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Synthesis of [18-C-6]-β³-(*L*)-DOPA, first β-amino acid with a crown-ether receptor side-chain

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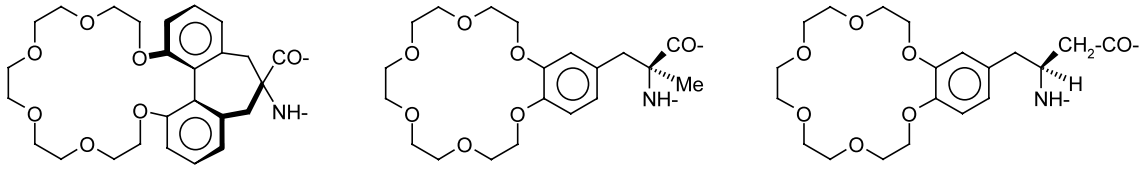
Abstract—Terminally protected Boc-β³-(*L*)-DOPA-OMe has been synthesized from (*L*)-DOPA by the *Arndt–Eistert* homologation procedure. Then, a first crown-ether derivative, Boc-[18-C-6]-β³-(*L*)-DOPA-OMe, has been obtained by bis-*O*-alkylation of the catechol function with cyclization, using Cs_2CO_3 as base and pentaethyleneglycol ditosylate as alkylating agent, in DMF at 60°C.

In the past decade, an increasing amount of work has been devoted to the construction of molecular receptors and devices based on peptidic frameworks.[1] In that field, the pioneering studies of Voyer et al.[2] have highlighted the interest of synthetic α-amino acid derivatives of (*L*)-DOPA, bearing a crown-ether receptor on their side-chain, which can be easily assembled in structurally well-defined nanometer-scale peptidic architectures of bis-crown as well as polymeric crown compounds, in view of preparation of peptide-based ion-selective molecular receptors for alkali metal, ammonium and di-ammonium ions, as well as artificial ion channels. According to the well-documented ability of β-amino acids to induce helical conformations of the backbone of their peptide oligomers (3_{14} or 2.5_{12} helices),[3] different in nature and even more stable than those adopted by peptides based on α-amino acids, we found it interesting to introduce crown-ether receptors on the side-chains of such β-amino acids, to investigate the structure of their short-chain peptide oligomers and that of their corresponding 'sandwich' complexes. Previously, we have synthesized crown-carrier α,α-disubstituted α-amino-acids able to induce 3_{10} helices,[4] where the side chains of residues at *i* and *i*+3 positions of the backbone are well superposed as in the case of the 3_{14} helices of β-amino acid oligomers: [20-C-6]-Bip possessing an axially chiral 2,2′,6,6′-tetrasubstituted biphenyl frame,[5] and derivatives with α-carbon chirality, [15-C-5]-α-Me-(*L*)-DOPA, [18-C-6]-α-Me-(*L*)-DOPA (Fig. 1), [benzo-18-C-6]-α-Me-(*L*)-DOPA and [benzo-24-C-8]-α-Me-(*L*)-DOPA.[6] In the present communication, we report the synthesis of terminally protected β³-(*L*)-DOPA and of a first crown-ether derivative: [18-C-6]-β³-(*L*)-DOPA (Fig. 1).

For their synthesis, we considered the classical *Arndt–Eistert* homologation of either N-Boc or N-Fmoc protected α-amino acids, developed by Seebach et al.[7] Application of this method to (*L*)-DOPA required the selective protection of both the amino group and the side chain OH groups of the catechol function. Thus, H-(*L*)-DOPA-OH was first converted to H-(*L*)-DOPA-



(S)-[20-C-6]-Bip [18-C-6]-α-Me-*(L)*-DOPA [18-C-6]-β³-*(L)*-DOPA

Figure 1. Structure of the crown-carrier amino acids (S)-[20-C-6]Bip,[5] [18-C-6]-α-Me-(*L*)-DOPA[6] and [18-C-6]-β³-(*L*)-DOPA.

Keywords: β-amino acids; β-peptides; β³-(*L*)-DOPA; crown-ethers.

