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New crown-carrier $C^{\alpha,\alpha}$-disubstituted glycines derived from α-methyl-(L)-DOPA

Karen Wright, Francesca Melandri, Caroline Cannizzo, Michel Wakselman and Jean-Paul Mazaleyrat*

University of Versailles, SIRCOB, ESA CNRS 8086, Bât. Lavoisier, 45 Avenue des Etats-Unis, F-78000 Versailles cedex, France

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Abstract—The side-chain catechol function of α-methyl-(L)-DOPA was utilized for the synthesis of a new series of crown-carrier $C^{\alpha,\alpha}$-disubstituted glycines. During *N*-protection of α-methyl-(L)-DOPA methyl ester (H-Mdp-OMe) with Boc anhydride, the formation of *N*,*O*-di-Boc derivatives was observed. Selective aminolysis of the catechol *tert*-butyl carbonate group was achieved using pyrrolidine as nucleophile. Treatment of the resulting Boc-Mdp-OMe by Cs_2CO_3 in MeOH, followed by bis-*O*-alkylation with cyclization using various polyethyleneglycol ditosylates or catechol-derived bis-polyethyleneglycol ditosylates in DMF at 60°C, led to the derivatives Boc-[15-C-5]-Mdp-OMe, Boc-[18-C-6]-Mdp-OMe, Boc-[benzo-18-C-6]-Mdp-OMe, Boc-[benzo-24-C-8]-Mdp-OMe and then after saponification, to the corresponding N^{α}-protected amino acids. The tripeptides Fmoc-Ala-[18-C-6]-Mdp-Ala-OMe and Boc-Aib-[18-C-6]-Mdp-Ala-OMe were prepared in solution by using Ala and Aib UNCAs for coupling at the N terminus of the [18-C-6]-Mdp residue and the EDC/HOAt method for coupling Ala at its C terminus.

Within the current developing strategies for peptide-based nanotechnology, synthetic α-amino acids bearing a crown ether are of great interest for the preparation of ion selective molecular receptors and artificial ion channels, since they can be easily assembled in structurally well-defined nanometer-scale architectures of bis-crown as well as polymeric crown compounds with a peptidic framework.[1] In the past few years, a series of crown-carrier derivatives of (L)-DOPA,[1,2] lysine[3] or glutamic acid,[4] have been synthesized for the construction of peptidic molecular specific receptors for alkali metal, ammoniums and di-ammonium ions. Application of this strategy to C^{α}-tetrasubstituted α-amino acids should result in more defined and predictable peptidic structures, according to their well-established ability to induce folded (helical) conformations of the peptide backbone.[5] In this view, we have previously described the synthesis of the first crown-carrier, axially dissymmetric $C^{\alpha,\alpha}$-disubstituted glycine: [20-C-6]-Bip, with a 2,2′,6,6′-tetrasubstituted-1,1′-biphenyl frame, and of some of its peptides (Fig. 1).[6–8] However, we could not prepare this amino acid in an enantiomerically pure state, because of extensive racemization occuring at several stages of the synthesis.[8] Following a route previously established by Voyer et al.[1,2] in the case of (L)-DOPA, we have now taken advantage of the catechol function of the commercially available α-methyl-(L)-DOPA to prepare a new series of crown-carrier $C^{\alpha,\alpha}$-disubstituted glycines with α-carbon chirality instead of axial chirality: [15-C-5]-Mdp (**1**), [18-C-6]-Mdp (**2**), [benzo-18-C-6]-Mdp (**3**) and [benzo-24-C-8]-Mdp (**4**). Achiral, indane-based $C^{\alpha,\alpha}$-disubstituted amino acid derivatives with a crown-ether side chain have also been recently synthesized.[9]

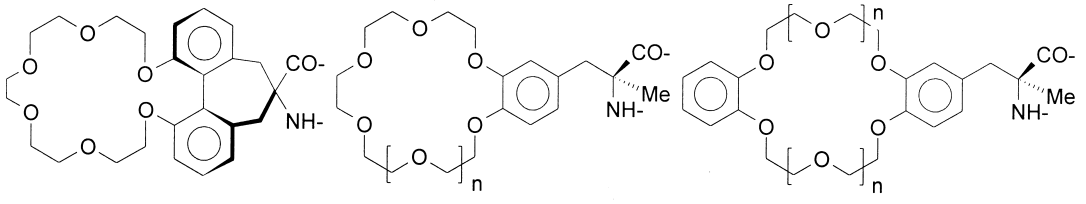

Figure 1. Structure of the title crown-carrier $C^{\alpha,\alpha}$-disubstituted glycines.

Keywords: crown-ethers; $C^{\alpha,\alpha}$-disubstituted glycines; α-methyl-(L)-DOPA.
* Corresponding author. Fax: +33-01-39-25-44-52; e-mail: jean-paul.mazaleyrat@chimie.uvsq.fr

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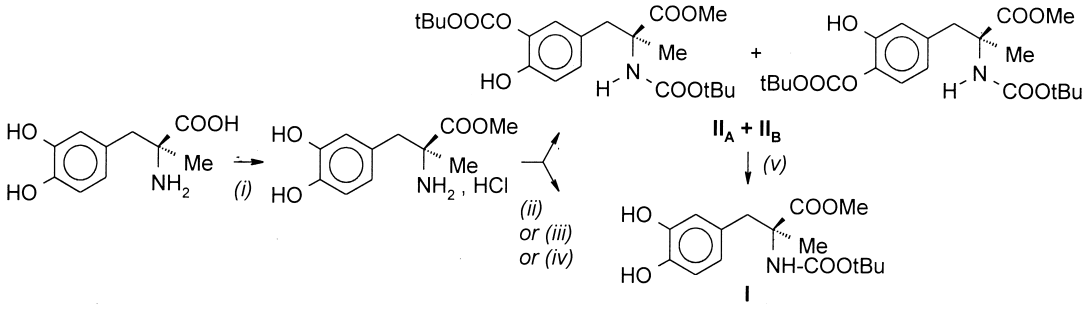

Figure 2. Synthesis of Boc-Mdp-OMe (**I**) from (L)-α-methyl-DOPA. (i) $SOCl_2$; MeOH; 60°C; 7 days, (ii) Boc_2O; $NaHCO_3$; *tert*-BuOH/DMF; 60°C; 2 days, (iii) Boc_2O; $NaHCO_3$; H_2O/THF; rt; 5 days, (iv) Boc_2O; TEA; CH_3CN/THF; rt; 6 days, (v) pyrrolidine; CH_2Cl_2; rt; 3 h.

