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A New Chiral α-Aminoacid with only Axial Dissymmetry: Synthesis and X-Ray Analysis of a 1,1'-Binaphthyl-Substituted α-Aminoisobutyric Acid (Bin) and of its Biphenyl Analogue (Bip).

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Abstract : Racemic as well as optically 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 by bis-alkylation of a glycine *tert*-butyl ester Schiff base. The free aminoacids Bin and Bip, as well as their C- and/or N-protected derivatives have been obtained. X-ray analysis of H-Bip-OtBu and H-(S)Bin-OH is presented.

Among the increasing number of studies concerning unusual amino acid derivatives, synthesis and structural analysis of peptide fragments incorporating α,α-disubstituted glycines have acquired considerable importance in the design of analogs of bioactive peptides.[1-3] The best studied member of this family, α-aminoisobutyric acid (Aib; α-methyl alanine), as well as the chiral α-ethyl alanine (Iva) are present in naturally occuring peptide antibiotics and amphiphilic ionophores peptaibols.[4] Aib and others α,α-disubstituted α-amino acids, including their cyclized analogs Ac_nc, have been used in modifications of peptide hormone sequences, in order to make these more resistant to enzymatic degradation and to stabilize preferred conformations of the peptide backbone, by conformational constraints known to increase the 3_{10}-/α-helix content.[1] Exploitation of their homopolymers as precise molecular rulers or scaffolding blocks in the *de novo* design of protein and enzyme mimetics,[5] as well as model compounds for mechanistic studies of biological processes such as protein folding [6] has also been considered.

In the present paper, we report the synthesis of new α-amino acids disubstituted at the α carbon: Bip **1** and Bin **2** (Fig. 1), which are biphenyl and binaphthyl, respectively, substituted analogs of Aib. Bip **1** may be regarded either as a particular $C^{\alpha,\alpha}$-dibenzylglycine [2] in which the two phenyl rings are covalently bound, or as a

di-benzo-1-aminocycloheptane-1-carboxylic acid Ac7c.[3] *Bin* **2** *represents a new example of a chiral atropoisomeric* α*-amino acid with an achiral (*C_2*-symmetry of the binaphthyl moiety) disubstituted* α *carbon atom.*[7] The amino acids **1** and **2** are expected to induce interesting special conformational and optical properties in connexion with the yet unexplored relationship between axial chirality and helix handedness, when incorporated in peptides.

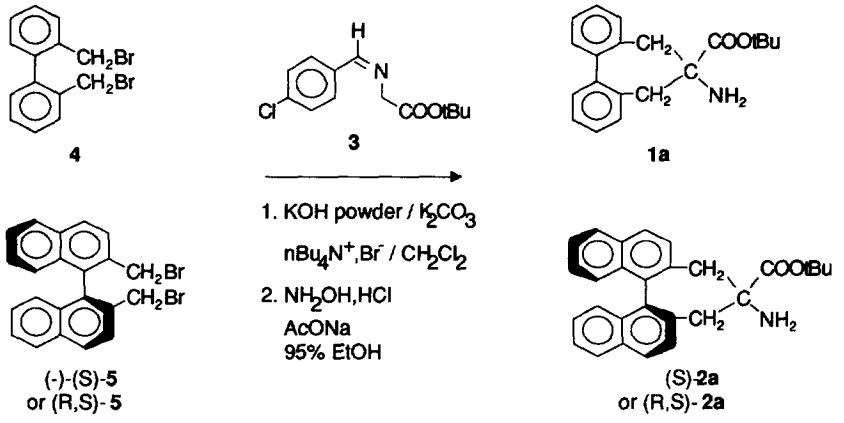

Figure 1. Synthesis of H-Bip-OtBu (**1a**) and H-Bin-OtBu (**2a**) under phase transfer conditions.

