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Synthesis of α,α-Disubstituted-β-Aminoacids with Axial Chirality

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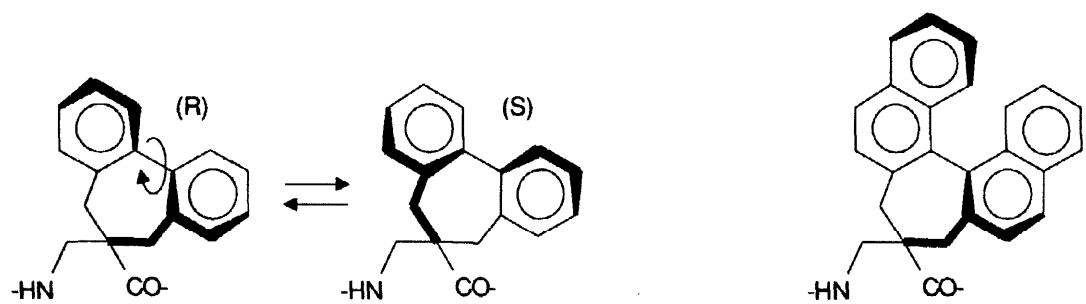
Abstract : 6-aminomethyl-6,7-dihydro-5*H*-dibenzo[a,c]cycloheptene-6-carboxylic acid ethyl ester H-β²-Bip-OEt **1a** and its 1,1'-binaphthyl optically pure analog (R) H-β²-Bin-OEt **2a**, have been readily synthesized by bis-alkylation of ethyl cyanoacetate with 2,2'-*bis*-(bromomethyl)-1,1'-diphenyl or optically pure (+)-(R)- 2,2'-*bis*-(bromomethyl)-1,1'-binaphthyl, followed by $NaBH_4$ / $CoCl_2$ selective reduction of the cyano group. The N-Boc protected derivatives and short peptides of these novel aminoacids have also been prepared.

The field of « β-peptides » has recently attracted a considerable and renewed interest.[1-3] Short oligomers of certain β-aminoacids form surprisingly stable secondary structures such as turns, β-sheet-like arrangements, or helical conformations (3_{14} or 2.5_{12} helices),[2,3] different in nature from those adopted by oligomers of α-aminoacids and α,α-disubstituted glycines (3.6_{13} or 3_{10} helices).[4,5]



β²-Bip **1** (R)-β²-Bin **2**

Figure 1 : Novel α,α-disubstituted-β-aminoacid derivatives with only axial chirality.

Following our earlier work with the synthesis of axially chiral α,α-disubstituted-α-aminoacids Bip and Bin,[6] shown to behave as helix inducers in short-chain peptides,[7] we have now synthesized the corresponding α,α-disubstituted-β-aminoacid derivatives β²-Bip **1** and β²-Bin **2** (Fig. 1).[8,9] These compounds may be regarded as 1,1'-biphenyl and 1,1'-binaphthyl-substituted β-amino pivalic acid (β-Api).[10] Although they both possess an axial chirality, only the binaphthyl derivatives **2** can be isolated in enantiomerically pure state and are optically stable, while fast interconversion between the (R) and (S) enantiomers (conformers) of the biphenyl derivatives **1** occurs at room temperature, because of the low rotation barrier along the 1,1' bond.[6b,11]

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For the synthesis of **1** and **2**, we considered the bis-alkylation of ethylcyanoacetate by 2,2'-*bis*-(bromomethyl)-1,1'-diphenyl **3** and enantio-pure 2,2'-*bis*-(bromomethyl)-1,1'-binaphthyl (+)-(R)-**4**,[12] respectively, in dimethylformamide at room temperature, with potassium carbonate as base. As expected from the previously experienced high tendency of these dibromides for intramolecular bis-alkylation of the active methylene of benzylidene derivatives of glycine esters, with formation of a seven-membered carbon ring, the resulting cyanoesters **5** (82 %) and (−)-(R)-**6** (79 %),[13] were obtained with excellent yields (Fig. 2).

