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Synthesis of terminally protected (*S*)-β^3-H-DOPA by Arndt–Eistert homologation: an approach to crowned β-peptides

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Abstract—Terminally protected Boc-(*S*)-β^3-H-DOPA-OMe has been synthesized from L-DOPA by the Arndt–Eistert homologation procedure. During the synthesis, the side-chain catechol group was temporarily protected by benzylation. The absence of racemization was demonstrated by ^{19}F NMR analysis of the (+)-(*R*)- and (−)-(*S*)-α-methoxy-α-trifluoromethyl-α-phenyl-acetamide derivatives. The catechol function of Boc-(*S*)-β^3-H-DOPA-OMe may be used for crown-ether formation, a step towards the construction of crowned β-peptides.

1. Introduction

The naturally occurring L-3,4-dihydroxyphenylalanine (L-DOPA) is the biosynthetic precursor of dopamine, the most successful therapeutic agent in the treatment of Parkinson's disease. Moreover, it seems likely that L-DOPA has an intrinsic biological activity, different to that of dopamine in many aspects, and '···is about to start a new career as a brain neurotransmitter substance in its own right'.[1] The catechol group in itself, a very efficient iron chelator, is a typical binding site found in numerous siderophores, which are responsible for the take-up and transport of metal ions through membranes in nature.[2] Catechol-containing peptides have been synthesized as potential new oxidation catalysts[3] and are important targets in the design of iron chelators against oxidative damage in biological processes.[4] The catechol side-chain of L-DOPA is also responsible for the adhesive and cohesive properties of mussel adhesive proteins (Maps), and has recently been exploited in the design of Map mimetic polymers for the synthesis of nonfouling surfaces.[5] The above reports highlight the potential usefulness of designed analogues of L-DOPA, which could be used as informative models in comparative studies. As illustration, (*S*)-αMe-DOPA, a C^{α}-tetrasubstituted analogue, is a potent inhibitor of L-DOPA decarboxylase and has become a commercial anti-hypertensive drug.[6] Herein, we report the synthesis of another analogue of L-DOPA, which in our view is of the greatest interest: the corresponding β-homo amino acid (*S*)-β^3-H-DOPA (Fig. 1).[7–9]

The (*S*)-β^3-H-DOPA residue belongs to the now well-recognized and rapidly growing class of β-amino acids. In recent years, following the pioneering studies of Gellman and Seebach, who have shown that β-peptides may adopt stable secondary structures in a larger variety than their α-peptide counterparts,[10] several β-peptides

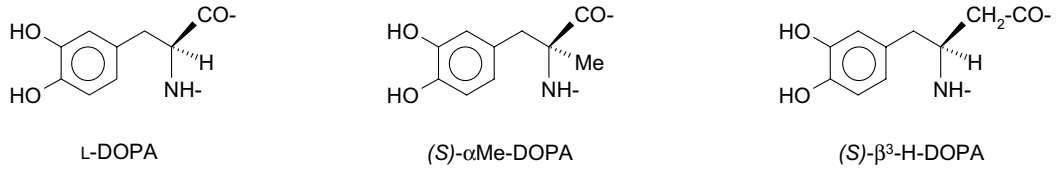

Figure 1. Chemical structures of L-DOPA, (*S*)-αMe-DOPA and (*S*)-β^3-H-DOPA.

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as well as peptide hybrids containing both α- and β-amino acids, have been synthesized and shown to possess both biological activity and increased resistance to enzymic degradation.[10,11] Furthermore, Seebach and Ghadiri have demonstrated that nanotubes based on the self-assembly of cyclic β-peptides may behave as artificial transmembrane ion channels.[12] In relation with the above mentioned properties of β-peptides, the design of the (*S*)-β^3-H-DOPA residue was dictated to us by the opportunity to take advantage of its catechol function to introduce crown ethers on its side chain, in order to eventually dispose of crown-carrier β-amino acids and β-peptides,[13] to be compared to the crowned α-peptides of Voyer and co-workers,[14] derived from L-DOPA, as well as to the crowned α-peptides based on crowned C^{α}-tetrasubstituted α-amino acids derived from (*S*)-αMe-DOPA previously synthesized and investigated by us in a joint study with Toniolo and co-workers.[13b,15]

2. Results and discussion

For the synthesis of terminally protected Boc–(*S*)-β^3-H-DOPA-OMe **I** (Fig. 2),[16] we considered the classical Arndt–Eistert homologation of either *N*-Boc or *N*-Fmoc protected α-amino acids, previously developed by Seebach and co-workers.[17] 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. Initially, terminal protection of H-L-DOPA-OH was achieved through conversion to H-L-DOPA-OMe**.**HCl[18,19] and then to Boc-L-DOPA-OMe **1**[19,20] {mp 135 °C, lit.[19] mp 133–135 °C; lit.[20] mp 140–141 °C, $[\alpha]_D^{25} = +7$ (*c* 1.0, MeOH); lit.[19], $[\alpha]_D^{26} = +7.6$ (*c* 1.2, MeOH)}, by described procedures.[18–22]

Then, for lateral orthogonal protection of the catechol function, compound **1** was treated with potassium carbonate, sodium iodide, *n*-$Bu_4N^+Br^-$ as catalyst and a large excess of benzyl bromide in refluxing acetone. In our hands, the use of acetone as solvent instead of ethanol,[19–22] referring to the mentioned dibenzylation of other terminally protected derivatives of L-DOPA,[21] and to the previously described dibenzylation of 3,4-dihydroxy-5-fluorobenzyl cyanide,[23] resulted in a much higher yield and a cleaner reaction. Interestingly, the addition of *n*-$Bu_4N^+Br^-$ as catalyst also resulted in a shorter reaction time and favoured the formation of the desired dialkylated product over the monoalkylated intermediate. The fully protected amino acid Boc-L-DOPA[OBn]$_2$-OMe **2** {mp 112 °C, $[\alpha]_D^{25} = +35$ (*c* 0.5, CH_2Cl_2)}[24] was obtained in 95% yield after chromatography, while when the same experimental conditions (K_2CO_3/NaI in refluxing acetone) were previously applied without *n*-$Bu_4N^+Br^-$ catalyst,[13a] chromatographic separation of the monobenzylated side-product from the dibenzylated compound **2** had to be performed, and then the benzylation reaction repeated in order to eventually obtain **2** in 85% yield (see Experimental).

