 69.62 (Cα); 66.70 (Z); 41–38 (broad) (Cβ coalescing); 27.82 (OtBu). Anal.($C_{28}H_{29}NO_4$) calcd. C: 75.82; H: 6.59; N: 3.16; found C: 76.09; H: 6.74; N: 3.16.

(RS)-2′,1′:1,2;1″,2″:3,4-Dinaphthcyclohepta-1,3-diene-6-benzyloxycarbonylamino-6-carboxylic acid tert*-butyl ester **2h***

Prepared in the same way as **1h** from the aminoester (R,S)-**2b** (0.278 g; 0.68 mmol) and Z-OSu (0.186 g; 0.75 mmol) in acetonitrile (15 ml). Yield 0.360 g (97.6%) after column chromatography (SiO_2; eluent I), as a white solid foam. Mp=127°C. Rf=0.52 (I). ^1H NMR ($CDCl_3$): 7.95–7.22, m, 17H (Ar–H); 5.16, s (broad), 2H (Z); 4.98, s (broad), 1H (NH); 3.32, d (13.0) and 2.41, d (13.0), 2H (CH_2 β); 3.18, d (broad, 13.6) and 3.09, d (13.6), 2H (C′H_2 β); 1.45, s, 9H (OtBu). ^{13}C NMR ($CDCl_3$): 171.14 (COOtBu); 154.93 (OCONH); 136.43–125.24 (CAr); 81.70 (OtBu); 70.18 (Cα); 66.69 (Z); 42.00 (Cβ); 38.35 (C′β); 27.82 (OtBu). Anal.($C_{36}H_{33}NO_4$, 0.5 H_2O) calcd. C: 78.23; H: 6.20; N: 2.53; found C: 78.51; H: 6.31; N: 2.61.

(+)-(S)-2h was prepared in the same way from (+)-(S)-**2b** (0.666 g; 1.63 mmol) and Z-OSu (0.446 g; 1.79 mmol) in acetonitrile (40 ml). Yield 0.826 g (93.4%) after column chromatography (SiO_2; eluent I), as a white solid foam. Mp=129°C. Anal.($C_{36}H_{33}NO_4$) calcd. C: 79.53; H: 6.12; N: 2.58; found C: 79.34; H: 6.21; N: 2.68. $[\alpha]^{25}_{589}$=+10.0, $[\alpha]^{25}_{578}$=+9.5, $[\alpha]^{25}_{546}$=+6.6, $[\alpha]^{25}_{436}$=–63.5, $[\alpha]^{25}_{365}$=−684.4 (c 0.5; MeOH).

*(RS)-2′,1′:1,2;1″,2″:3,4-Dinaphthcyclohepta-1,3-diene-6-benzyloxycarbonylamino-6-carboxylic acid ethyl ester **2i***

Prepared in the same way as **2h** from the aminoester (R,S)-**2a** (0.296 g; 0.78 mmol) and Z-OSu (0.213 g; 0.85 mmol) in acetonitrile (15 ml). Yield 0.308 g (77%) after preparative TLC (SiO_2; eluent I), as a white solid foam. Mp=105°C. Rf=0.41 (I). ^1H NMR ($CDCl_3$): 7.99–7.24, m, 17H (Ar–H); 5.22, d (12.2) and 5.15, d (12.2), 2H (Z); 5.21, s (broad), 1H (NH); 4.24, m (broad q), 2H (OEt); 3.40, d (13.0) and 2.47, d (13.0), 2H (CH_2 β); 3.24, d (broad, 13.8) and 3.16, d (13.8), 2H (C′H_2 β); 1.26, t (broad, 6.9), 3H (OEt). ^{13}C NMR ($CDCl_3$): 172.31 (COOEt); 154.96 (OCONH); 136.19–125.26 (CAr); 69.65 (Cα); 66.73 (Z); 61.49 (OEt); 41.76 (Cβ); 38.43 (C′β); 14.04 (OEt). Anal.($C_{34}H_{29}NO_4$, 0.5 H_2O) calcd. C: 77.84; H: 5.76; N: 2.67; found C: 78.21; H: 5.78; N: 2.72.