1. Results and discussion

1.1. Synthesis of terminally protected α-methyl-(L)-DOPA

Although numerous protected α-methyl-(L)-DOPA (Mdp) derivatives have been reported, including H-Mdp-OMe·HCl,[10,11] Boc-Mdp-OH,[10–12] Boc-[OMe]$_2$-Mdp-OH,[11] Boc-[OBzl]$_2$-Mdp-OH,[11] Z-[*O*,*O*-diphenylmethylene]-Mdp-OR,[13] H-[OBzl]$_2$-Mdp-OBzl,[14] Z-[OZ]$_2$-Mdp-OH,[15] and others, there is no report of a fully characterized Mdp residue with differential protection of the α-amino and carboxyl groups but leaving the side-chain catechol OH groups free, as necessary in order to proceed with crown-ether formation. The *N*-protected amino ester Boc-Mdp-OMe (**I**) (Fig. 2) which fulfills the above requirements, was previously obtained as a synthetic intermediate (not characterized) upon treatment of H-Mdp-OMe·HCl with Boc_2O in DMF/*tert*-BuOH 1:1 and $NaHCO_3$ at 60°C for 5 days.[11] However in our hands, performing the reaction either in the same experimental conditions, or with Boc_2O and $NaHCO_3$ in H_2O/THF at room temperature as previously described in the case of (L)-DOPA,[16] or with Boc_2O and Et_3N in THF/CH_3CN at room temperature,[17] *always* led to mixtures of **I** and the two isomers of Boc-[*O*-Boc,*O*-H]-Mdp-OMe (**II$_A$** and **II$_B$**) resulting from a further acylation of one of the catechol OH groups. Such competition between *O* and *N*-acylation is not surprising, because of the lower nucleophilicity of the sterically hindered N^{α} amino group of α-methyl-(L)-DOPA compared to (L)-DOPA. The desired compound **I** could be easily separated from (**II$_A$**+**II$_B$**) by chromatography but was obtained in a rather low yield, highlighting the need for a selective deacylation of the OBoc group with regard to both the NHBoc and the COOMe groups in order to convert (**II$_A$**+**II$_B$**) back into **I**. We considered pyrrolidine as a reagent of choice for a selective aminolysis of the OBoc group, according to the previously described selective deacetylation of aromatic acetates using this amine.[18] Indeed, treatment of the crude mixture **I**+**II$_A$**+**II$_B$** by pyrrolidine in dichloromethane at room temperature, efficiently led to pure **I** in ca. 67% yield after chromatography.

1.2. Synthesis of the crown-ethers

In a similar manner as previously reported for (L)-DOPA itself,[2b,e] the N^{α}-protected amino ester Boc-Mdp-OMe (**I**) was reacted with Cs_2CO_3 in MeOH. The resulting di-cesium salt was freed from methanol and then reacted with (i) tetraethyleneglycol ditosylate, (ii) pentaethyleneglycol ditosylate, (iii) 1,2-bis(5-tosyloxy-3-oxa-1-pentyloxy)-benzene[19b] or (iv) 1,2-bis(8-tosyloxy-3,6-dioxa-1-octyloxy)-benzene, in DMF at 60°C, to give the expected fully protected crown-carrier α-methyl-(L)-DOPA derivatives (Fig. 3) (i) Boc-[15-C-5]-Mdp-OMe **1a** (49%), (ii) Boc-[18-C-6]-Mdp-OMe **2a** (44%), (iii) Boc-[benzo-18-C-6]-Mdp-OMe **3a** (9%), and (iv) Boc-[benzo-24-C-8]-Mdp-OMe **4a** (32%), respectively, in variable yields (not optimized). Saponification of the ester function of **1a**, **2a** and **4a** was performed using a large excess of aqueous 1N NaOH/MeOH at 60°C for several hours, as usually required for α,α-disubstituted-amino esters,[20] and furnished the corresponding N^{α}-protected amino acids Boc-[15-C-5]-Mdp-OH **1b** (87%), Boc-[18-C-6]-Mdp-OH **2b** (95%) and Boc-[benzo-24-C-8]-Mdp-OH **4b** (88%).

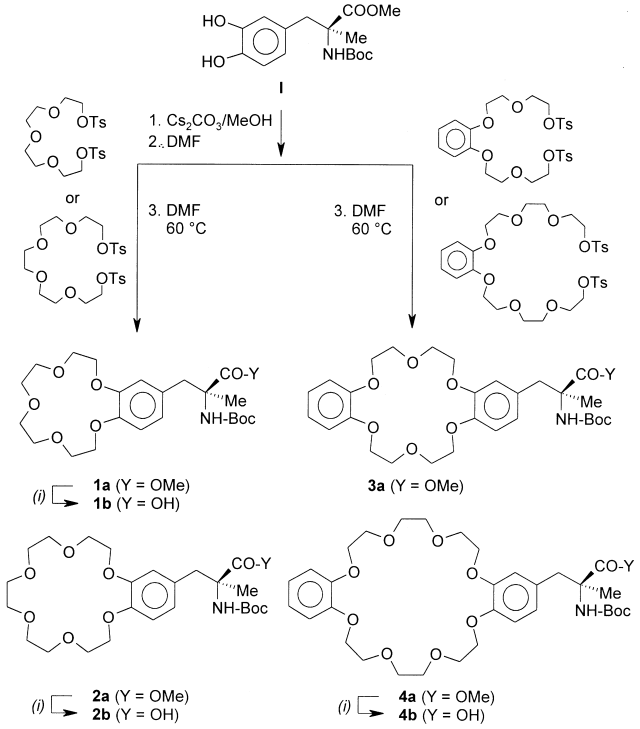

Figure 3. Synthesis of the crown-carrier N^{α}-protected amino esters **1a**–**4a** and amino acids **1b**–**4b** from N^{α}-*tert*-butyloxycarbonyl-α-methyl-(L)-DOPA methyl ester (**I**). (i) 1. aq. NaOH/MeOH; 60°C 2. H^+.

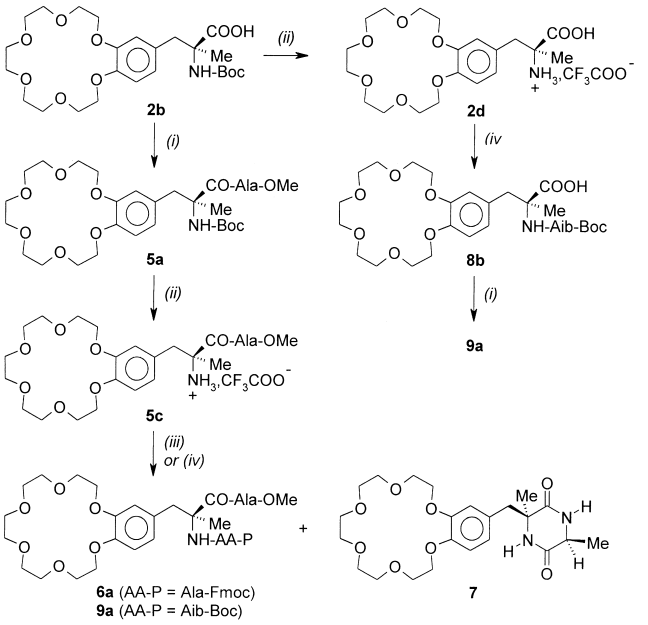

Figure 4. Solution synthesis of the tripeptides Fmoc-Ala-[18-C-6]-Mdp-Ala-OMe (**6a**) and Boc-Aib-[18-C-6]-Mdp-Ala-OMe (**9a**). (i) H-Ala-OMe·HCl; NMM; EDC; HOAt; CH_2Cl_2; rt, (ii) TFA/CH_2Cl_2 1:3, (iii) Fmoc-Ala-NCA; DIPEA; THF, (iv) Boc-Aib-NCA; DIPEA; THF.

