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N-t-Boc 6-Amino-1,11-(20-Crown-6)-6,7-Dihydro-5H-Dibenzo[a,c] cycloheptene-6-Carboxylic Acid Methyl Ester, the First Prototype of a Crown-Carrier-Axially Dissymmetric-α,α-Disubstituted Glycine

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Abstract : N-t-Boc 6-amino-1,11-(20-crown-6)-6,7-dihydro-5H-dibenzo[a,c]cycloheptene-6-carboxylic acid methyl ester: Boc-[20-C-6]-Bip-OMe **1**, a new crown-carrier-α,α-disubstituted glycine with axial dissymmetry and a potential building block for the synthesis of polypeptide supramolecular devices, has been synthesized at the racemic state by phase transfer bis-alkylation of a glycine *tert*-butyl ester Schiff base with 2,2'-*bis*-(bromomethyl)-6,6'-dimethoxy-1,1'-diphenyl, followed by demethylation, esterification, N-protection and crown formation upon cyclization of the di-cesium salt of the resulting diphenol with pentaethyleneglycol ditosylate. © 1997 Published by Elsevier Science Ltd.

The utility of peptide synthesis for the facile assembly of supramolecular architectures, considered as « highly desirable for a wide range of applications such as biosensors, molecular electronics and energy storage devices as well as for biomimicking natural systems »,[1a] has been recognized as an important strategy in the past few years.[1,2] However, to our knowledge, this concept had not yet been applied to α,α-disubstituted glycines, in spite of the now well documented strong tendency of such α-amino acids to stabilize either fully extended or folded (helical) conformations of the peptide backbone in polypeptides.[3]

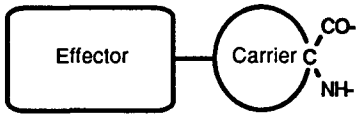

Figure 1 : Effector-carrier-α,α-disubstituted glycines.

The ability of α,α-disubstituted glycines to *induce organized predictable structures* makes them very attractive building blocks for the construction of supramolecular devices using peptides as framework.[3]

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Therefore, designed α,α-disubstituted glycines carrying an effector by means of a relatively rigid carrier frame (Fig.1), for which structural simplification in order to have an achiral α-carbon atom can be easily achieved, are likely to be organized in synthetic peptides bearing multiple effectors in a well defined and controlled spatial organization.

Only a few representative examples of such compounds are known. Rebek *et al.*[4] have prepared *bis*-(adenine) and *bis*-(thymine)-carrier-α,α-disubstituted glycines and their di- and tri-peptides, as prototypes of potential self-replicating systems. Recent results about peptides incorporating a 1,1'-binaphthyl-substituted α-aminoisobutyric acid (Bin) residue [5] as a rigid fluorescent effector and a TOAC residue [6] as a rigid fluorescence quencher effector, also confirm the interest of this concept.[7]

In pioneering studies, Voyer *et al.*[1] have taken advantage of the cathecol function of L-DOPA to synthesize a series of L-alanine polypeptides incorporating several (21-crown-7)-L-phenylalanine or (18-crown-6)-L-phenylalanine residues with appropriate spacing for the observation of supramolecular properties. We have now designed crown-carrier-α,α-disubstituted glycines of types **A**, **B** and **C** (Fig. 2) in which the carrier frames are indane, cyclopentane and 2,2'-*bis*-(methylene)-1,1'-biphenyl, respectively, as new promising building blocks for the preparation of supramolecular devices. In the present paper, we report the synthesis of the racemic N-t-Boc 6-amino-1,11-(20-crown-6)-6,7-dihydro-5H-dibenzo[a,c]cycloheptene-6-carboxylic acid methyl ester **1** (type **C** with n = 4), which presents the special interest of being an *axially chiral* molecule.

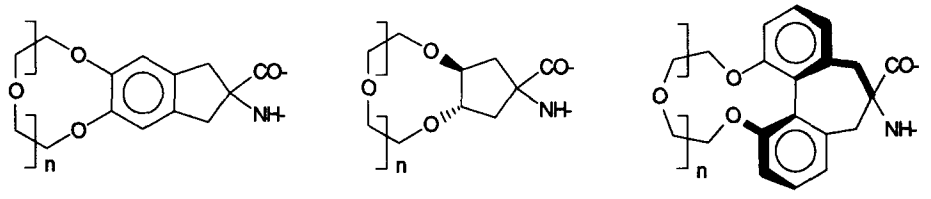

Figure 2 : Designed crown-carrier-α,α-disubstituted glycines.

For the preparation of 6-amino-1,11-dimethoxy-6,7-dihydro-5H-dibenzo[a,c]cycloheptene-6-carboxylic acid *tert*-butyl ester H-[MeO]$_2$-Bip-OtBu **4**, a precursor of the compound **1**, we choosed a direct route involving bis-alkylation of the glycine *tert*-butyl ester Schiff base **3** (Fig. 3) by 2,2'-*bis*-(bromomethyl)-6,6'-dimethoxy-1,1'-diphenyl **2**, readily available from 2-amino-3-methoxybenzoic acid.[8] Phase transfer conditions using tetrabutylammonium bromide as catalyst with potassium carbonate and ground potassium hydroxide in dichloromethane,[9] previously applied by us [5] with success for 2,2'-*bis*-(bromomethyl)-1,1'-biphenyl and 2,2'-*bis*-(bromomethyl)-1,1'-binaphthyl alkylating agents, also worked efficiently here to give, after acidic cleavage of the Schiff base on silica gel followed by chromatographic purification , the aminoester **4** with 64 % yield.[10]

Treatment of **4** by boron tribromide[11] in dichloromethane allowed demethylation of the methoxy groups and simultaneously cleaved the *tert*-butyl ester group, to give H-[HO]$_2$-Bip-OH,HBr, which was directly esterified in refluxing methanol and 98 % H_2SO_4 to the corresponding 6-amino-1,11-dihydroxy-6,7-dihydro-5H-dibenzo[a,c] cycloheptene-6-carboxylic acid methyl ester H-[HO]$_2$-Bip-OMe **5**,[10] obtained with 73 % yield after chromatography.