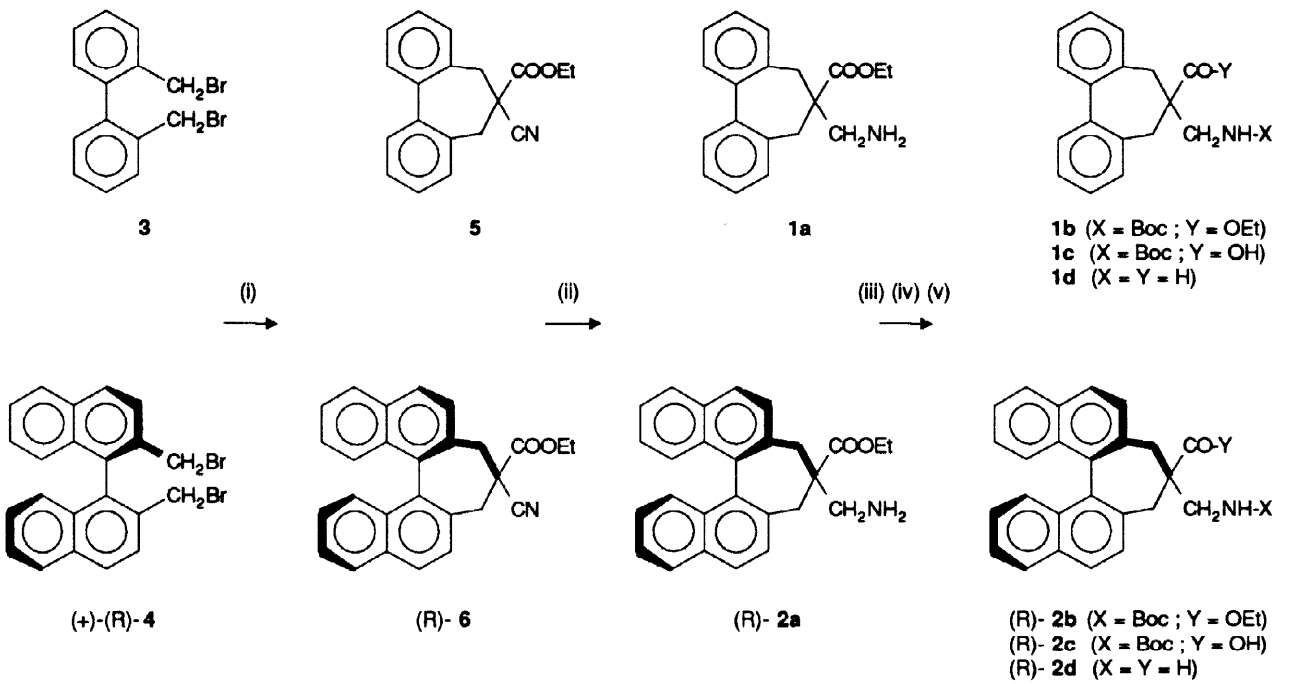

Figure 2 : Synthetic scheme for the preparation of α,α-disubstituted-β-aminoacid derivatives **1** and (R)-**2**. *(i)* EtOOC-CH_2-CN; DMF; K_2CO_3 *(ii)* $NaBH_4$; $CoCl_2$; MeOH *(iii)* Boc_2O; CH_3CN *(iv)* 1N NaOH; MeOH; 80 °C *(v)* TFA:CH_2Cl_2 1:1.

Selective reduction of the cyano group of **5** and (−)-(R)-**6** was accomplished by means of sodium borohydride (10 equiv) and cobalt (II) chloride (2 equiv) in methanol at room temperature, and gave the aminoesters **1a** (76 %) and (−)-(R)-**2a** (59 %),[13] respectively. This result demonstrates that the cobalt-assisted $NaBH_4$ reduction method of nitriles in the presence of an ester function,[14] is also efficient in the case of *gem*-cyanoesters. In our hands, attempts to use $CoCl_2$ in catalytic amount (10 % mol/mol) with an excess of $NaBH_4$ in 2:1 THF:H_2O, a procedure optimized for benzonitrile by Ganem *et al.*[14a,d] in order to avoid the harshly acidic workup necessary for decomposition of the Co_2B complexes, surprisingly only resulted in reduction of the ester group.