1.2.1. Peptide coupling conditions in solution: synthesis of tripeptides based on the [18-C-6]-Mdp residue. As a first step to the synthesis of peptides based on these new crown-carrier $C^{\alpha,\alpha}$-disubstituted glycines, the tripeptides **6a** and **9a** (Fig. 4) based on the [18-C-6]-Mdp residue were prepared in order to find suitable coupling conditions in solution.[21] The EDC/HOBt method,[22] generally recognized to be efficient for coupling at the C-terminus of $C^{\alpha,\alpha}$-disubstituted glycines,[21] including $C^{\alpha,\alpha}$-diphenylglycine,[23] was chosen first for the coupling of **2b** with H-Ala-OMe, but gave the dipeptide Boc-[18-C-6]-Mdp-Ala-OMe **5a** in only 28% yield. Using the CIP/HOAt method previously shown to allow the coupling between two Aib residues,[24] **5a** was obtained in 40% yield. Finally, in our hands, the EDC/HOAt[25] method was found to be the most efficient, giving **5a** in 69% yield after purification. Furthermore, the crude reaction product, obtained after extraction in ca. 98% yield, consisted of almost pure **5a**, contaminated only by traces of a side product which was identified by ^{1}H NMR as 1-chloromethyloxy-7-aza-1,2,3-benzotriazole ($ClCH_2OAt$) resulting from substitution of the reaction solvent CH_2Cl_2 by HOAt. This crude product could be used directly in the next step, in which urethane-protected amino acid *N*-carboxy anhydrides (UNCAs),[26] previously employed with success in the coupling of Phe with Aib[27a] and of Aib with Aib in THF,[27b] were utilized for coupling of both Ala and Aib at the N terminus of the [18-C-6]-Mdp residue. In this way, crude **5a** was *N*-deprotected in TFA/CH_2Cl_2 1:3 to give **5c**, which again was not isolated but directly coupled with an excess of Fmoc-Ala-NCA in the presence of DIPEA, to afford the tripeptide Fmoc-Ala-[18-C-6]-Mdp-Ala-OMe **6a** in 67% overall yield from **2b** after chromatography. However, coupling of **5c** with the more hindered Boc-Aib-NCA gave the desired Boc-Aib-[18-C-6]-Mdp-Ala-OMe **9a** in an only moderate yield (33%), because of cyclization of **5c** to the diketopiperazine *cyclo*-([18-C-6]-Mdp-Ala) **7**, isolated in 23% yield, in competition with the slow coupling reaction. Therefore, another strategy was applied in order to supress the possibility of such a cyclization side reaction: **2b** was first *N*-deprotected in TFA/CH_2Cl_2 1:3 to give the free amino acid trifluoroacetate **2d**, which could be successfully acylated at its N terminus without *C*-protection using Boc-Aib-NCA, to afford the dipeptide Boc-Aib-[18-C-6]-Mdp-OH **8b** in 78% yield. Then, coupling of **8b** with H-Ala-OMe by the EDC/HOAt method as above gave **9a** in 86% yield.

Chain elongation applied to **6a** and **9a** will afford peptides rich in Aib and/or Ala residues both known to be helix inducers,[5] and containing two or more [18-C-6]-Mdp residues also expected to be easily accomodated in 3_{10} helices because of their C^{α}-tetrasubstitution.[5] In these *expected short-chain peptide helices*, positioning of the [18-C-6]-Mdp residues at i and $i+3$ positions of the main chain should allow a parallel orientation of their side-chain crown-ether receptors, with the opportunity for cooperative binding.[1,2] Solution synthesis of similar peptides based on the [15-C-5]-Mdp, [benzo-18-C-6]-Mdp and [benzo-24-C-8]-Mdp residues, is also under way, to examine their conformational analysis as well as their complexing abilities.

2. Experimental

2.1. Abbreviations

(L)-DOPA, β-3,4-dihydroxyphenyl-(L)-alanine; α-methyl-(L)-DOPA (Mdp), α-methyl-β-3,4-dihydroxyphenyl-(L)-alanine; [15-C-5]-Mdp, α-methyl-β-3,4-(15-crown-5)-phenyl-(L)-alanine; [18-C-6]-Mdp, α-methyl-β-3,4-(18-crown-6)-phenyl-(L)-alanine; [benzo-18-C-6]-Mdp, α-methyl-β-3,4-(benzo-18-crown-6)-phenyl-(L)-alanine; [benzo-24-C-8]-Mdp, α-methyl-β-3,4-(benzo-24-crown-8)-phenyl-(L)-alanine; Aib, α-aminoisobutyric acid; Boc, *tert*-butoxycarbonyl; Fmoc, 9-fluorenylmethoxycarbonyl; CIP, 2-chloro-1,3-dimethylimidazolidinium hexafluorophosphate; EDC, 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide; HOBt, 1-hydroxy-1,2,3-benzotriazole; HOAt, 1-hydroxy-7-aza-1,2,3-benzotriazole; NCA, *N*-carboxy anhydride; UNCA, urethane protected α-amino acid *N*-carboxy anhydride; TFA, trifluoroacetic acid; Me, methyl; Et, ethyl; *n*Bu, *n*-butyl; *t*Bu, *tert*-butyl; TEA, triethylamine; NMM, *N*-methylmorpholine; DIPEA, diisopropylethylamine; THF, tetrahydrofuran; DMF, *N*,*N*-dimethylformamide; EtOAc, ethyl acetate; TLC, thin layer chromatography.

2.2. General

Melting points were determined by means of a capillary tube immersed in an oil bath (Tottoli apparatus, Büchi) and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, the solvent $CDCl_3$ or CD_3OD being used as internal standard (δ=7.27 or 3.31 ppm for ^{1}H and 77.00 or 49.00 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 thermostatted cell. Analytical TLC and preparative column

chromatography were performed on Kieselgel F 254 and on Kieselgel 60 (0.040–0.063 mm) (Merck), respectively, with the following eluent systems: 2.5% MeOH–97.5% CH_2Cl_2 (A); 5% MeOH–95% CH_2Cl_2 (B); 10% MeOH–90% CH_2Cl_2 (C); 20% MeOH–80% CH_2Cl_2 (D); 50% MeOH–50% CH_2Cl_2 (E); 5% EtOAc–95% CH_2Cl_2 (F); CH_2Cl_2–*n*BuOH–EtOAc–MeOH–AcOH–H_2O 8:4:3:2.5:1:0.5 (G). The TLC chromatograms were visualized by UV fluorescence (254 nm) and/or developed by ninhydrin/TFA reaction, as appropriate. 3-(3,4-Dihydroxyphenyl)-2-methyl-(L)-alanine sesquihydrate, tetraethyleneglycol ditosylate and pentaethyleneglycol ditosylate, were purchased from Aldrich. Fmoc-(L)-alanine *N*-carboxy anhydride (Fmoc-Ala-NCA) and Boc-α-methyl-alanine *N*-carboxy anhydride (Boc-Aib-NCA) were purchased from Fluka and Isochem, respectively.

2.2.1. α-Methyl-β-3,4-dihydroxyphenyl-(L)-alanine methyl ester hydrochloride. $SOCl_2$ (37.5 mL) was added dropwise to an ice-cold suspension of α-methyl-(L)-DOPA sesquihydrate H-Mdp-OH·1.5H_2O (11.90 g; 50 mmol) in MeOH (125 mL). The resulting clear yellow solution was stirred at 65°C for 6 days, and then evaporated in vacuo, the residue being repeatedly evaporated to dryness from H_2O/acetone, as previously described.[10,11] The obtained crude H-Mdp-OMe·HCl (13.80 g) was pure by NMR and was used in the next step without further purification. ^{1}H NMR (CD_3OD): 6.76 [d, J=8.0 Hz, 1H, ArH^5], 6.62 [d, J=2.1 Hz, 1H, ArH^2], 6.51 [dd, J=8.0, 2.1 Hz, 1H, ArH^6], 3.84 [s, 3H, OCH_3], 3.16 [d, J=14.2 Hz, 1H] and 2.95 [d, J=14.2 Hz, 1H, $ArCH_2^{\beta}$], 1.60 [s, 3H, CH_3^{β}]. ^{13}C NMR (CD_3OD): 172.4 [C=O], 146.8, 146.5 [C^{Ar}–O], 125.3, 122.6, 118.0, 116.7 [C^{Ar}], 62.0 [C^{α}], 53.8 [OCH_3], 43.6 [$ArCH_2^{\beta}$], 22.5 [CH_3^{β}].