For the synthesis of both Bin and Bip, we considered the bis alkylation of aldimine or ketimine derivatives of glycine esters, a widely used method for the synthesis of both α-amino acids and $C^{\alpha,\alpha}$-disubstituted α-amino acids.[8] We were quite confident that such *C,C-bis*-alkylation would be effective in the case of both 2,2'-bis(bromomethyl)-1,1'-biphenyl and 2,2'-bis(bromomethyl)-1,1'-binaphthyl alkylating agents, according to the generally observed *N,N-bis*-alkylation of amines by these reagents.[9] As expected, alkylation of the glycine *tert*-butyl ester Schiff base **3** by both dibromides **4** and either racemic (R,S)-**5** [10] or optically pure (-)-(S)-**5** [10] under phase transfer conditions according to M. J. O'Donnell *et al.*,[8c,d] the best method in our hands, led to good yields of the desired amino esters H-Bip-OtBu **1a** (75 %) and H-Bin-OtBu (R,S)-**2a** (76 %) or (S)-**2a** (81%), respectively.[11]

Treatment of the racemic compound (R,S)-**2a** by Mosher's (-)-(S)-α-methoxy-α-trifluoromethyl-α-phenyl-acetic acid [12] anhydride in acetonitrile led to a *ca* 1.2:1 mixture of the diastereoisomeric amido esters $Ph(OCH_3)(CF_3)CCO$-Bin-OtBu (S,S)-**2b** and (SR)-**2b**, with distinct signals in ^1H NMR, ^{19}F NMR and ^{13}C NMR. These two compounds 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)-**2a** gave the single amido ester (S,S)-**2b**, with 0.5-1 % of the other isomer, demonstrating that (S)-**2a** was optically pure or nearly so. The recorded absence of racemization during the alkylation process is

not surprizing, considering the previously demonstrated very high optical stability of 2,2'-bis(methylene)-substituted-1,1'-binaphthyls,[9a] 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. Deprotection of the aminoesters **1a** and **2a** in TFA/CH_2Cl_2 1:1 gave the free aminoacids H-Bip-OH **1c** and H-Bin-OH (R,S)-**2c** / (S)-**2c**. Other C- and/or N-protected derivatives H-Bip-OEt (**1d**), H-Bin-OEt (**2d**), Boc-Bip-OH (**1e**), Boc-Bin-OH (**2e**), Boc-Bip-OtBu (**1f**), Boc-Bin-OtBu (**2f**), Boc-Bip-OEt (**1g**), Boc-Bin-OEt (**2g**), Z-Bip-OtBu (**1h**), Z-Bin-OtBu (**2h**), Z-Bin-OEt (**2i**), Z-Bip-OH (**1j**) and Z-Bin-OH (**2j**) were prepared by standard methods.[11]

X-ray analysis of the crystal structures of H-Bip-OtBu **1a** and H-(S)Bin-OH **2c** (Fig. 2) revealed interesting features concerning the conformation of the seven-membered cycle of these molecules (Table 1).

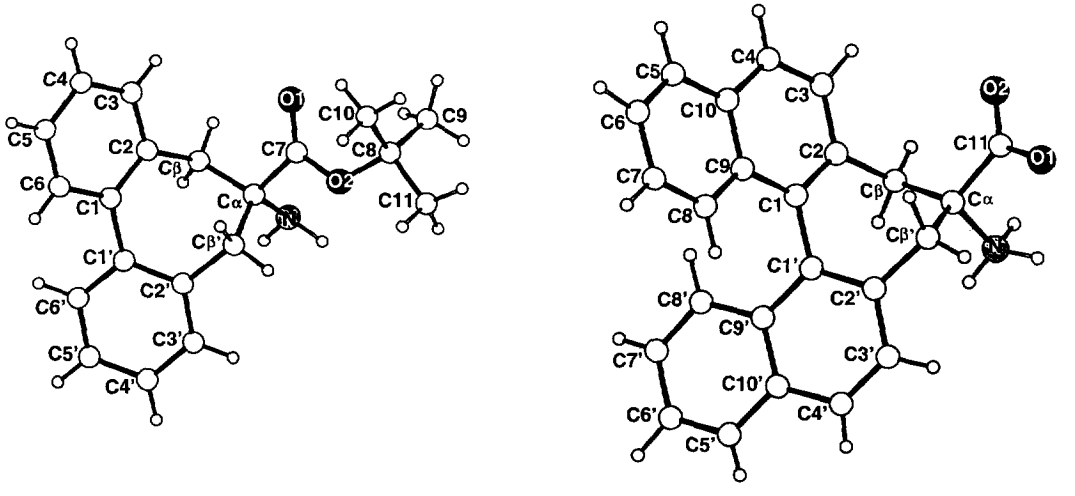

Figure 2. The molecular structures of H-Bip-OtBu (**1a**) and H-(S)Bin-OH (**2c**).