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OMe·HCl[8,9] and then to Boc-(*L*)-DOPA-OMe **1**[9,10] (Fig. 2) by described procedures.[8–12]

Two alternative pathways were then applied, in which the crown-ether part of the molecule was introduced either at the first stage of the synthesis or at the last one. In path A, the catechol function of **1** was treated with potassium carbonate, sodium iodide and a large excess of benzyl bromide in refluxing acetone,[13,14] to afford the fully protected amino acid Boc-(*L*)-DOPA[OBn]$_2$-OMe **2**[15] in 85% yield after chromatography. Saponification of the ester function with 1N aqueous NaOH in MeOH/THF at room temperature followed by acidification, gave pure Boc-(*L*)-DOPA[OBn]$_2$-OH **3**[15] in 87% yield (crude), which was activated to the mixed anhydride Boc-(*L*)-DOPA[OBn]$_2$-OCOOEt by treatment with ethyl chloroformate and triethylamine in THF at −10°C for 15 min. Subsequent reaction with diazomethane led to the diazoketone Boc-(*L*)-DOPA[OBn]$_2$-CHN$_2$ **4**[15] in 80% yield. Wolff rearrangement[16] of **4** upon treatment by silver benzoate and triethylamine in MeOH with the exclusion of light,[7] afforded the fully protected β-amino ester Boc-β^3-(*L*)-DOPA[OBn]$_2$-OMe **5**[15] in 63% yield.