Saponification of the ester function of **2** was performed by using a slight excess of 1 M aqueous NaOH in MeOH/THF at room temperature, which after acidification and extraction, gave pure Boc-L-DOPA[OBn]$_2$-OH **3** in 87–96% yield {mp 120 °C, lit.[19] mp 105–107 °C; lit.[22] mp 139–141 °C, $[\alpha]_D^{25} = +14.4$ (*c* 0.4, MeOH); lit.[19] $[\alpha]_D^{25} = +14.2$ (*c* 1, MeOH)}. As a possible epimerization at the α-carbon of the present L-DOPA derivatives could occur in the strongly basic medium required for saponification, it is important to observe that our experimental conditions are somewhat milder than those described in the literature for saponification of the same compound **2** (large excess of 2 M aq NaOH in refluxing MeOH)[22] as well as for saponification of analogue **1** (large excess of 2 M aq NaOH in MeOH).[19] Epimerization could explain the difference between the recorded melting point of our sample and that from the literature (139–141 °C),[22] which is very close to the melting point of the racemic compound **3** (140–142 °C).[19] We have no explanation for the different melting point of **3** (105–107 °C) reported by Banergie and Ressler,[19] since the specific rotation of our sample $[\alpha]_D^{25} = +14.4$ (*c* 0.4, MeOH) perfectly fits with the value reported by these authors: $[\alpha]_D^{25} = +14.2$ (*c* 1, MeOH).[19]

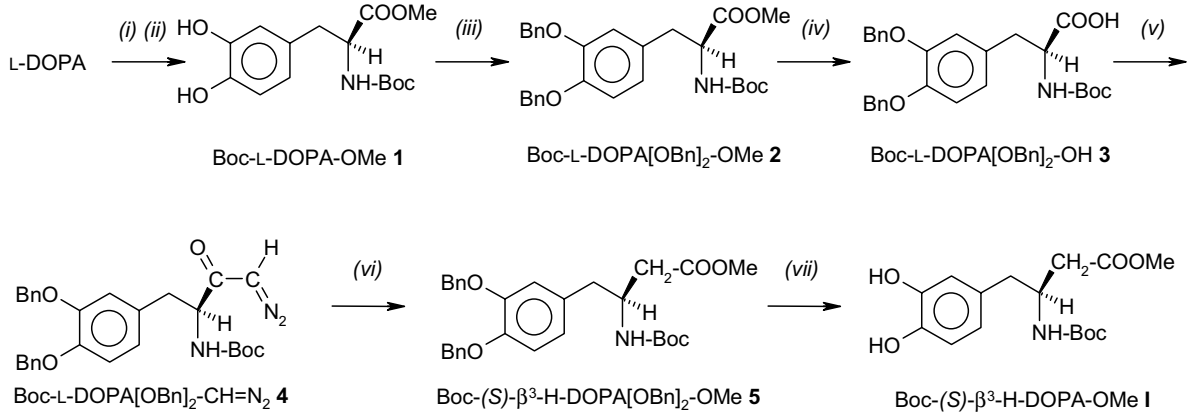

Figure 2. Synthesis of Boc-(*S*)-β^3-H-DOPA-OMe **I**. Reagents and conditions: (i) $SOCl_2$, MeOH, 0 °C to rt; (ii) Boc_2O, $NaHCO_3$, H_2O/THF, rt; (iii) BnBr, K_2CO_3, NaI, *n*-$Bu_4N^+Br^-$ (cat.), acetone, reflux; (iv) NaOH, MeOH/THF, rt; (v) (1) ClCOOEt, TEA, THF, −10 °C, 15 min; (2) CH_2N_2, Et_2O, 0 °C to rt, 18 h; (vi) AgOBz, TEA, MeOH/THF, −25 °C to rt; (vii) H_2, 10% Pd/C, MeOH/THF, rt.

Finally, while taking into account the above discrepancies, we decided to further investigate the question of the enantiomeric purity of compounds **2** and **3**, by NMR of their Mosher's amide derivatives.[17a] For this purpose, the *N*-Boc protecting group of an aliquot of **2** was cleaved by acidolysis in TFA/dichloroethane, which led to the amino ester H-L-DOPA[OBn]$_2$-OMe. In the absence of a sample of the corresponding racemic compound, two portions of that aliquot were acylated using a large excess of (+)-(*R*)-MTPA and (−)-(*S*)-MTPA (α-methoxy-α-trifluoromethyl-α-phenyl-acetic acid),[25] by the EDC [*N*-ethyl,*N*′-(3-dimethylaminopropyl)-carbodiimide]/HOBt [1-hydroxy-1,2,3-benzotriazole] method. This led to the diastereoisomeric amido esters (*R*)-Ph(OCH$_3$)(CF$_3$)C-CO-L-DOPA[OBn]$_2$-OMe **6A** and (*S*)-Ph(OCH$_3$)(CF$_3$)C-CO-L-DOPA[OBn]$_2$-OMe **6B**, respectively (Fig. 3),[26] having distinct CF$_3$ signals in ^{19}F NMR with toluene-d_8 as best solvent (Fig. 4), which allowed determination of the diastereoisomeric excess (de). An average >95% de was found for **6A** and **6B**, as expected for an enantiomerically pure, or nearly so, amino ester **2**, taking into account the synthetic nature (<100% ee) of the Mosher's acids.