2.2.2. N^{α}-*tert*-Butyloxycarbonyl-α-methyl-β-3,4-dihydroxyphenyl-(L)-alanine methyl ester (I). To an ice-cold solution of H-Mdp-OMe·HCl (2.615 g; 10 mmol) and Boc_2O (3.04 g; 14 mmol) in CH_3CN (40 mL)/THF (20 mL) (13.80 g) was added TEA (2 mL; 14 mmol). The solution was stirred at room temperature for 5 days, and then evaporated in vacuo. The residue was solubilized in H_2O/EtOAc. The separated organic phase was washed with 0.5N HCl (3×50 mL), then H_2O (2×200 mL), dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product which presented two TLC-spots of R_f=0.50 and 0.30 (B), was chromatographed on a 3×68 cm column of silica gel with eluent (B), to give (i) 1.550 g (37%) of a ca. 1:1 mixture of isomers (**II$_A$**+**II$_B$**) of Boc-[OBoc;OH]-Mdp-OMe, {R_f=0.50 (B). ^{1}H NMR ($CDCl_3$): ≈7.1 [m (broad), 1H, ArOH], 6.96 [d, J=8.2 Hz, 0.5H, ArH^5 of 1 isomer], 6.80 [d, J=1.8 Hz, 0.5H, ArH^2 of 1 isomer], 6.78 [d, J=8.2 Hz, 0.5H, ArH^5 of 1 isomer], 6.72 [dd, J=8.2, 1.8 Hz, 0.5H, ArH^6 of 1 isomer], 6.65 [d, J=1.8 Hz, 0.5H, ArH^2 of 1 isomer], 6.53 [dd, J=8.2, 1.8 Hz, 0.5H, ArH^6 of 1 isomer], 5.20 [s, 0.5H, NH of 1 isomer], 5.17 [s, 0.5H, NH of 1 isomer], 3.68 [s, 1.5H, OCH_3 of 1 isomer], 3.67 [s, 1.5H, OCH_3 of 1 isomer], 3.10 [m (broad d and d), 2H, $ArCH_2^{\beta}$ of 2 isomers], 1.47 [s, 9H, $OCOOC(CH_3)_3$ of 2 isomers], 1.40 [s, 12H, $NHCOOC(CH_3)_3$ and CH_3^{β} of 2 isomers]}, (ii) 0.257 g of (**I**) contaminated by (**II$_A$**+**II$_B$**) and (iii) 0.746 g (23%) of pure (**I**). The combined fractions containing the mixture (**II$_A$**+**II$_B$**) (1.550+0.257 g) were dissolved in CH_2Cl_2 (50 mL) and pyrrolidine (1.5 mL; 18 mmol) was added. The solution was stirred at room temperature for 3 h, diluted with CH_2Cl_2 (100 mL), extracted with 0.5N HCl (3×100 mL), and then H_2O (2×100 mL), dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product presented only one UV-positive TLC-spot of R_f=0.30 (B) corresponding to (I), and a second ninhydrin/TFA positive TLC-spot of R_f=0.60 (B) corresponding to *N*-Boc-pyrrolidine. Chromatography on a 2.3×53 cm column of silica gel with eluent (A) gave 0.987 g of analytically pure Boc-Mdp-OMe (I) as a white amorphous solid, for a total of 1.733 g (53%). In a duplicate run, a mixture of crude H-Mdp-OMe·HCl obtained after esterification of H-Mdp-OH·1.5H_2O (5.00 g; 21.0 mmol) (vide supra), Boc_2O (7.50 g; 34.4 mmol) and Et_3N (4.5 mL; 32 mmol) in CH_3CN (60 mL) and THF (30 mL) was reacted in the same experimental conditions as above. The crude product obtained after work-up was directly treated with pyrrolidine (8.5 mL; 102 mmol) in CH_2Cl_2 (150 mL) at room temperature for 3 h. Extraction as above followed by repeated column chromatography, afforded 4.55 g of pure (I) (67% overall yield from α-methyl-(L)-DOPA). In another run, a mixture of H-Mdp-OMe·HCl (0.32 g; 1.2 mmol), Boc_2O (0.54 g; 2.5 mmol) and $NaHCO_3$ (0.58 g; 6.9 mmol) in DMF (1 mL) and *tert*-BuOH (1 mL) was stirred at 60°C for 5 days, as previously described.[11] Extraction as above gave a crude product presenting two main TLC-spots of R_f=0.50 and 0.30 (B), corresponding to (**II$_A$**+**II$_B$**) and (**I**), respectively (vide supra). In another run, a mixture of crude H-Mdp-OMe·HCl obtained after esterification of H-Mdp-OH·1.5H_2O (0.883 g; 3.71 mmol), Boc_2O (0.890 g; 4.08 mmol) and $NaHCO_3$ (0.620 g; 7.4 mmol) in H_2O (7.5 mL) and THF (5 mL) was stirred at room temperature for 5 days, as previously described in the case of (L)-DOPA.[16] The crude product obtained after work-up was chromatographed on a 2.3×30 cm column of silica gel with eluent (A), to give (i) 0.454 g of pure (**I**) and (ii) 0.508 g of a mixture (**I**+**II$_A$**+**II$_B$**) which was treated with pyrrolidine (0.5 mL) in CH_2Cl_2 (25 mL) at room temperature for 3 h, extracted as above and chromatographed on a 2.3×46 cm column of silica gel with eluent (A), to give 0.287 g of pure (**I**) for a total of 0.741 g (62% overall). Mp=140°C. R_f=0.30 (B). ^{1}H NMR ($CDCl_3$): 6.74 [d, J=8.1 Hz, 1H, ArH^5], 6.60 [d, J=1.8 Hz, 1H, ArH^2], 6.46 [dd, J=8.1, 1.8 Hz, 1H, ArH^6], 5.19 [s (broad), 1H, NH], 3.74 [s, 3H, OCH_3], 3.15 [d (broad), 1H] and 3.04 [d, J=13.0 Hz, 1H, $ArCH_2^{\beta}$], 1.51 [s (broad), 3H, CH_3^{β}], 1.46 [s, 9H, $(CH_3)_3$ Boc]. ^{13}C NMR ($CDCl_3$): 174.9 [C=O], 154.8 [C=O Boc], 143.8, 143.1 [C^{Ar}–O], 128.0, 122.1, 117.0, 115.1 [C^{Ar}], 80.0 [O–C Boc], 60.2 [C^{α}], 52.5 [OCH_3], 41.7 [$ArCH_2^{\beta}$], 28.2 [$(CH_3)_3$ Boc], 23.3 [CH_3^{β}]. $[\alpha]_{589}^{25}$=−35.0°, $[\alpha]_{578}^{25}$=−39.2°, $[\alpha]_{546}^{25}$=−44.9°, $[\alpha]_{436}^{25}$=−81.3°, $[\alpha]_{365}^{25}$=−133.6° (*c* 0.2; MeOH). Anal. for $C_{16}H_{23}NO_6 \cdot 0.5H_2O$: calcd C 57.47, H 7.23, N 4.18; found C 57.43, H 6.89, N 3.81.