2′,1′:1,2;1″,2″:3,4-Dibenzcyclohepta-1,3-diene-6-(9-fluorenylmethyloxycarbonylamino)-6-carboxylic acid tert-*butyl ester* ***1k***

Prepared in the same way as **1h** from the aminoester **1b** (0.309 g; 1.0 mmol) and Fmoc-OSu (0.405 g; 1.2 mmol) in acetonitrile (10 ml). Yield 0.413 g (78%) after column chromatography (SiO_2; eluent V) as a white solid foam. Mp. 98°C. Rf=0.56 (V). ^{1}H NMR ($CDCl_3$): 7.85–7.18, m, 16H (Ar–H); 5.05, s (broad), 1H (NH); 4.49, s (broad), 2H (Fmoc); 4.28, m, 1H (Fmoc); 3.1–2.2, m (broad), 4H (CH_2 β coalescing); 1.47, s, 9H (OtBu). Anal. ($C_{35}H_{33}NO_4$, 0.25 H_2O) calcd. C: 78.41; H: 6.30; N: 2.61; found C: 78.61; H: 6.35; N: 2.51.

(RS)-2′,1′:1,2;1″,2″:3,4-Dinaphthcyclohepta-1,3-diene-6-(9-fluorenylmethyloxycarbonylamino)-6-carboxylic acid tert-*butyl ester* ***2k***

Prepared in the same way as **1k** from the aminoester (R,S)-**2b** (0.409g; 1 mmol) and Fmoc-OSu (0.405 g; 1.2 mmol) in acetonitrile (10 ml). Yield 0.495g (78%) after column chromatography (SiO_2; eluent V) as a white solid foam. Mp. 156°C. Rf=0.38 (V). ^{1}H NMR ($CDCl_3$): 7.99–7.24, m, 20H (Ar–H); 4.96, s (broad), 1H (NH); 4.63, m, 1H (Fmoc); 4.42, s (broad), 1H (Fmoc); 4.30, m, 1H (Fmoc); 3.26, dd (broad,12.9–13.1), 2H (CH_2 β); 3.12, d(broad, 13.1), 1H (CH_2 β); 2.38, d (12.9), 1H (CH_2 β); 1.49, s, 9H (OtBu). ^{13}C NMR ($CDCl_3$): 171.02 (COOtBu); 154.87 (OCONH); 143.80–119.91 (CAr); 81.69 (OtBu); 70.05 (Cα); 66.35 (CH_2,Fmoc); 47.28 (CH, Fmoc); 42.06 (Cβ); 38.01 (C′β); 27.88 (OtBu). Anal. ($C_{43}H_{37}NO_4$, 0.5 H_2O) calcd. C: 80.60; H: 5.98; N: 2.19; found C: 8O.84; H: 6.25; N: 1.99.

*2′,1′:1,2;1″,2″:3,4-Dibenzcyclohepta-1,3-diene-6-*tert-*butyloxycarbonylamino-6-carboxylic acid* ***1f***