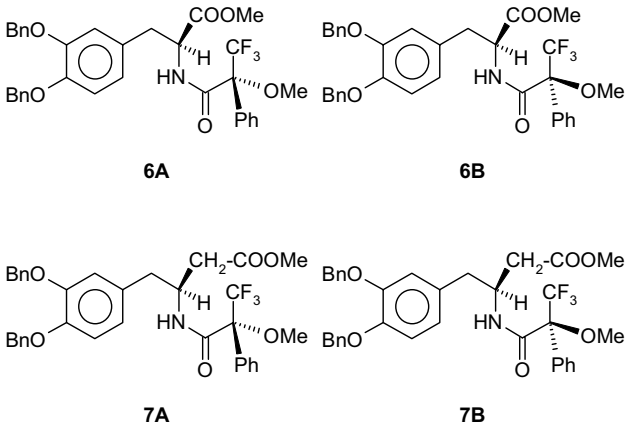

Figure 3. Chemical structures of the pairs of Mosher's amides (*R*)-Ph(OCH$_3$)(CF$_3$)C-CO-L-DOPA[OBn]$_2$-OMe **6A**, (*S*)-Ph(OCH$_3$)-(CF$_3$)C-CO-L-DOPA[OBn]$_2$-OMe **6B**, and (*R*)-Ph(OCH$_3$)(CF$_3$)C-(*S*)-β^3-H-DOPA[OBn]$_2$-OMe **7A**, (*S*)-Ph(OCH$_3$)(CF$_3$)C-(*S*)-β^3-H-DOPA-[OBn]$_2$-OMe **7B**, obtained from **2** and **5**, respectively.

In a second experiment, an aliquot of Boc-L-DOPA[OBn]$_2$-OH **3** obtained after saponification of **2** was re-esterified back to **2** with tetramethylsilyldiazomethane and then *N*-deprotected to the amino ester H-L-DOPA[OBn]$_2$-OMe of the same assumed enantiomeric purity as its precursor **3**. This aliquot was coupled with (+)-(*R*)-MTPA by the EDC/HOBt method and the resulting amido ester **6A** analyzed by ^{19}F NMR in toluene-d_8 as above.[26] Again >95% de was found for **6A**, demonstrating the absence of racemization in the saponification reaction of **2** to **3** under the employed experimental conditions.

In the next Arndt–Eistert homologation step, the carboxylic acid group of **3** 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 freshly prepared diazomethane in diethyl ether from 0 °C to rt led to the diazoketone Boc-L-DOPA[OBn]$_2$-CHN$_2$ **4** {mp 127 °C, $[\alpha]_D^{25} = +18$ (*c* 0.5, MeOH)}, which was isolated in 90% yield after chromatography, but was later advantageously used as crude material directly in the next step. Wolff rearrangement[27] of **4** upon treatment with silver benzoate and triethylamine in MeOH with the exclusion of light,[17] afforded the fully protected β-amino ester (*S*)-Boc-β^3-H-DOPA[OBn]$_2$-OMe **5** {mp 122 °C, $[\alpha]_D^{25} = -14$ (*c* 0.4, MeOH)} in 63–67% yield.

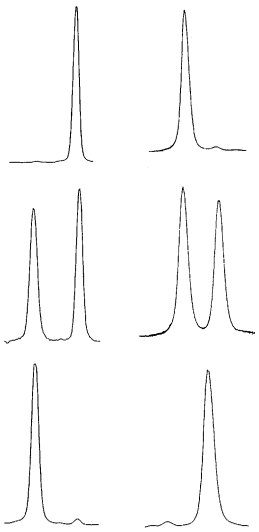

Figure 4. The CF$_3$ signals in the ^{19}F NMR spectra of the Mosher's amides (Fig. 3). Left: **6A** (top), **6A+6B** (center) and **6B** (bottom) in toluene-d_8; right: **7A** (top), **7A+7B** (center) and **7B** (bottom) in CDCl$_3$.

Here again, the absence of epimerization of the C-activated mixed anhydride, was checked by ^{19}F NMR of the diastereoisomeric amido esters (*R*)-Ph(OCH$_3$)(CF$_3$)C-(*S*)-β^3-H-DOPA[OBn]$_2$-OMe **7A** and (*S*)-Ph(OCH$_3$)(CF$_3$)C-(*S*)-β^3-H-DOPA[OBn]$_2$-OMe **7B** (Fig. 3),[26] obtained after *N*-deprotection of an aliquot of **5** in TFA/dichloroethane followed by coupling of two portions of the resulting (*S*)-H-β^3-H-DOPA-[OBn]$_2$-OMe with a large excess of (+)-(*R*)-MTPA and (−)-(*S*)-MTPA, respectively, by the EDC/HOBt method as above. The distinct CF$_3$ signals in ^{19}F NMR with CDCl$_3$ as best solvent (Fig. 4) allowed the determination of the diastereoisomeric excess. An average of >95% de was found for **7A** and **7B**, demonstrating the absence of an appreciable racemization in the Arndt–Eistert homologation of **3** to **5**, as expected from the previous studies of Seebach and co-workers[17] relative to many other amino acid structures. Finally, deprotection of the catechol function of **5** by hydrogenolysis over palladium on charcoal, afforded the desired (*S*)-Boc-β^3-H-DOPA-OMe **I** {$[\alpha]_D^{25} = -22$ (*c* 0.1, MeOH)} in 93–99% yield.

It is interesting to point out that our goal was to synthesize a relatively large amount of (*S*)-Boc-β^3-H-DOPA-OMe **I** in order to use this compound as starting material for further studies. This implied carrying out each step of the reaction sequence on a multigram scale and repeating the experiments. Therefore, the present work

constitutes a practical synthesis of the novel β-amino acid residue (*S*)-β^3-H-DOPA, which altogether has been obtained at a ca. 15 g scale from L-DOPA by a straightforward sequence devoid of appreciable racemization. As emphasized earlier, (*S*)-Boc-β^3-H-DOPA-OMe was synthesized in view of its potential use as a building block for the construction of new families of crowned-β-peptides. However, based on the extensive studies involving L-DOPA derivatives and/or catechol-containing derivatives and peptides, we believe that (*S*)-β^3-H-DOPA itself has a great future beyond our present interest and we hope that it will be considered by other research groups for a variety of applications and designs.