2.2.3. N^{α}-*tert*-Butyloxycarbonyl-α-methyl-β-3,4-(15-crown-5)-phenyl-(L)-alanine methyl ester (1a). Similar experimental conditions as those previously reported by Voyer et al.[2b,e] were applied: a solution of Boc-Mdp-OMe (**I**) (1.625 g; 5 mmol) and Cs_2CO_3 (1.792 g; 5.5 mmol) in degassed MeOH (20 mL) was stirred under argon atmosphere at 45°C for 15 min, then evaporated to dryness in vacuo to leave a brown foam. DMF (5 mL) was added

and the resulting mixture was evaporated to dryness under high vacuum at 45°C in order to completely remove the residual methanol. The residue was re-dissolved in DMF (50 mL) and the mixture heated at 60°C under argon atmosphere. A solution of tetraethyleneglycol ditosylate (2.767 g; 5.5 mmol) in DMF (20 mL) was added dropwise over a 2 h period. The mixture was magnetically stirred at 60°C for 16 h and then evaporated to dryness under high vacuum. The residue was taken up in CH_2Cl_2 (250 mL) and 5% $NaHCO_3$ (100 mL). The decanted CH_2Cl_2 solution was washed with 5% $NaHCO_3$ (2×100 mL), then with H_2O (2×100 mL), dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was chromatographed on a 3×66 cm column of silica gel with eluent (G). The fractions containing the desired product were combined and the solution was evaporated to dryness in vacuo at 45°C. Aqueous 5% $NaHCO_3$ (200 mL) was added to the residue and the mixture was again evaporated to dryness in vacuo at 45°C in order to completely remove the eluent components nBuOH and AcOH. The residue was taken up in CH_2Cl_2 (250 mL) and H_2O (200 mL). The basic aqueous $NaHCO_3$ phase obtained after shaking and decantation was extracted with CH_2Cl_2 (50 mL). The combined CH_2Cl_2 phase was washed with H_2O (3×150 mL), dried ($MgSO_4$), filtered and evaporated in vacuo, to afford 1.177 g (49%) of pure Boc-[15-C-5]-Mdp-OMe **1a** as a pale yellow glass. R_f=0.30 (G). ^{1}H NMR ($CDCl_3$): 6.77 [d, J=8.5 Hz, 1H, ArH^5], 6.61 [dd, J=8.1, 1.8 Hz, 1H, ArH^6], 6.60 [d, J=1.8 Hz, 1H, ArH^2], 5.13 [s (broad), 1H, NH], 4.11 [m, 4H, OCH_2], 3.90 [m, 4H, OCH_2], 3.76 [s (broad), 8H, OCH_2], 3.74 [s, 3H, OCH_3], 3.26 [d (broad), J=13.6 Hz, 1H] and 3.11 [d, J=13.6 Hz, 1H, $ArCH_2{}^{\beta}$], 1.54 [s (broad), 3H, $CH_3{}^{\beta}$], 1.46 [s, 9H, $(CH_3)_3$ Boc]. ^{13}C NMR ($CDCl_3$): 174.6 [C═O], 154.5 [C═O Boc], 148.9, 148.3 [C^{Ar}–O], 129.5, 123.0, 116.3, 113.8 [C^{Ar}], 79.7 [O–C Boc], 71.2, 70.7, 69.8, 69.1 [OCH_2], 60.6 [C^{α}], 52.6 [OCH_3], 41.5 [$ArCH_2{}^{\beta}$], 28.6 [$(CH_3)_3$ Boc], 23.8 [$CH_3{}^{\beta}$]. $[\alpha]_{589}{}^{25}=-31.8°$, $[\alpha]_{578}{}^{25}=-33.5°$, $[\alpha]_{546}{}^{25}=-39.6°$, $[\alpha]_{436}{}^{25}=-71.8°$, $[\alpha]_{365}{}^{25}=-113.8°$ (c 0.29; MeOH). ESI$^+$ MS m/z (relative intensity): 522 (6) $[M,K]^+$, 506 (100) $[M,Na]^+$. Anal. for $C_{24}H_{37}NO_9$: calcd C 59.61, H 7.71, N 2.89; found C 59.16, H 7.71, N 2.67.

2.2.4. N^{α}-*tert*-Butyloxycarbonyl-α-methyl-β-3,4-(18-crown-6)-phenyl-(L)-alanine methyl ester (2a). Treatment of (**I**) (1.625 g; 5 mmol) and Cs_2CO_3 (1.792 g; 5.5 mmol) with pentaethyleneglycol ditosylate (3.006 g; 5.5 mmol) in DMF (70 mL), under the same experimental conditions, work-up and purification as for the preparation of **1a**, led to 1.172 g (44%) of pure Boc-[18-C-6]-Mdp-OMe **2a** as a pale yellow glass. R_f=0.35 (G). ^{1}H NMR ($CDCl_3$): 6.72 [d, J=8.6 Hz, 1H, ArH^5], 6.56 [dd, J=8.5, 1.8 Hz, 1H, ArH^6], 6.56 [d, J=1.8 Hz, 1H, ArH^2], 5.12 [s (broad), 1H, NH], 4.08 [m, 4H, OCH_2], 3.86 [m, 4H, OCH_2], 3.74–3.69 [m, 4H, OCH_2], 3.69 [s, 3H, OCH_3], 3.69–3.64 [m, 4H, OCH_2], 3.64 [s (broad), 4H, OCH_2], 3.20 [d (broad), 1H] and 3.06 [d, J=13.6 Hz, 1H, $ArCH_2{}^{\beta}$], 1.49 [s (broad), 3H, $CH_3{}^{\beta}$], 1.42 [s, 9H, $(CH_3)_3$ Boc]. ^{13}C NMR ($CDCl_3$): 174.2 [C═O], 154.1 [C═O Boc], 148.3, 147.8 [C^{Ar}–O], 129.1, 122.6, 115.9, 113.5 [C^{Ar}], 79.2 [O–C Boc], 70.6, 70.5, 69.5, 69.4, 68.9, 68.8 [OCH_2], 60.1 [C^{α}], 52.3 [OCH_3], 41.1 [$ArCH_2{}^{\beta}$], 28.2 [$(CH_3)_3$ Boc], 23.4 [$CH_3{}^{\beta}$]. $[\alpha]_{589}{}^{25}=-32.1°$, $[\alpha]_{578}{}^{25}=-33.8°$, $[\alpha]_{546}{}^{25}=-40.8°$, $[\alpha]_{436}{}^{25}=-73.5°$, $[\alpha]_{365}{}^{25}=-121.2°$ (c 0.32; MeOH). ESI$^+$ MS m/z (relative intensity): 1077 (1) $[2M,Na]^+$, 566 (2) $[M,K]^+$, 550 (100) $[M,Na]^+$. Anal. for $C_{26}H_{41}NO_{10}$: calcd C 59.19, H 7.83, N 2.65; found C 59.34, H 7.89, N 2.31.