The N-Boc protected derivatives were synthesized in two steps from the C-protected derivatives **1a** and (−)-(R)-**2a**, which were first treated by Boc anhydride in acetonitrile at room temperature,[6b,15] to give the fully protected compounds **1b** (98 %) and (−)-(R)-**2b** (63 %).[13] Saponification of the α,α-disubstituted ester function of Boc-β^2-Bip-OEt **1b** and Boc-β^2-Bin-OEt **2b** in aqueous 1N NaOH/MeOH required a relatively high temperature of *ca* 80 °C, like for Boc-Bip-OEt and Boc-Bin-OEt,[6b] but gave good yields in **1c** (92 %) and (−)-(R)-**2c** (95 %).[13] Finally, cleavage of the Boc group of **1c** and (−)-(R)-**2c** in TFA:CH_2Cl_2 1:1 at room temperature led to **1d** (79 %) and (−)-(R)-**2d** (72 %),[13] as ammonium trifluoroacetates.

The EDC/HOBt peptide coupling procedure was examined for both C and N-terminus of the β^2-Bip residue **1**, using (L)-alanine as second component. Coupling of Boc-β^2-Bip-OH **1c** with H-Ala-OMe, HCl and one equivalent of triethylamine, gave Boc-β^2-Bip-Ala-OMe **1e** [13] (Fig. 3) in 87 % yield. Cleavage of the Boc protecting group in TFA:CH_2Cl_2 1:1 at room temperature, followed by extraction of the free aminoester H-β^2-Bip-Ala-OMe with EtOAc - 5 % $NaHCO_3$ and its direct coupling with Boc-Ala-OH, led to Boc-Ala-β^2-Bip-Ala-OMe **1f** [13] (Fig. 3) in 90 % overall yield. These results are in agreement with the known efficiency of the EDC/HOBt method for coupling at a α,α-disubstituted COOH function,[6b,16] and with the relatively unhindered NH_2 function of β^2-aminoacids.

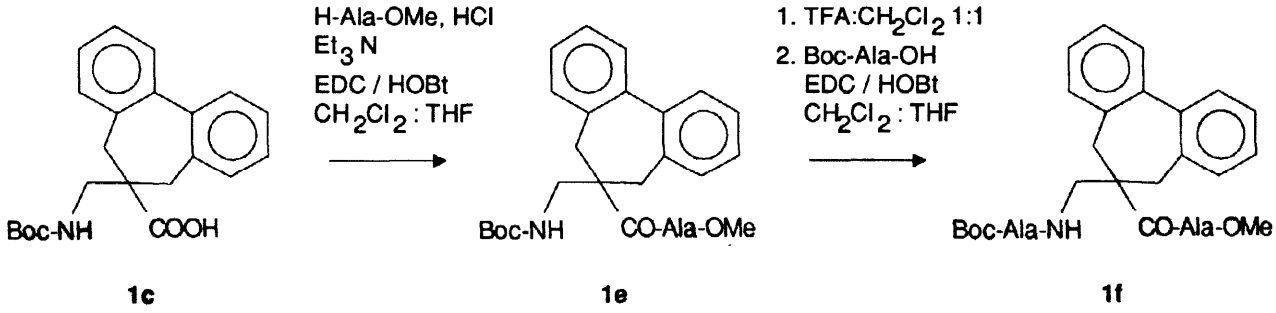

Figure 3 : Coupling of (L)-alanine at the C- and N-terminus of the β^2-Bip residue.

The new α,α-disubstituted-β-aminoacid derivatives β^2-Bip **1** and β^2-Bin **2**, here shown to be easily accessible, should be interesting building blocks for the synthesis of atropoisomeric β-peptide oligomers: [β^2-Bip]$_n$ and [β^2-(R)-Bin]$_n$ in view of analysis of their conformational properties. Although incorporation of a geminally disubstituted aminoacid residue is expected to prevent the formation of a helical secondary structure in a β-peptide,[3b,17] the steric bulk of the biphenyl or binaphthyl groups at the α,α-position could possibly drive the dihedral angle NCsp^3-Csp^{3}O to a favorable helix-inducing gauche conformation.[18] Cyclopeptides of type c[β^2-Bip]$_n$ and c[β^2-(R) and/or (S)-Bin]$_n$ should also be interesting targets, as potential inducers of new chiral tubular structures.[3c-e]

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17 To date, only α-substituted, β-substituted and α,β-disubstituted 3-amino-propionic acids,[3] as well as *trans*-amino cyclohexane or cyclopentane carboxylic acids,[2] have been incorporated in helical β-peptides.

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