3. Experimental

3.1. General

Melting points were determined using either a Mettler FP61 apparatus with a temperature raise of 3 °C/min or a Tottoli apparatus (Büchi), and are reported uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 77 MHz, respectively, the solvent $CDCl_3$ being used as the internal standard (δ = 7.27 ppm for ^{1}H and 77.00 ppm for ^{13}C). Splitting patterns are abbreviated as follows: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet. The optical rotations were measured with an accuracy of 0.3%, in a 1 dm thermostated cell. Analytical TLC and preparative column chromatography were performed on Kieselgel F 254 and Kieselgel 60 (0.040–0.063 mm) (Merck), respectively, with the following eluent systems: 1% EtOAc (ethyl acetate)–99% CH_2Cl_2 (A); 2% EtOAc–98% CH_2Cl_2 (B); 3% EtOAc–97% CH_2Cl_2 (C); 1% MeOH–99% CH_2Cl_2 (D); 3% MeOH–97% CH_2Cl_2 (E); 5% MeOH–95% CH_2Cl_2 (F); 10% MeOH–90% CH_2Cl_2 (G). UV light (λ = 254 nm) allowed visualization of the spots after TLC runs for all compounds, even at low concentration. The special apparatus used for the preparation of diazomethane was purchased from Aldrich.

3.2. (*S*)-Methyl *N*-(*tert*-butyloxycarbonyl)-3,4-bis(hydroxy)phenylalanine carboxylate, Boc-L-DOPA-OMe 1

In a round-bottomed flask containing MeOH (60 mL) cooled to 0 °C, was slowly added $SOCl_2$ (10 mL) and then H-L-DOPA-OH (5.0 g, 25.4 mmol) in small portions. The reaction mixture was stirred at rt for 24 h and evaporated in vacuo, to afford H-L-DOPA-OMe·HCl (6.28 g) as a white solid. To a solution of this compound (5.96 g, 24.1 mmol) and $NaHCO_3$ (4.04 g, 48.2 mmol) in water (49 mL) was added a solution of Boc_2O (5.25 g, 24.1 mmol) in THF (36 mL). The mixture was magnetically stirred at rt for 18 h and THF then evaporated in vacuo. The mixture was extracted with EtOAc (3 × 150 mL), the combined organic phase was washed with 0.5 M HCl (2 × 25 mL), then H_2O (2 × 25 mL), dried over $MgSO_4$ filtered and evaporated in vacuo. The obtained white solid was crystallized from MeOH/H_2O 2.8:1, to afford Boc-L-DOPA-OMe **1** (7.36 g, 98%). Mp 138 °C, lit.[19] mp 133–135 °C; lit.[20] mp 140–141 °C. R_f = 0.35 (F). ^{1}H NMR ($CDCl_3$): δ 1.41 [s, 9H, CH_3Boc], 2.99 and 2.90 [dd and dd, J = 13.9, 5.6 Hz and J = 13.9, 6.8 Hz, 2H, $ArCH_2$], 3.72 [s, 3H, OCH_3], 4.53 [m, 1H, CHα], 5.08 [d, J = 8.3 Hz, 1H, NH], 6.50 [dd, J = 9.9 and 1.7 Hz, 1H, ArH], 6.66 [d (br), 1H, ArH], 6.75 [d, J = 8.1 Hz, 1H, ArH]. ^{13}C NMR ($CDCl_3$): δ 28.2 (CH_3Boc), 37.7 ($ArCH_2$), 52.4 (OCH_3), 54.7 (CHα), 80.6 (O–C Boc), 115.3, 116.1, 121.3, 128.0, 143.1, 144.0 (CAr), 155.6 (CO Boc), 172.8 (CO). $[\alpha]_D^{25}$ = +7; $[\alpha]_{578}^{25}$ = +7; $[\alpha]_{546}^{25}$ = +8; $[\alpha]_{436}^{25}$ = +18; $[\alpha]_{365}^{25}$ = +43 (*c* 1.2, MeOH); lit.[19] $[\alpha]_D^{26}$ = +7.6 (*c* 1.2, MeOH). Another run gave 85% yield and mp 135 °C.[13a] Other runs gave 88–95% yields.

3.3. (*S*)-Methyl *N*-(*tert*-butyloxycarbonyl)-3,4-bis(benzyloxy)phenylalanine carboxylate, Boc-L-DOPA[OBn]$_2$-OMe 2

To a solution of **1** (10.35 g, 33.3 mmol) in acetone (170 mL) were added K_2CO_3 (10 g, 73 mmol), NaI (0.5 g, 6.6 mmol), *n*-$Bu_4N^+Br^-$ (2.14 g, 6.6 mmol) and $PhCH_2Br$ (11.9 mL, 100 mmol). The reaction mixture was refluxed under argon atmosphere for ca. 4 h and evaporated in vacuo. The residue was taken up in CH_2Cl_2 (500 mL) and water (200 mL). After decantation, the separated aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phase was washed with water (2 × 100 mL), dried over $MgSO_4$, filtered and evaporated in vacuo. The obtained crude product was chromatographed on a column of silica gel with eluent (A), then (B), to afford Boc-L-DOPA[OBn]$_2$-OMe **2** (15.56 g, 95%) as a white solid. Mp 112 °C. R_f = 0.44 (B). ^{1}H NMR ($CDCl_3$): δ 1.44 [s, 9H, CH_3Boc], 3.00 [m (poorly resolved ABX system), 2H, $ArCH_2$], 3.65 [s, 3H, OCH_3], 4.54 [m, 1H, CHα], 4.97 [d, J = 7.9 Hz, 1H, NH], 5.30 [s, 4H, OCH_2Ph], 6.65 [dd, J = 8.2 and 1.9 Hz, 1H, ArH] ; 6.74 [d, J = 1.9 Hz, 1H, ArH]; 6.87 [d, J = 8.1 Hz, 1H, ArH]; 7.41 [m, 10H, ArHOBn]. ^{13}C NMR ($CDCl_3$): δ 28.7 (CH_3Boc), 38.2 ($ArCH_2$), 52.5 (OCH_3), 54.8 (CHα), 71.7, 71.8 (OCH_2Ph), 80.3 (O–C Boc); 115.6, 116.6, 122.7, 127.7, 128.2, 137.7, 148.5, 149.3 (CAr); 155.5 (CO Boc); 172.7 (CO). $[\alpha]_D^{25}$ = +35; $[\alpha]_{578}^{25}$ = +36; $[\alpha]_{546}^{25}$ = +42; $[\alpha]_{436}^{25}$ = +72; $[\alpha]_{365}^{25}$ = +130 (*c* 0.5, CH_2Cl_2), lit.[21] $[\alpha]_D$ = +25.0 (*c* 2, CH_2Cl_2) for the corresponding ethyl ester. Anal. Calcd for $C_{29}H_{33}NO_6$ (491.562): C, 70.85; H, 6.77; N, 2.85. Found: C, 70.81; H, 6.75; N, 2.78. Other similar runs all gave ca. 90% yield. In a previous experiment, to a suspension of Boc-L-DOPA-OMe (11.3 g, 36.4 mmol), K_2CO_3 (10.56 g, 76.5 mmol) and NaI (1.1 g, 7.2 mmol) in acetone (220 mL), was added $PhCH_2Br$ (8.7 mL; 76.5 mmol). The mixture was stirred at 50 °C for 4 h and evaporated in vacuo. The residue was taken up in CH_2Cl_2 (500 mL), the organic solution washed with 3 × 100 mL H_2O, dried over $MgSO_4$ filtered and evaporated in vacuo. The crude product was chromatographed on a column of silica gel with eluent (D) to give 10.2 g of pure dibenzylated compound **2**, and a mixture of mono and dibenzylated compounds. This mixture was treated again with K_2CO_3 (7.5 g), NaI (0.41 g) and $PhCH_2Br$ (6.3 mL) in refluxing acetone