2.2.5. N^{α}-*tert*-Butyloxycarbonyl-α-methyl-β-3,4-(benzo-18-crown-6)-phenyl-(L)-alanine methyl ester (3a). Catechol (5.50 g; 50 mmol) and sodium hydroxide (4.00 g; 100 mmol) were added to *n*BuOH (100 mL) previously degassed under an argon stream. The mixture was heated under an argon atmosphere at 80°C for 90 min. until no solid remained. Chloro-ethoxy-ethanol (12.6 mL; 120 mmol) was slowly added in portions, and the mixture was stirred at 110°C for 72 h. The solvent was evaporated in vacuo, the residue was triturated with CH_2Cl_2 and the resulting suspension was filtered through a bed of Celite on a sintered glass filter. The filtrate was evaporated in vacuo and the residue purified by chromatography on a 5×38 cm column of silica gel with eluent (B), to give 6.40 g (45%) of 1,2-bis(5-hydroxy-3-oxa-1-pentyloxy)-benzene[19] as a yellow syrup. R_f=0.40 (C). ^{1}H NMR ($CDCl_3$): 6.80 [s, 4H, ArH], 4.02 [m (t-like), 4H, OCH_2], 3.85 [s (broad), 2H, OH], 3.76 [m, 4H, OCH_2], 3.64 [m, 4H, OCH_2], 3.55 [m (t-like), 4H, OCH_2]. ^{13}C NMR ($CDCl_3$): 148.3 [C^{Ar}–O], 121.3, 113.8 [C^{Ar}], 72.5, 69.1, 68.4, 61.2 [OCH_2]. The diol (3.20 g; 11.2 mmol) was dissolved in 20 mL dry pyridine and cooled to −10°C on an ice/salt bath. Toluenesulphonyl chloride (5.54 g; 29.0 mmol) was dissolved in 10 mL dry pyridine, and added slowly in portions to the diol solution. The mixture was left at 4°C for 18 h, diluted with ice cold CH_2Cl_2 and poured onto iced water. The two phases were separated and the aqueous phase was extracted twice with cold CH_2Cl_2. The combined organic phases were washed twice with iced 2N HCl and once with iced brine. The solution was dried over $MgSO_4$, filtered and evaporated in vacuo. The residue was purified by chromatography on a 3×40 cm column of silica gel with eluent (F), to give 2.50 g (37%) of 1,2-bis(5-tosyloxy-3-oxa-1-pentyloxy)-benzene[19] as a yellow syrup. R_f=0.35 (F). ^{1}H NMR ($CDCl_3$): 7.76 [d, J=8.5 Hz, 4H] and 7.28 [d, J=8.5 Hz, 4H, ArH Tos], 6.88 [m, 4H, ArH], 4.15 [m, 4H, OCH_2], 4.04 [m, 4H, OCH_2], 3.75 [m, 8H, OCH_2], 2.38 [s, 6H, CH_3 Tos]. Treatment of (**I**) (0.940 g; 2.89 mmol) and Cs_2CO_3 (1.03 g; 3.18 mmol) with this ditosylate (1.89 g; 3.18 mmol) in DMF (45 mL), under the same experimental conditions, work-up and purification as for the preparation of **1a**, led to 0.143 g (9%) of pure Boc-[benzo-18-C-6]-Mdp-OMe **3a** as a pale yellow glass. R_f=0.60 (G). ^{1}H NMR ($CDCl_3$): 6.88 (m, 4H, ArH), 6.75 [d, J=7.7 Hz, 1H, ArH^5 Mdp], 6.60 [dd, J=7.7, 1.8 Hz, 1H, ArH^6 Mdp], 6.59 [d, J=1.8 Hz, 1H, ArH^2 Mdp], 5.12 [s (broad), 1H, NH], 4.16 [m, 8H, OCH_2], 4.02 [m, 8H, OCH_2], 3.74 [s, 3H, OCH_3], 3.27 [d (broad), 1H] and 3.11 [d, J=13.6 Hz, 1H, $ArCH_2{}^{\beta}$], 1.53 [s (broad), 3H, $CH_3{}^{\beta}$], 1.46 [s, 9H, $(CH_3)_3$ Boc]. ^{13}C NMR ($CDCl_3$): 174.6 [C═O], 154.5 [C═O Boc], 148.9 [C^{Ar}–O], 148.5, 147.9 [C^{Ar}–O Mdp], 129.4, 122.9, 121.5, 115.6, 113.7, 113.2 [C^{Ar}], 79.7 [O–C Boc], 70.1, 68.9 [OCH_2], 60.6 [C^{α}], 52.6 [OCH_3], 41.6 [$ArCH_2{}^{\beta}$], 28.6 [$(CH_3)_3$ Boc], 23.8 [$CH_3{}^{\beta}$]. $[\alpha]_{589}{}^{25}=-27.7°$, $[\alpha]_{578}{}^{25}=-28.8°$, $[\alpha]_{546}{}^{25}=-34.2°$, $[\alpha]_{436}{}^{25}=-60.4°$, $[\alpha]_{365}{}^{25}$ (abs) $\approx-96°$ (c 0.26; MeOH). ESI$^+$ MS m/z (relative intensity): 598 (100) $[M,Na]^+$, 576 (12) $[M,H]^+$. Anal. for $C_{30}H_{41}NO_{10}\cdot 0.5H_2O$: calcd C 61.63, H 7.24, N 2.39; found C 61.69, H 7.42, N 2.01.