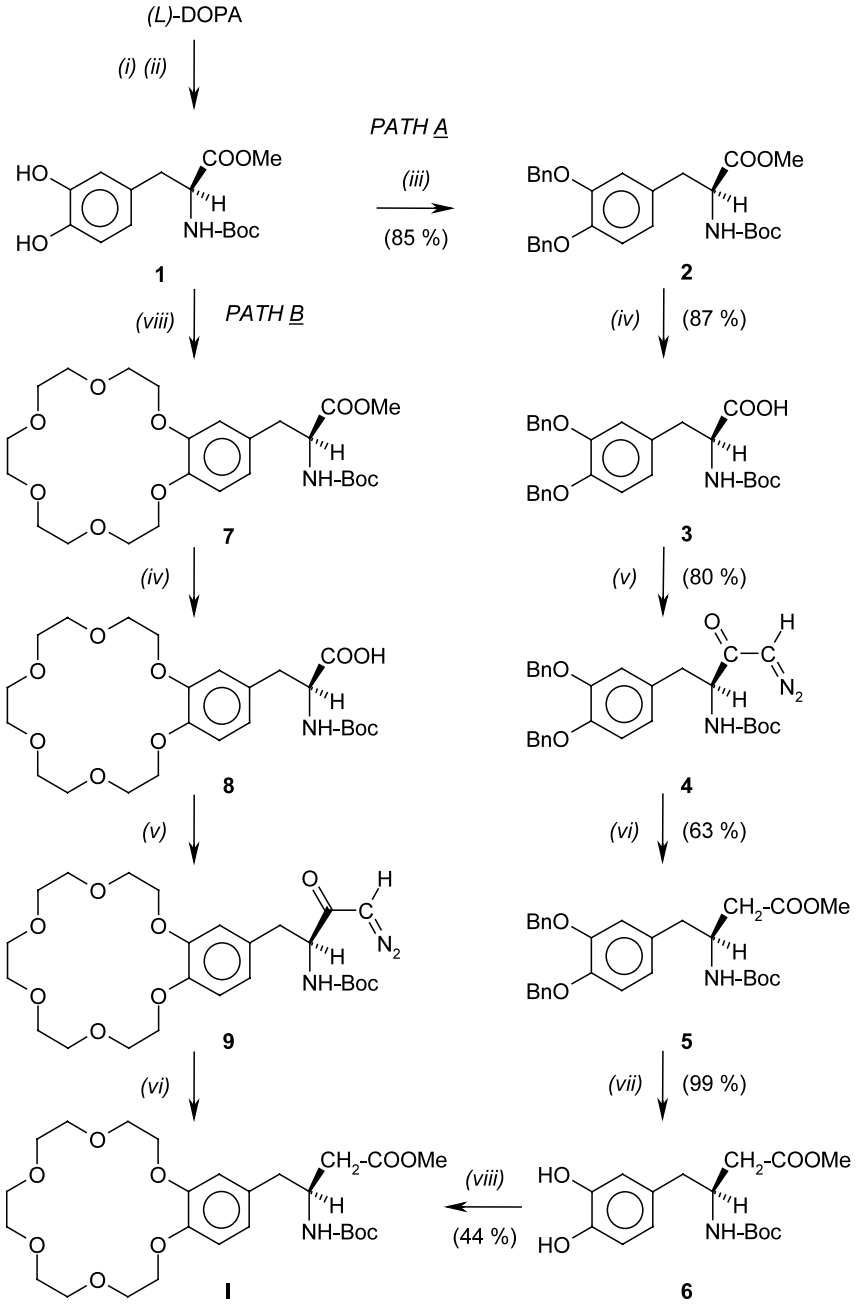

Figure 2. Synthesis of Boc-[18-C-6]-β^3-(*L*)-DOPA-OMe **I**: (i) $SOCl_2$, MeOH, 0°C to rt; (ii) Boc_2O, $NaHCO_3$, H_2O/THF, rt; (iii) BnBr, K_2CO_3, NaI, acetone, 50°C; (iv) NaOH, MeOH/THF, rt; (v) 1. ClCOOEt, TEA, THF, −10°C, 15 min, 2. CH_2N_2, Et_2O, 0°C to rt, 18 h; (vi) AgOBz, TEA, THF, −25°C to rt; (vii) H_2, 10% Pd/C, MeOH, 3.4 atm, rt; (viii) Cs_2CO_3, $TsOCH_2$–$(CH_2OCH_2)_4$–CH_2OTs, DMF, 60°C.

Finally, deprotection of the catechol function of **5** by hydrogenolysis with H_2/Pd–C (Parr apparatus), gave the desired Boc-β^3-(*L*)-DOPA-OMe **6**[15] in 99% yield. Applying similar experimental conditions as those previously reported by Voyer et al.[2a,d] and then by us for the preparation of both [20-C-6]-Bip[5] and [18-C-6]-α-Me-(*L*)-DOPA,[6] the terminally protected amino acid **6** was reacted with cesium carbonate in methanol at 45°C. The solution was evaporated in vacuo, the residue was solubilized in DMF and the solution was again evaporated in vacuo at 45°C in order to completely remove methanol. To the so-obtained di-cesium salt of **6** was added DMF and the resulting diluted solution (0.1 mol/l) was reacted at 60°C with a DMF solution (0.25 mol/l) of pentaethylene glycol ditosylate (1.1 equiv. mol/mol) which was added dropwise during a 1 h period. The reaction mixture was stirred at 60°C for 18 h, DMF was evaporated in vacuo, the crude product was extracted and then purified by chromatography as previously described,[6] to afford Boc-[18-C-6]-β^3-(*L*)-DOPA-OMe **I**[15] in 44% yield.

We also investigated a second route (path B) in which the N-protected crown-carrier α-amino ester Boc-[18-C-6]-(*L*)-DOPA-OMe **7**[2d] and then its N-protected α-amino acid analogue Boc-[18-C-6]-(*L*)-DOPA-OH **8**[2d] were first prepared from **1**, allowing the suppression of the two steps of protection/deprotection of the catechol function required in path A. However, when the *Arndt–Eistert* homologation was applied to compound **8** under the same experimental conditions as above, the resulting samples of the diazoketone Boc-[18-C-6]-(*L*)-DOPA-CHN_2 **9** and then of the rearranged final N-protected β^3-amino ester **I**, were of a poor quality even after purification. Furthermore, the unidentified impurities observed by NMR were found to be impossible to remove by standard chromatography.

In summary, it appears that route A, although involving more steps, should be preferred to route B in which careful HPLC would probably be necessary for purification. The availability of Boc-β^3-(*L*)-DOPA-OMe **6** itself only in route A also presents the advantage of allowing the convergent synthesis of a variety of analogues with different crown-ethers or other receptors anchored on the side-chain of β^3-(*L*)-DOPA by taking advantage of the catechol function. The synthesis of such a series of compounds and their corresponding β-peptide oligomers is under way to examine their conformational behaviour as well as their complexing abilities. As emphasized earlier, stable helical secondary structures are expected in short-chain β-peptides involving such crown-carrier β^3-(L)-DOPA residues, with the opportunity for cooperative binding.

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