From the free aminoacid: A mixture of H-Bip-OH **1d** (0.100 g; 0.39 mmol) and Boc_2O (0.171 g; 0.79 mmol) in N NaOH (10 ml) and dioxane (10 ml) was stirred at room temperature. More Boc_2O (ca 0.05 g) was added after 6 days of stirring and again after 10 days, the progress of the reaction being followed by analytical TLC. After 12 days, the mixture was made acidic by addition of an excess of 0.5 M HCl and extracted with ethyl acetate. The organic phase was washed with brine, dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residue was chromatographed on a preparative TLC plate of silicagel with eluent III to give 0.061 g (44%) of pure **1f**. *By saponification of the N-Boc aminoacid ethyl ester*: To a solution of Boc-Bip-OEt **1e** (0.255 g; 0.67 mmol) in MeOH (15 ml) was added N NaOH (15 ml). The resulting suspension (strong white precipitate of starting material) remained unchanged when stirred at room temperature for hours, but gradually clarified when heated at 75°C in a water bath. After 3 hours of refluxing, the clear solution was allowed to cool to room temperature overnight. Evaporation of methanol *in vacuo* gave a clear colorless solution which was acidified by addition of an excess of 0.5 M HCl, resulting in the formation of a strong white precipitate. The precipitate was collected by filtration, abundently washed with water and air dried to give 0.225 g (95.3%) of analytically pure **1f** as a white powder. Mp=293°C. Rf=0 (I); 0.30 (IV). ^{1}H NMR (CD_3OD): 7.44–7.16, m, 8 H (Ar–H); 2.99, d (13.1), 2H and 2.5, s (broad), 2H (CH_2 β coalescing); 1.49, s, 9H (Boc). ^{13}C NMR (CD_3OD): 176.47 (COOH); 157.06 (OCONH); 142.08–128.55 (CAr); 80.41 (Boc); 70.39 (Cα); 42–38 (broad) (Cβ coalescing); 28.78 (Boc). Anal.($C_{21}H_{23}NO_4$, 0.25 H_2O) calcd. C: 70.47; H: 6.62; N: 3.91; found C: 70.41; H: 6.47; N: 3.94.

*(RS)-2′,1′:1,2;1″,2″:3,4-Dinaphthcyclohepta-1,3-diene-6-*tert-*butyloxycarbonylamino-6-carboxylic acid* ***2f***

From the free aminoacid: To a suspension of H-Bin-OH hydrochloride (R,S)-**2d** (0.195 g; 0.5 mmol) in acetonitrile (10 ml) was added triethylamine (0.101 g; 1 mmol) then Boc_2O (0.218 g; 1 mmol). The reaction mixture was stirred at room temperature for 18 h and gradually clarified. The clear solution was evaporated and the residue solubilized in a mixture of 0.5 M HCl and ether with stirring. The decanted ethereal phase was washed with 0.5 M HCl then twice with brine, dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residue was chromatographed on a 1.5×40 cm column of silicagel with

eluent III to give 0.079 g (35%) of pure (R,S)-**2f**. *By saponification of the N-Boc aminoacid ethyl ester*: A suspension of Boc-Bin-OEt (R,S)-**2e** (0.141 g; 0.29 mmol) in MeOH (10 ml) and N NaOH (10 ml) was stirred at 75°C for 2 h. The resulting clear solution was allowed to cool to room temperature, acidified by addition of an excess of 0.5 M HCl and extracted with ether. The ethereal solution was washed twice with water, dried ($MgSO_4$), filtered and evaporated *in vacuo* to give 0.128 g (96.4%) of pure (R,S)-**2f** as a white solid. Mp=283°C. Rf=0.24 (III); 0.33 (IV). ^{1}H NMR (CD_3OD): 7.95–7.20, m, 12H (Ar–H); 3.27, d (13.8) and 3.02, d (13.8), 2H (CH_2 β); 3.08, d (13.2) and 2.49, d (13.2), 2H (C′H_2 β); 1.49, s, 9H (Boc). ^{13}C NMR (CD_3OD): 176.53 (COOH); 157.04 (OCONH); 136.92–126.17 (CAr); 80.45 (Boc); 70.86 (Cα); 42.39 (Cβ); 38.35 (C′β); 28.79 (Boc). Anal. ($C_{29}H_{27}NO_4$, H_2O) calcd. C: 73.86; H: 6.20; N: 2.97; found C: 73.88; H: 5.99; N: 2.86.