2.2.6. N^{α}-*tert*-Butyloxycarbonyl-α-methyl-β-3,4-(benzo-24-crown-8)-phenyl-(L)-alanine methyl ester (4a). Treatment of catechol (1.10 g; 10 mmol) and sodium hydroxide (0.80 g; 20 mmol) in degassed *n*BuOH (20 mL) with chloro-ethoxy-ethoxy-ethanol (3.48 mL; 24 mmol) under the same experimental conditions and work-up as for the preparation of 1,2-bis(5-hydroxy-3-oxa-1-pentyloxy)-benzene, followed by chromatography on a 3×42 cm column of silica gel with eluent (B), and then (C), gave 2.208 g (59%) of 1,2-bis(8-hydroxy-3,6-dioxa-1-octyloxy)-benzene as a yellow syrup. R_f=0.35 (C). ^{1}H NMR ($CDCl_3$): 6.91 [s, 4H, ArH], 4.17 [m (t-like), 4H, OCH_2], 3.87 [m (t-like), 4H, OCH_2], 3.69 [m, 12H, OCH_2], 3.60 [m (t-like), 4H, OCH_2], 3.29 [s (broad), 2H, OH]. ^{13}C NMR ($CDCl_3$): 148.7 [C^{Ar}–O], 121.5, 114.6 [C^{Ar}], 72.5, 70.6, 70.2, 69.6, 68.6, 61.3 [OCH_2]. Treatment of this diol (2.20 g; 5.88 mmol) with toluenesulphonyl chloride (2.91 g; 15.28 mmol) in dry pyridine (15 mL) under the same experimental conditions and work-up as for the preparation of 1,2-bis(5-tosyloxy-3-oxa-1-pentyloxy)-benzene, followed by chromatography on a 3×40 cm column of silica gel with eluent (A), gave 3.09 g (77%) of 1,2-bis(8-tosyloxy-3,6-dioxa-1-octyloxy)-benzene as a yellow syrup. R_f=0.65 (A). ^{1}H NMR ($CDCl_3$): 7.79 [d, *J*=8.2 Hz, 4H] and 7.33 [d, *J*=8.5 Hz, 4H, ArH Tos], 6.91 [s, 4H, ArH], 4.14 [m, 8H, OCH_2], 3.82 [m (t-like), 4H, OCH_2], 3.68 [m, 8H, OCH_2], 3.61 [m, 4H, OCH_2], 2.42 [s, 6H, CH_3 Tos]. [Note: in a duplicate experiment, the diol (3.526 g; 9.43 mmol) was reacted with toluene-sulphonyl chloride (4.67 g; 24.5 mmol) under the same experimental conditions and work-up as above, to give 5.42 g of crude product consisting in a mixture of 1,2-bis(8-tosyloxy-3,6-dioxa-1-octyloxy)-benzene TsO–X–OTs and TsO–X–Cl resulting from substitution of one of the tosyl groups by a chloride anion present in the reaction mixture.[28] These two compounds of very close R_f could not be completely separated by conventional chromatography and presented identical or very similar chemical shifts in ^{1}H NMR, but their ratio could be estimated by integration of the aromatic protons signals of the tosyl group(s) compared to integration of the aromatic protons of the catechol moiety. The following fractions were obtained after chromatography on a 4.5×24 cm column of silica gel with gradient elution from CH_2Cl_2 to eluent (A): (i) 0.199 g (4%) (TsO–X–OTs/TsO–X–Cl≈1:3) (ii) 0.856 g (15%) (TsO–X–OTs/TsO–X–Cl ≈1:1) (iii) 1.591 g (26%) (TsO–X–OTs/TsO–X–Cl≈3:1). These mixtures were used as well as the pure ditosylate for *O*-alkylation of (**I**) with crown-ether formation (see later).] Treatment of (**I**) (0.989 g; 3.04 mmol) and Cs_2CO_3 (1.09 g; 3.35 mmol) with 1. 992 g (3.04 mmol) of a mixture of 1,2-bis(8-tosyloxy-3,6-dioxa-1-octyloxy)-benzene TsO–X–OTs (80% mol/mol by ^{1}H NMR i.e. 2.43 mmol) and the corresponding TsO–X–Cl (vide supra) (20% mol/mol by ^{1}H NMR i.e. 0.61 mmol) in DMF (50 mL), under the same experimental conditions and work-up as for the preparation of **1a**, led to a crude product which presented the same TLC profile as the crude product obtained upon treatment of (**I**) (0.564 g; 1.74 mmol) and Cs_2CO_3 (0.622 g; 1.91 mmol) with 1. 055 g (1.74 mmol) of a mixture of TsO–X–OTs (45% mol/mol by ^{1}H NMR i.e. 0.78 mmol) and the corresponding TsO–X–Cl (55% mol/mol by ^{1}H NMR i.e. 0.95 mmol) in DMF (35 mL). The combined crude products were purified by repeated chromatography on a 3×66 cm column of silica gel with eluent (G). The fractions containing the desired product were combined, the solution was evaporated to dryness in vacuo at 45°C and the residue worked-up as in the preparation of **1a**, to afford 1.025 g (32%) of pure Boc-[benzo-24-C-8]-Mdp-OMe **4a** as a yellow glass. A duplicate initial experiment in which (**I**) (1.418 g; 4.36 mmol) and Cs_2CO_3 (1.56 g; 4.80 mmol) were reacted with 3.09 g (4.53 mmol) of NMR pure 1,2-bis(8-tosyloxy-3,6-dioxa-1-octyloxy)-benzene, under the same experimental conditions and work-up as above, gave 0.349 g (12%) of pure **4a**. R_f=0.55 (G). ^{1}H NMR ($CDCl_3$): 6.83 [m (s-like), 4H, ArH], 6.71 [d, *J*=8.8 Hz, 1H, ArH^5 Mdp], 6.56 [dd, ≈*J*=8, 1.8 Hz, 1H, ArH^6 Mdp], 6.55 [d, *J*=2.0 Hz, 1H, ArH^2 Mdp], 5.14 [s (broad), 1H, NH], 4.08 [m, 8H, OCH_2], 3.85 [m, 8H, OCH_2], 3.78 [s, 8H, OCH_2], 3.68 [s, 3H, OCH_3], 3.20 [d (broad), 1H] and 3.06 [d, *J*=13.6 Hz, 1H, $ArCH_2^{\beta}$], 1.48 [s (broad), 3H, CH_3^{β}], 1.41 [s, 9H, $(CH_3)_3$ Boc]. ^{13}C NMR ($CDCl_3$): 174.1 [C=O], 154.0 [C=O Boc], 148.6 [C^{Ar}–O], 148.2, 147.6 [C^{Ar}–O Mdp], 129.1, 122.6, 121.1, 115.8, 113.8, 113.3 [C^{Ar}], 79.1 [O–C Boc], 70.9, 69.6, 69.2, 69.1 [OCH_2], 60.0 [C^{α}], 52.1 [OCH_3], 41.0 [$ArCH_2^{\beta}$], 28.1 [$(CH_3)_3$ Boc], 23.3 [CH_3^{β}]. $[\alpha]_{589}^{25}$=−27.8°, $[\alpha]_{578}^{25}$=−29.6°, $[\alpha]_{546}^{25}$=−33.3°, $[\alpha]_{436}^{25}$=−59.7° (*c* 0.21; MeOH). ESI$^+$ MS *m*/*z* (relative intensity): 686 (100) $[M,Na]^+$, 664 (35) $[M,H]^+$. Anal. for $C_{34}H_{49}NO_{12}\cdot 0.5H_2O$: calcd C 60.70, H 7.49, N 2.08; found C 60.46, H 7.48, N 1.75.

2.2.7. N^{α}-*tert*-Butyloxycarbonyl-α-methyl-β-3,4-(15-crown-5)-phenyl-(L)-alanine (1b). To a solution of **1a** (1.151 g; 2.38 mmol) in MeOH (75 mL) was added 1N NaOH (75 mL), and the mixture was stirred at 60°C for 24 h. Methanol was evaporated in vacuo at 40°C with portions of H_2O added. The resulting aqueous basic solution (ca. 150 mL) was extracted with Et_2O (150 mL), cooled by addition of ice, then acidified by addition of a large excess of 0.5N HCl and extracted with CH_2Cl_2 (4×50 mL). The combined CH_2Cl_2 phases were washed with H_2O (200 mL), dried ($MgSO_4$), filtered and evaporated in vacuo, to afford 0.968 g (87%) of pure Boc-[15-C-5]-Mdp-OH **1b** as a pale yellow glass. R_f=0.25 (G). ^{1}H NMR ($CDCl_3$): 8.47 [s (broad), 1H, COOH], 6.68 [d (broad), *J*=8.8 Hz, 1H, ArH^5], 6.62 [m (broad s), 2H, ArH^6 and ArH^2], 5.32 [s (broad), 1H, NH], 4.02 [m (broad), 4H, OCH_2], 3.81 [m (broad), 4H, OCH_2], 3.68 [s (broad), 8H, OCH_2], 3.26 [d (broad), 1H] and 3.08 [d, *J*=13.6 Hz, 1H, $ArCH_2^{\beta}$], 1.51 [s (broad), 3H, CH_3^{β}], 1.40 [s, 9H, $(CH_3)_3$ Boc]. ^{13}C NMR ($CDCl_3$): 176.6 [COOH], 154.2 [C=O Boc], 148.2, 147.6 [C^{Ar}–O], 129.5, 122.6, 115.7, 113.2 [C^{Ar}], 79.0 [O–C Boc], 70.5, 70.1, 69.3, 68.5, 68.4 [OCH_2], 59.9 [C^{α}], 40.5 [$ArCH_2^{\beta}$], 28.2 [$(CH_3)_3$ Boc], 23.4 [CH_3^{β}]. $[\alpha]_{589}^{25}$=−9.1°, $[\alpha]_{578}^{25}$=−9.1°, $[\alpha]_{546}^{25}$=−11.9°, $[\alpha]_{436}^{25}$=−18.8°, $[\alpha]_{365}^{25}$=−28.1° (*c* 0.21; MeOH). Anal. for $C_{23}H_{35}NO_9$: calcd C 58.83, H 7.51, N 2.98; found C 58.45, H 7.55, N 2.75.