	Bip **1a**	Bin **2c**	Torsion angles (°)	Bip **1a**	Bin **2c**	Colc.[a]
C_α-C_β	1.545	1.539	C_α-C_β-C_2-C_1	-71.1	-71.9	-70.9
C_β-C_2	1.501	1.513	C_β-C_2-C_1-$C_{1'}$	3.3	0.9	3.7
C_2-C_1	1.407	1.386	C_2-C_1-$C_{1'}$-$C_{2'}$	46.5	53.8	52.9
C_1-$C_{1'}$	1.486	1.495	C_1-$C_{1'}$-$C_{2'}$-$C_{\beta'}$	1.2	-5.4	-3.4
$C_{1'}$-$C_{2'}$	1.397	1.388	$C_{1'}$-$C_{2'}$-$C_{\beta'}$-C_α	-74.1	-69.3	-73.5
$C_{2'}$-$C_{\beta'}$	1.514	1.502	$C_{2'}$-$C_{\beta'}$-C_α-C_β	47.9	44.9	42.8
$C_{\beta'}$-C_α	1.538	1.532	$C_{\beta'}$-C_α-C_β-C_2	37.7	40.3	44.5

Table 1. Bond lengths and torsion angles of the seven-membered ring of H-Bip-OtBu **1a** ($C_{20}H_{23}NO_2$, M=309.4. Monoclinic, An(Nr.9), Z=4, a=10.435(1). b=17.256(2), c=9.991(2) Å, β=103.44(1)°. Conventional-R factor 0.045) and H-(S)Bin-OH **2c** ($C_{26}H_{27}NO_4$, M=417.5. Monoclinic, $P2_1$(Nr.4), Z=2, a=12.705(3), b=6.411(2), c=13.942(2) Å, β=95.38(1)°. Conventional-R factor 0.058). Structures solved using SHELXS86 program (Sheldrick, G. M. *Program for the Solution of Crystal Structures.* 1986. University of Göttingen, Germany) and refined with SHELXL93 (Sheldrick, G. M. *Program for the Refinement of Crystal Structures.* 1994. University of Göttingen). Tables of atomic coordinates, bond distances, angles and selected torsion angles deposited with the main crystal parameters, anisotropic displacement parameters and observed/calculated structure factors at the Cambridge Crystallographic Data Center. *(a)* Average values for 17 colchicin derivatives (from CSD data bank).

As expected, the bond lengths and the torsion angles were far different from the ones of the parent Ac$_7$c derivatives,[3b,c] because of the presence of the two benzo or naphtho substituents enforcing two couples of torsion angles to be close to 0°. On the other hand, the conformation of **1a** and **2c** was strikingly similar to the preferred conformation of a large number of colchicin derivatives,most of them exhibiting antitumoral activity.[13] For both Bin and Bip, the cycle was pseudo-symmetrical with a non crystallographic C_2 axis passing through Cα and the middle of the opposite bond. The torsion angle along the 1-1' bond was 46.5° for **1a** and 53.8° for **2c**, according to the greater steric hindrance brought by the extra phenyl rings present in Bin.

As already pointed out, Bin and Bip are members of new families of highly hydrophobic axially chiral α,α-symmetrically disubstituted α-amino acids, which *must* have intrinsic applications in the design of protein mimetics, because of their pseudo C_2 -symmetry. The related α,α-disubstituted α-amino phosphonic, phosphinic, sulfonic acids and α-hydroxy acids are also of interest. The synthesis of such compounds as well as the conformational and optical properties of their homopolymers and peptide derivatives are now being explored in our laboratory.

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