(150 mL). After chromatography, a combined sample of pure **2** (15.30 g, 85%) was obtained, with $[\alpha]_D^{25} = +42$ (*c* 0.5, CH_2Cl_2).[13a]

3.4. (*S*)-*N*-(*tert*-Butyloxycarbonyl)-3,4-bis(benzyloxy)-phenylalanine carboxylic acid, Boc-L-DOPA[OBn]$_2$-OH 3

To a solution of **2** (14.98 g, 30.5 mmol) in MeOH (50 mL) and THF (100 mL), cooled to 0 °C, was added a solution of aqueous NaOH (38 mL; 38 mmol). The mixture was magnetically stirred at rt for 24 h, cooled to 0 °C and acidified to pH ~2 by addition of a solution of 0.5 M HCl (85 mL). The solution was concentrated in vacuo in order to eliminate most of the solvents, MeOH and THF, and then extracted with three portions of CH_2Cl_2 (3 × 300 mL). The organic phase was washed with water (200 mL), dried over $MgSO_4$, filtered and evaporated in vacuo, to afford pure Boc-L-DOPA[OBn]$_2$-OH **3** (14.10 g, 97%) as a white solid. Other runs gave 87% yield (crude),[13a] 96% yield (crude), and 89% yield (after column chromatography). Mp 120 °C, lit.[19] mp 105–107 °C; lit.[22] mp 139–141 °C. $R_f = 0.54$ (G). ^{1}H NMR ($CDCl_3$): δ 1.42 [s, 9H, CH_3Boc], 3.04 [m (poorly resolved ABX system), 2H, $ArCH_2$], 4.52 [m, 1H, CHα]; 4.93 [d (br), 1H, NH], 5.11 [s, 4H, OCH_2Ph], 6.69 [d, $J = 7.6$ Hz, 1H, ArH], 6.80 [s, 1H, ArH], 6.85 [d, $J = 8.0$ Hz, 1H, ArH], 7.37 [m, 10H, ArH OBn], 8.36 [s (br), 1H, COOH]. ^{13}C NMR ($CDCl_3$): δ 28.2 (CH_3Boc), 36.1 ($ArCH_2$), 48.6 (CHα), 70.2, 70.2 (OCH_2Ph), 77.9 (O–C Boc), 114.4, 115.7, 121.8, 127.4, 127.6, 127.7, 127.8, 128.3, 128.4, 131.2, 137.5, 146.8, 148.0 (CAr), 155.4 (CO Boc), 173.9 (CO). $[\alpha]_D^{25} = +14.4$; $[\alpha]_{578}^{25} = +15$; $[\alpha]_{546}^{25} = +16$; $[\alpha]_{436}^{25} = +31$; $[\alpha]_{365}^{25} = +62$ (*c* 0.5, MeOH); lit.[19] $[\alpha]_D^{25} = +14.2$ (*c* 1, MeOH). Anal. Calcd for $C_{28}H_{31}NO_6 \cdot H_2O$ (495.552): C, 67.85; H, 6.71; N, 2.82. Found: C, 67.76; H, 6.38; N, 2.68.

3.5. (*S*)-*N*-(*tert*-Butyloxycarbonyl)-3,4-bis(benzyloxy)-phenylalanine diazoketone, Boc-L-DOPA[OBn]$_2$-CHN_2 4

For preparation of diazomethane [*Caution*: *explosive*. The generation and handling with diazomethane require special precautions][28] a solution of KOH pellets (3.70 g, 66 mmol) in water (7 mL) was introduced in a specially designed glass apparatus (Aldrich). Carbitol (22 mL) and diethyl ether (7 mL) were then added. The mixture was magnetically stirred and heated at 70 °C, while a solution of Diazald® (14.1 g, 66 mmol) in diethyl ether (95 mL) placed in an addition funnel, was added dropwise. The resulting distillate of an ethereal solution of diazomethane was maintained at 0 °C by means of an ice-water cooling bath for a few minutes until its use in the following step. In a three-necked round-bottomed flask containing **3** (6.30 g, 13.2 mmol) was added THF (85 mL). The solution was magnetically stirred under an argon atmosphere and cooled to ca. −15 °C (ice-salt bath). Triethylamine (1.84 mL, 13.2 mmol) was added, followed by ethyl chloroformate (1.25 mL, 13.2 mmol). The resulting white suspension was stirred from −15 to 0 °C for 15–20 min and the freshly prepared ethereal solution of diazomethane added. The reaction mixture was allowed to warm-up to rt and then stirred for 18 h. After dilution with EtOAc (600 mL), the organic solution was successively extracted with saturated aqueous solutions of $NaHCO_3$ (100 mL), NH_4Cl (100 mL) and NaCl (100 mL), dried over $MgSO_4$, filtered and evaporated in vacuo. The crude product was chromatographed on a column of silica gel with eluents (D), then (E), to afford pure Boc-L-DOPA[OBn]$_2$-CHN_2 **4** (5.94 g, 90%) as a white solid. Other similar runs gave 77–80%[13a] yields. In other runs the crude products (89–96% yields) were used in the next step (Wolff rearrangement to **5**) without chromatographic purification. Mp 127 °C. $R_f = 0.40$ (C). ^{1}H NMR ($CDCl_3$): δ 1.43 [s, 9H, CH_3Boc], 2.91 [m, 2H, $ArCH_2$], 4.33 [m, 1H, CHα], 5.08 [m (br), 2H, NH and CH=N_2], 5.14 [s, 4H, OCH_2Ph], 6.69 [dd, $J = 8.3$ and 2.0 Hz, 1H, ArH], 6.80 [d (br), 1H, ArH], 6.87 [d, $J = 8.3$ Hz, 1H, ArH]; 7.32 [m, 10H, ArHOBn]. ^{13}C NMR ($CDCl_3$): δ 28.3 (CH_3Boc), 38.1 ($ArCH_2$), 54.3 (CH=N_2), 58.4 (CHα), 71.2, 71.3 (OCH_2Ph), 80.0 (O–C Boc); 115.3, 116.2, 122.3, 127.4, 127.7, 127.8, 128.4, 128.5, 129.5, 137.1, 137.2, 148.0, 148.9 (CAr); 155.1 (CO Boc); 193.3 (CO). $[\alpha]_D^{25} = +18$; $[\alpha]_{578}^{25} = +18$; $[\alpha]_{546}^{25} = +20$; $[\alpha]_{436}^{25} = +36$ (*c* 0.5, MeOH). Anal. Calcd for $C_{29}H_{31}N_3O_5$ (501.562): C, 69.44; H, 6.23; N, 8.38. Found: C, 69.58; H, 6.26; N, 8.07.