(+)-(S)-2f was prepared in the same way as (R,S)-**2f** by saponification of (+)-(S)-**2e** (1.372 g; 2.85 mmol) in MeOH (70 ml) and N NaOH (70 ml) at 75°C for 3 h. The white precipitate obtained after evaporation of methanol and acidification of the solution was filtered, abundently washed with water and dried *in vacuo* over KOH pellets to into give 1.241 g (96%) of analytically pure (+)-(S)-**2f** as a white powder. Mp=264°C. Anal.($C_{29}H_{27}NO_4$, 0.5 H_2O) calcd. C: 75.30; H: 6.10; N: 3.03; found C: 74.87; H: 6.05; N: 3.07. $[\alpha]^{25}_{589}$=+46.6, $[\alpha]^{25}_{578}$=+47.6, $[\alpha]^{25}_{546}$=+50.2, $[\alpha]^{25}_{436}$=+8.6, $[\alpha]^{25}_{365}$=−644.6 (c 0.5; MeOH).

2′,1′:1,2;1″,2″:3,4-Dibenzcyclohepta-1,3-diene-6-benzyloxycarbonylamino-6-carboxylic acid ***1j***

To a solution of Z-Bip-OtBu **1h** (0.772 g; 1.74 mmol) in CH_2Cl_2 (5 ml) was added TFA (5 ml). The solution was stirred at room temperature for 4 h and evaporated *in vacuo*. The residue was solubilized in a mixture of 0.5 M HCl and ether with stirring. The decanted ethereal phase was washed twice with water, dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residue was chromatographed on a 1.5×40 cm column of silicagel with eluent (IV) to give 0.582 g (86.3%) of pure **1j** as a white amorphous solid. Mp=155°C. Rf=0.35 (IV). ^{1}H NMR ($CDCl_3$): 10.3, s (broad), 1H (COOH); 7.4–7.2, m, 12 H (Ar–H); 5.33, s (broad), 1H (NH); 5.13, s (broad), 2H (Z); 3.4–3, m (broad) and 3.2–2.2, m (broad), 4H (CH_2 β coalescing). ^{1}H NMR (CD_3OD): 7.39–7.11, m, 13 H (Ar–H); 5.11, s (broad), 2H (Z); 3.05, d (13.1), 2H and 3.2–2.2, m (broad), 2H (CH_2 β coalescing). ^{13}C NMR ($CDCl_3$): 177.40 (COOH); 155.41 (OCONH); 140.5–127.0 (CAr); 69.17 (Cα); 67.09 (Z); 39.55 (broad) (Cβ coalescing). Anal.($C_{24}H_{21}NO_4$, 0.6 H_2O) calcd. C: 72.38; H: 5.62; N: 3.52; found C: 72.11; H: 5.36; N: 3.39.

(RS)-2′,1′:1,2;1″,2″:3,4-Dinaphthcyclohepta-1,3-diene-6-benzyloxycarbonylamino-6-carboxylic acid ***2j***

Prepared as for **1j** from (R,S)-**2h** (0.343 g; 0.63 mmol) in CH_2Cl_2 (5 ml) and TFA (5 ml) at room temperature for 4 h. Yield 0.280 g (91%) crude, as an analytically pure white powder. *By saponification of the N-Z aminoacid ethyl ester*: Prepared as for **2f** from (R,S)-**2i** (0.140 g; 0.27 mmol) in MeOH (30 ml) and N NaOH (30 ml) at 75°C for 3 h. Yield 0.109 g (82.6%) after evaporation of methanol, acidification and extraction with ether, as a white solid. Mp=156°C. Rf=0.13 (III); 30 (IV). ^{1}H NMR (CD_3OD): 7.95–7.21, m, 17H (Ar–H); 5.19, d (12.8) and 5.08, d (12.8), 2H (Z); 3.11, d (13.2) and 2.54, d (13.2), 2H (CH_2 β); 3.27, d (broad, 13.8) and 3.04, d (13.8), 2H (C′H_2 β). ^{13}C NMR ($CDCl_3$): 177.29 (COOH); 155.47 (OCONH); 135.97–125.22 (CAr); 69.81 (Cα); 67.04 (Z); 41.52 (Cβ); 38.39 (C′β). ^{13}C NMR (CD_3OD): 176.42 (COOH); 157.38 (OCONH); 138.27–126.13 (CAr); 71.21 (Cα); 67.27 (Z); 42.37 (Cβ); 38.31 (C′β). Anal.($C_{32}H_{25}NO_4$, 0.5 H_2O) calcd. C: 77.40; H: 5.28; N: 2.82; found C: 77.16; H: 5.44; N: 2.71.