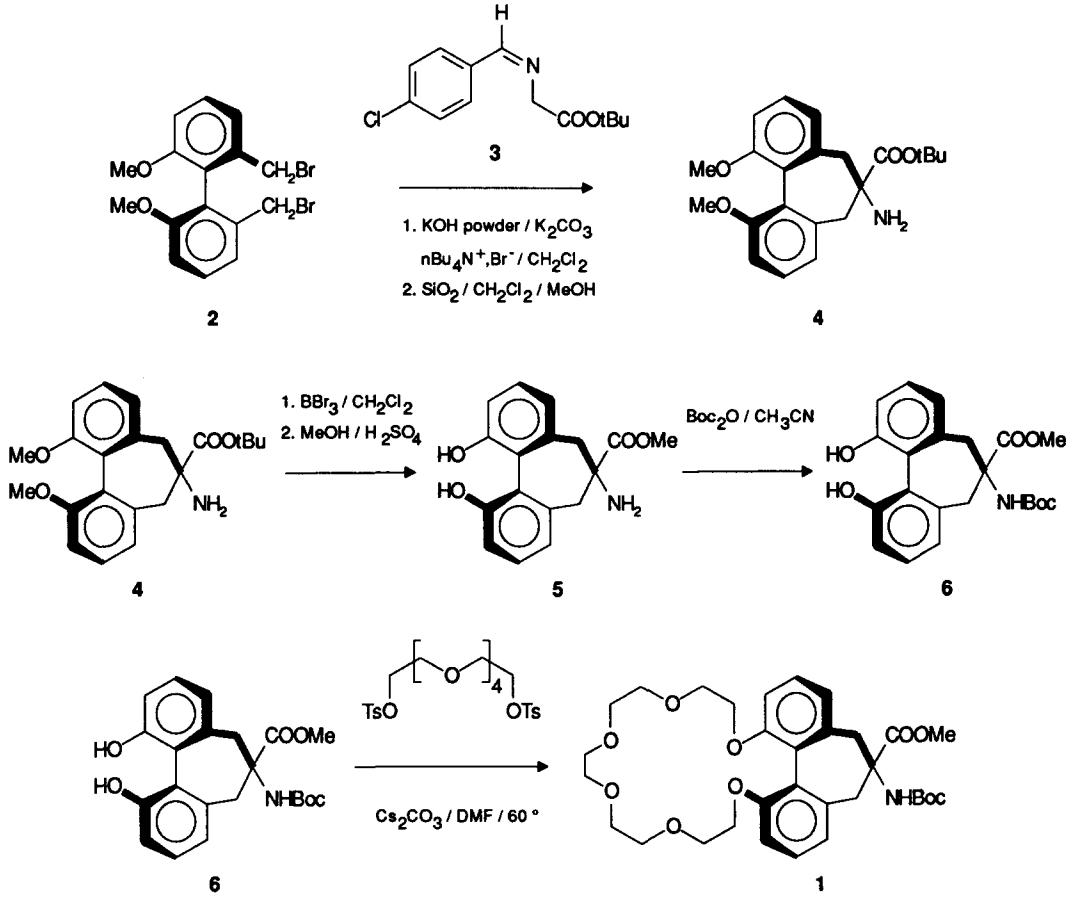

Figure 3 : Synthetic scheme for the preparation of Boc-[20-C-6]-Bip-OMe **1**.

The compound **5** was then treated with an excess of Boc anhydride in acetonitrile, and the resulting di-protected aminoacid Boc-[HO]$_2$-Bip-OMe **6** (93 % yield)[10] was reacted with cesium carbonate in methanol at 45 °C. Methanol was evaporated *in vacuo* and the residue solubilized in DMF. The solvent was again evaporated *in vacuo* at 45 °C in order to completely remove methanol. The resulting cesium di-salt of **6** was treated with 1 equivalent mol/mol of pentaethylene glycol ditosylate under high dilution conditions in DMF at

60 °C for 21 hours to give Boc-[20-C-6]-Bip-OMe **1** as a pure analytical sample in 38 % yield [10] after chromatography.

Within the concept of supramolecular devices using peptides as framework, the present study illustrates the interest of crown-carrier-α,α-disubstituted glycines as new building blocks. Furthermore, the opportunity to incorporate *steric* and *chiral barriers* into these crown-ethers is also of great interest for the design of complementary binding features in host-guest chemistry.[12] According to our preliminary results,[7,13] peptides incorporating (1,1'-biphenyl)- or (1,1'-binaphthyl)-substituted α-aminoisobutyric acid residues (Bip or Bin) [5] tend to fold into bends and helices. On these bases, one may expect a similar organization induced by the crown-carrier-Bip residue **1**. Resolution of **1** and/or its precursors or derivatives, as well as incorporation of **1** into peptides, will be soon examined in our laboratory.

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