3.6. (*S*)-Methyl *N*-(*tert*-butyloxycarbonyl)-β^3-homo-3,4-bis(benzyloxy)phenylalanine carboxylate, (*S*)-Boc-β^3-H-DOPA[OBn]$_2$-OMe 5

In a three-necked round-bottomed flask containing **4** (5.94 g, 11.9 mmol) was added MeOH (360 mL) and anhydrous THF (250 mL). The solution was magnetically stirred under an argon atmosphere with exclusion of light, and cooled to ca. −15 °C (ice-salt bath). A solution of silver benzoate (0.298 g, 1.30 mmol) in anhydrous triethylamine (4.78 mL; 34.4 mmol) was added, the reaction mixture allowed to slowly warm up to rt and stirred for 3 h. The solvents were evaporated in vacuo and the residue taken up in EtOAc (300 mL). The organic solution was successively extracted with saturated aqueous solutions of $NaHCO_3$ (2 × 150 mL), NH_4Cl (2 × 150 mL) and NaCl (2 × 150 mL), dried over $MgSO_4$, filtered and evaporated in vacuo. The obtained crude product, a brownish solid, was chromatographed on a column of silica gel with eluent (C), to afford (*S*)-Boc-β^3-H-DOPA[OBn]$_2$-OMe **5** (3.67 g, 61%) as a white solid. Other similar runs gave 62–63%[13a] yields. Mp 122 °C. $R_f = 0.34$ (C). ^{1}H NMR ($CDCl_3$): δ 1.43 [s, 9H, CH_3Boc], 2.43 [m (partly resolved ABX system), $J_{AB} = 15.8$ Hz, 2H, CH_2COOMe], 2.74 [m (partly resolved ABX system), $J_{AB} = 13.5$ Hz, 2H, $ArCH_2$], 3.68 [s, 3H, OCH_3], 4.13 [m, 1H, CHα], 4.98 [d, $J = 7.7$ Hz, 1H, NH], 5.13 [s, 2H, OCH_2Ph], 5.14 [s, 2H, OCH_2Ph], 6.68 [dd, $J = 8.3$ and 2.0 Hz, 1H, ArH], 6.80 [d (br), 1H, ArH], 6.87 [d, $J = 8.3$ Hz, 1H, ArH], 7.40 [m, 10H, ArH OBn]. ^{13}C NMR ($CDCl_3$): δ 28.3 (CH_3Boc), 37.4 ($ArCH_2$), 39.7 (CH_2COOMe), 48.7 (CHα), 51.5 (OCH_3), 71.3, 71.4 (OCH_2Ph), 79.3 (O–C Boc), 115.3, 116.4, 122.3, 127.2, 127.4, 127.6, 127.7, 128.4, 131.0, 137.2, 137.4, 147.8, 148.9 (CAr), 155.0 (CO Boc),

172.0 (CO). $[\alpha]_D^{25} = -14$; $[\alpha]_{578}^{25} = -14$; $[\alpha]_{546}^{25} = -17$; $[\alpha]_{436}^{25} = -33$; $[\alpha]_{365}^{25} = -58$ (*c* 0.5, MeOH). Anal. Calcd for $C_{30}H_{35}NO_6$ (505.588): C, 71.26; H, 6.98; N, 2.77. Found: C, 71.26; H, 6.99; N, 2.74.

3.7. (*S*)-Methyl *N*-(*tert*-butyloxycarbonyl)-β^3-homo-3,4-bis(hydroxy)phenylalanine carboxylate, (*S*)-Boc-β^3-H-DOPA-OMe I