(+)-(S)-2j was prepared as for **1j** from (+)-(S)-**2h** (0.815 g; 1.50 mmol) in CH_2Cl_2 (15 ml) and TFA (15 ml) at room temperature for 4 h. The crude product obtained after extraction with ether was solubilized in methanol. The solution was treated with activated charcoal, filtered and evaporated *in vacuo* to give 0.514 g (70.3%) of analytically pure (+)-(S)-**2j** as a white crystalline powder. Mp=167°C. Anal.($C_{32}H_{25}NO_4$, H_2O) calcd. C: 76.02; H: 5.38; N: 2.77; found C: 76.09; H: 5.32; N:

2.86. $[\alpha]^{25}_{589}$=+15.1, $[\alpha]^{25}_{578}$=+14.9, $[\alpha]^{25}_{546}$=+12.9, $[\alpha]^{25}_{436}$=−56.0, $[\alpha]^{25}_{365}$=−712.0 (c 0.5; MeOH).

2′,1′:1,2;1″,2″:3,4-Dibenzcyclohepta-1,3-diene-6-(9-fluorenylmethyloxycarbonylamino)-6-carboxylic acid ***1l***

Prepared in the same way as **1j** from **1k** (0.331 g; 0.62 mmol) in CH_2Cl_2 (3 ml) and TFA (3 ml) at room temperature for 4 h. Yield 0.278 g (94%) crude as a white powder. Mp. 146°C. Rf=0.59 (IV). ^{1}H NMR ($CDCl_3$): 7.78–7.17, m, 16H (Ar–H); 6.39, s (broad), >1H (COOH + H_2O); 5.31, s, 1H (NH); 4.52, m (broad), 2H (Fmoc); 4.24, m, 1H (Fmoc); 3.18–2.83, m (broad), 4H (CH_2 β coalescing). Anal. ($C_{31}H_{25}NO_4$, 0.5 H_2O) calcd. C: 76.84; H: 5.41; N: 2.89; found C: 76.92; H: 5.91; N: 2.77.

(RS)-2′,1′:1,2;1″,2″:3,4-Dinaphthcyclohepta-1,3-diene-6-(9-fluorenylmethyloxycarbonylamino)-6-carboxylic acid (2l)

Prepared in the same way as **1l** from (R,S)-**2k** (0.453 g; 0.72 mmol) in CH_2Cl_2 (3 ml) and TFA (3 ml) at room temperature for 4 h. Yield 0.386 g (93%) crude as a white powder. Mp. 177°C. Rf=0.50 (IV). ^{1}H NMR ($CDCl_3$): 7.98–7.20, m, 20H (Ar–H); 6.10, s (broad), >1H (COOH + H_2O); 5.02, s, 1H (NH); 4.64, m,1H (Fmoc); 4.39, m (broad), 1H (Fmoc); 4.24, m, 1H (Fmoc); 3.30, d (12.5) and 2.37, d (12.5), 2H ($CH_2\beta$); 3.19, d (13.3) and 3.09, d (13.3), 2H ($C'H_2\beta$). Anal. ($C_{39}H_{29}NO_4$, 0.9 H_2O) calcd. C: 79.14; H: 5.24; N: 2.37; found C: 79.14; H: 5.38; N: 2.41.

Acknowledgements

We thank Aurelia Boutboul for her contribution to this work as a student.

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(Received in UK 12 December 1996)