To a solution of **5** (2.00 g, 3.96 mmol) in a mixture of MeOH (60 mL) and THF (60 mL) kept under an argon stream was added 10% Pd/C (1.0 g). The mixture was maintained under an H_2 atmosphere and stirred at rt for 18 h. Filtration and evaporation of the solvents in vacuo gave a brownish oil, which was chromatographed on a column of silica gel with eluent (F), to afford pure (*S*)-Boc-β^3-H-DOPA-OMe **I** (1.22 g, 95%) as a yellow oil. Other similar runs gave 84–99%[13a] yields. $R_f = 0.38$ (F). ^{1}H NMR ($CDCl_3$): δ 1.38 [s, 9H, CH_3Boc], 2.45 [m (partly resolved ABX system), $J_{AB} = 15.8$ Hz, 2H, CH_2COOMe], 2.64 [m (poorly resolved ABX system), 2H, $ArCH_2$], 3.63 [s, 3H, OCH_3], 4.09 [m, 1H, CHα], 5.29 [d, $J = 8.8$ Hz, 1H, NH], 6.49 [dd, $J = 8.1$ and 1.8 Hz, 1H, ArH], 6.71 [d (br), 1H, ArH], 6.74 [d, $J = 8.1$ Hz, 1H, ArH], 7.17 [s (br), 2H, ArOH]. ^{13}C NMR ($CDCl_3$): δ 28.1 (CH_3Boc), 37.6 ($ArCH_2$), 39.8 (CH_2COOMe), 48.9 (CHα), 51.6 (OCH_3), 79.9 (O–C Boc), 115.3, 116.2, 121.2, 129.5, 142.8, 144.0 (CAr), 155.7 (CO Boc), 172.4 (CO). $[\alpha]_D^{25} = -22$; $[\alpha]_{578}^{25} = -23$; $[\alpha]_{546}^{25} = -28$; $[\alpha]_{436}^{25} = -46$; $[\alpha]_{365}^{25} = -65$ (*c* 0.1, MeOH). Anal. Calcd for $C_{16}H_{23}NO_6$ (325.352): C, 59.06; H, 7.12; N, 4.31. Found: C, 59.15; H, 7.21; N, 4.08.

3.8. (*R*)-Ph(OCH_3)(CF_3)C-CO-L-DOPA[$OBn]_2$-OMe 6A and (*S*)-Ph(OCH_3)(CF_3)C-CO-L-DOPA[$OBn]_2$-OMe 6B obtained from 2 and 3

To a solution of **2** (0.100 g, 0.20 mmol) in 1,2-dichloroethane (2 mL) cooled to 0 °C was added TFA (0.72 mL). The solution was magnetically stirred at 0 °C for 30 min and evaporated in vacuo at 25 °C [*Note*: we have observed the occurrence of a partial debenzylation of the ArOBn groups in TFA/CH_2Cl_2 1:2 when the solution is kept at room temperature for several hours]. The residue was dissolved in CH_2Cl_2 (100 mL), the solution then successively washed with 5% aq $NaHCO_3$ (2 × 50 mL) and brine (2 × 50 mL), dried over $MgSO_4$, filtered and evaporated in vacuo, to furnish crude H-L-DOPA[$OBn]_2$-OMe (0.058 g, 74%). In the next step, to a solution of this compound (0.019 g, 0.048 mmol), (+)-(*R*)-MTPA (α-methoxy-α-trifluoromethyl-α-phenylacetic acid) (0.017 g, 0.072 mmol) and HOBt (0.013 g, 0.096 mmol) in CH_2Cl_2 (1 mL), was added EDC (0.014 g, 0.072 mmol). The solution was magnetically stirred at rt for 18 h, diluted with CH_2Cl_2 (50 mL), and successively extracted with 0.5 M HCl (2 × 25 mL), 5% $NaHCO_3$ (2 × 25 mL) and brine (2 × 25 mL), dried over $MgSO_4$, filtered and evaporated in vacuo. The crude product was chromatographed on a preparative TLC plate of silica gel with eluent (A),[26] to afford the amido ester (*R*)-Ph(OCH_3)(CF_3)C-CO-L-DOPA[$OBn]_2$-OMe **6A** (0.015 g, 51%). ^{1}H NMR ($CDCl_3$): δ 3.09 [m (poorly resolved ABX system), 2H, $ArCH_2$], 3.19 [m, 3H, OCH_3 from MTPA], 3.68 [s, 3H, OCH_3], 4.85 [m, 1H, CHα], 5.14 [s, 2H, OCH_2Ph], 5.15 [s, 2H, OCH_2Ph], 6.66 [dd (br), $J = 8.0$ Hz, 1H, ArH], 6.79 [d, $J = 1.5$ Hz, 1H, ArH], 6.88 [d, $J = 8.1$ Hz, 1H, ArH], 7.2–7.5 [m, 16H, ArH OBn, ArH from MTPA and NH] (some of the signals corresponding to the other diastereoisomer, that is, the enantiomer of **6B**, present in <5% ratio). ^{19}F NMR (toluene-d_8): δ −69.14 (ca. 99%); −69.00 (ca. 1%) [de ~ 98%].

In a parallel manner, to a solution of crude H-L-DOPA[$OBn]_2$-OMe (0.023 g, 0,059 mmol), (−)-(*S*)-MTPA (0.021 g, 0.089 mmol) and HOBt (0.016 g, 0.12 mmol) in CH_2Cl_2 (1 mL), was added EDC (0.017 g, 0.089 mmol). The solution was magnetically stirred at rt for 18 h. Work-up as above, followed by preparative TLC on silica gel with eluent (A),[26] afforded the amido ester (*S*)-Ph(OCH_3)(CF_3)C-CO-L-DOPA[$OBn]_2$-OMe **6B** (0.018 g, 50%). ^{1}H NMR ($CDCl_3$): δ 3.05 [m (partly resolved ABX system), $J = 13.9$ Hz, 2H, $ArCH_2$], 3.43 [m, 3H, OCH_3 from MTPA], 3.70 [s, 3H, OCH_3], 4.91 [s, 2H, OCH_2Ph], 4.92 [m, 1H, CHα], 5.12 [s, 2H, OCH_2Ph], 6.42 [dd, $J = 8.1$ and 1.6 Hz, 1H, ArH]; 6.59 [d, $J = 1.7$ Hz, 1H, ArH]; 6.74 [d, $J = 8.1$ Hz, 1H, ArH]; 7.2–7.5 [m, 16H, ArH OBn, ArH from MTPA and NH] (some of the signals corresponding to the other diastereoisomer, i.e., the enantiomer of **6A**, present in <5% ratio). ^{19}F NMR (toluene-d_8): δ −69.14 (ca. 3.5%); −69.00 (ca. 96.5%) [de ~ 93%].

In the same manner, to a solution of **3** (0.102 g, 0.21 mmol) in CH_2Cl_2 (2 mL) and anhydrous MeOH (2 mL) kept under an argon atmosphere, was added by syringe $TMSCHN_2$ (158 μL, 0.32 mmol). The solution was magnetically stirred at rt for 6 h and evaporated in vacuo. The crude product was chromatographed on a preparative TLC plate of silica gel with eluent (A), to afford Boc-L-DOPA[$OBn]_2$-OMe **2** (0.064 g, 62%). In the next step, a solution of **2** (0.025 g, 0.05 mmol) in 1,2-dichloroethane (1 mL) cooled to 0 °C was treated with TFA (0.36 mL) for 30 min. Work-up as above gave crude H-L-DOPA[$OBn]_2$-OMe (0.013 g, 0.03 mmol), which was dissolved in CH_2Cl_2 (1 mL) and coupled with (+)-(*R*)-MTPA (0.012 g, 0.05 mmol) in the presence of EDC (0.009 g, 0.05 mmol) and HOBt (0.009 g, 0.07 mmol), at rt for 18 h. Work-up as above, followed by preparative TLC on silica gel with eluent (A),[26] afforded the amido ester (*R*)-Ph(OCH_3)(CF_3)C-CO-L-DOPA[$OBn]_2$-OMe **6A** (0.008 g, 40%). ^{1}H NMR ($CDCl_3$): see above. ^{19}F NMR (toluene-d_8): δ −69.14 (ca. 97.5%), −69.00 (ca. 2.5%) [de ~ 95%].

3.9. (*R*)-Ph(OCH_3)(CF_3)C–(*S*)-β^3-H-DOPA[$OBn]_2$-OMe 7A and (*S*)-Ph(OCH_3)(CF_3)C-(*S*)-β^3-H-DOPA[$OBn]_2$-OMe 7B obtained from 5

To a solution of **5** (0.147 g; 0.29 mmol) in 1,2-dichloroethane (3 mL) cooled to 0 °C was added TFA (1 mL). The solution was magnetically stirred at 0 °C for 35 min and evaporated in vacuo at 25 °C. The residue was dissolved in CH_2Cl_2 (100 mL), the solution then successively washed with 5% aq $NaHCO_3$ (2 × 50 mL) and brine (2 × 50 mL), dried over $MgSO_4$, filtered and

evaporated in vacuo, to furnish crude (*S*)-H-β^3-H-DOPA[OBn]$_2$-OMe (0.129 g). In the next step, to a solution of this compound (0.051 g, 0.13 mmol), (+)-(*R*)-MTPA (0.045 g, 0.19 mmol) and HOBt (0.035 g, 0.26 mmol) in CH_2Cl_2 (2 mL), was added EDC (0.036 g, 0.19 mmol). The solution was magnetically stirred at rt for 18 h, diluted with CH_2Cl_2 (50 mL), and successively extracted with 0.5 M HCl (2 × 25 mL), 5% $NaHCO_3$ (2 × 25 mL) and brine (2 × 25 mL), dried over $MgSO_4$, filtered and evaporated in vacuo. The crude product was chromatographed on a preparative TLC plate of silica gel with eluent (C),[26] to afford the amido ester (*R*)-Ph(OCH$_3$)(CF$_3$)C-(*S*)-β^3-H-DOPA[OBn]$_2$-OMe **7A** (0.048 g, 59%). ^{1}H NMR ($CDCl_3$): δ 2.49 [d, J = 5.7 Hz, 2H, CH_2COOMe], 2.86 [m (partly resolved ABX system), J_{AB} = 13.7 Hz, 2H, ArCH_2], 3.25 [m, 3H, OCH$_3$ from MTPA], 3.62 [s, 3H, OCH$_3$], 4.47 [m, 1H, CHα], 5.15 [s, 4H, OCH$_2$Ph], 6.70 [dd, J = 8.0 and 1.9 Hz, 1H, ArH], 6.84 [d, J = 1.9 Hz, 1H, ArH], 6.88 [d, J = 8.2 Hz, 1H, ArH], 7.2–7.5 [m, 16H, ArH OBn, ArH from MTPA and NH] (some of the signals corresponding to the other diastereoisomer, i.e., the enantiomer of **7B**, present in <5% ratio). ^{19}F NMR ($CDCl_3$): δ −69.40 (ca. 1.5%), −69.31 (ca. 98.5%) [de ∼ 97%].

In a parallel manner, to a solution of crude (*S*)-H-β^3-H-DOPA[OBn]$_2$-OMe (0.051 g, 0,12 mmol), (−)-(*S*)-MTPA (0.045 g, 0.19 mmol) and HOBt (0.035 g, 0.26 mmol) in CH_2Cl_2 (2 mL), was added EDC (0.036 g, 0.19 mmol). The solution was magnetically stirred at rt for 18 h. Work-up as above, followed by preparative TLC on silica gel with eluent (C),[26] afforded the amido ester (*S*)-Ph(OCH$_3$)(CF$_3$)C-(*S*)-β^3-H-DOPA[OBn]$_2$-OMe **7B** (0.054 g, 72%). ^{1}H NMR ($CDCl_3$): δ 2.56 [m, 2H, CH_2COOMe], 2.82 [m, 2H, ArCH_2], 3.25 [m, 3H, OCH$_3$ from MTPA], 3.70 [s, 3H, OCH$_3$], 4.55 [m, 1H, CHα], 5.05 [s, 2H, OCH$_2$Ph], 5.15 [s, 2H, OCH$_2$Ph], 6.63 [dd, J = 8.2 and 2.0 Hz, 1H, ArH], 6.78 [d, J = 1.9 Hz, 1H, ArH], 6.84 [d, J = 8.1 Hz, 1H, ArH], 7.2–7.5 [m, 16H, ArH OBn, ArH from MTPA and NH] (some of the signals corresponding to the other diastereoisomer, i.e., the enantiomer of **7A**, present in <5% ratio). ^{19}F NMR ($CDCl_3$): δ −69.40 (ca. 97.5%), −69.31 (ca. 2.5%) [de ∼ 95%].

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16. The terminal protecting groups of our target Boc-(*S*)-β^3-H-DOPA-OMe **I**, were chosen because of their stability to the basic conditions (Cs_2CO_3/DMF) required in the planned further step of crown-ether formation.[13–15] The access to the corresponding Fmoc-(*S*)-β^3-H-DOPA-OH derivative, if needed, should be straightforward either by Arnt–Eistert homologation of Fmoc-L-DOPA-OH with convenient lateral protection, or from **I** by saponification

of the ester function, N^{α}-Boc deprotection and N^{α}-Fmoc protection.
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