2.2.8. N^{α}-*tert*-Butyloxycarbonyl-α-methyl-β-3,4-(18-crown-6)-phenyl-(L)-alanine (2b). Saponification of **2a** (0.927 g; 1.76 mmol) in MeOH (75 mL) and 1N NaOH (75 mL) under the same experimental conditions (60°C; 24 h) and work-up as for the preparation of **1b**, led to 0.856 g (95%) of pure Boc-[18-C-6]-Mdp-OH **2b** as a pale yellow glass. R_f=0.25 (G). ^{1}H NMR ($CDCl_3$): 9.06 [s

(broad), 1H, COOH], 6.69 [d, J=8.5 Hz, 1H, ArH^5], 6.64 [s (broad), 1H, ArH^2 Mdp], 6.63 [d (broad), ≈J=8 Hz, 1H, ArH^6 Mdp], 5.30 [s (broad), 1H, NH], 4.06 [m (broad), 4H, OCH_2], 3.83 [m (broad), 4H, OCH_2], 3.75–3.64 [m (broad), 8H, OCH_2], 3.63 [s, 4H, OCH_2], 3.27 [d (broad), 1H] and 3.10 [d, J=13.4 Hz, 1H, $ArCH_2^{\beta}$], 1.53 [s (broad), 3H, CH_3^{β}], 1.41 [s, 9H, $(CH_3)_3$ Boc]. ^{13}C NMR ($CDCl_3$): 176.7 [COOH], 154.3 [C=O Boc], 148.0, 147.3 [C^{Ar}–O], 129.6, 122.6, 115.5, 113.0 [C^{Ar}], 79.1 [O–C Boc], 70.4, 70.3, 69.35, 69.30, 68.5, 68.4 [OCH_2], 60.1 [C^{α}], 40.6 [$ArCH_2^{\beta}$], 28.3 [$(CH_3)_3$ Boc], 23.5 [CH_3^{β}]. $[\alpha]_{589}^{25}$=−5.8°, $[\alpha]_{578}^{25}$=−5.8°, $[\alpha]_{546}^{25}$=−7.1°, $[\alpha]_{436}^{25}$=−13.8°, $[\alpha]_{365}^{25}$=−16.7° (*c* 0.24; MeOH). ESI^+ MS *m/z* (relative intensity): 1065 (2)) $[2M,K]^+$, 1049 (11)) $[2M,Na]^+$, 552 (15) $[M,K]^+$, 536 (100) $[M,Na]^+$. Anal. for $C_{25}H_{39}NO_{10}\cdot 1.5H_2O$: calcd C 55.54, H 7.83, N 2.59; found C 55.91, H 7.46, N 2.04.

2.2.9. N^{α}-*tert*-Butyloxycarbonyl-α-methyl-β-3,4-(benzo-24-crown-8)-phenyl-(L)-alanine (4b). Saponification of **4a** (1.364 g; 2.06 mmol) in MeOH (85 mL) and 1N NaOH (85 mL) under the same experimental conditions (60°C; 24 h) and work-up as for the preparation of **1b**, led to 1.177 g (88%) of pure Boc-[benzo-24-C-8]-Mdp-OH **4b** as a pale yellow glass. R_f=0.40 (G). ^{1}H NMR ($CDCl_3$): 7.91 [s (broad), 1H, COOH], 6.86 (m, 4H, ArH), 6.72 [d, J=8.3 Hz, 1H, ArH^5 Mdp], 6.66 [s (broad), 1H, ArH^2 Mdp], 6.65 [d (broad), ≈J=8 Hz, 1H, ArH^6 Mdp], 5.28 [s (broad), 1H, NH], 4.11 [m, 8H, OCH_2], 3.88 [m, 8H, OCH_2], 3.80 [s, 8H, OCH_2], 3.28 [d (broad), 1H] and 3.06 [d, J=13.2 Hz, 1H, $ArCH_2^{\beta}$], 1.54 [s (broad), 3H, CH_3^{β}], 1.44 [s, 9H, $(CH_3)_3$ Boc]. ^{13}C NMR ($CDCl_3$): 176.8 [COOH], 154.2 [C=O Boc], 148.6 [C^{Ar}–O], 148.1, 147.5 [C^{Ar}–O Mdp], 129.5, 122.7, 121.2, 115.8, 113.8, 113.3 [C^{Ar}], 79.1 [O–C Boc], 70.9, 69.6, 69.0 [OCH_2], 59.9 [C^{α}], 40.5 [$ArCH_2^{\beta}$], 28.2 [$(CH_3)_3$ Boc], 23.4 [CH_3^{β}]. $[\alpha]_{589}^{25}$=−4.2°, $[\alpha]_{578}^{25}$=−4.6°, $[\alpha]_{546}^{25}$=−6.9°, $[\alpha]_{436}^{25}$=−11.9°, $[\alpha]_{365}^{25}$=−14.9° (*c* 0.26; MeOH). Anal. for $C_{33}H_{17}NO_{12}\cdot H_2O$: calcd C 59.35, H 7.39, N 2.10; found C 59.05, H 7.17, N 1.75.

2.2.10. Boc-[18-C-6]-Mdp-Ala-OMe (5a). (1) By the EDC/HOBt method, to a suspension of **2b** (0.221 g; 0.43 mmol), HCl·H-Ala-OMe (0.180 g; 1.29 mmol) and HOBt (0.117 g; 0.86 mmol) in THF (3 mL) and CH_2Cl_2 (3 mL), was added TEA (0.180 mL; 1.29 mmol) and then a solution of EDC (0.124 g; 0.65 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at room temperature for 48 h and evaporated to dryness in vacuo. The residue was solubilized in EtOAc (150 mL) and 0.5N HCl (50 mL) with stirring. The separated organic phase was extracted with 0.5N HCl (4×50 mL), H_2O (100 mL), 5% $NaHCO_3$ (4×50 mL), H_2O (2×100 mL), dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was chromatographed on a 1.5×10 cm column of silica gel with eluents (B)–(E), successively. The fractions containing the desired product were combined and the solution was evaporated to dryness in vacuo at 45°C. The residue was taken up in CH_2Cl_2 (200 mL) and aqueous $NaHCO_3$ (100 mL). The decanted CH_2Cl_2 phase was washed with H_2O (2×200 mL), dried ($MgSO_4$), filtered and evaporated in vacuo, to give 0.073 g (28%) of pure **5a** (vide infra). (2) By the CIP/HOAt method, to a suspension of **2b** (0.198 g; 0.38 mmol), HCl·H-Ala-OMe (0.162 g; 1.16 mmol) and HOAt (0.058 g; 0.43 mmol) in CH_2Cl_2 (5 mL), was added DIPEA (0.410 mL; 2.32 mmol) and then CIP (0.119 g; 0.43 mmol). The mixture was stirred at room temperature for 24 h and evaporated to dryness in vacuo. The residue was extracted as above, to give 0.125 g of a crude product which consisted of almost pure **5a**, only contaminated by a side product (ca. 15% mol/mol by ^{1}H NMR) identified as 1-chloromethyloxy-7-aza-1,2,3-benzotriazole ($ClCH_2OAt$) (vide infra). Purification was achieved by preparative TLC on silica gel with eluent (G). The silica gel from the TLC zone containing the desired product was finely ground and extracted by the solvent mixture (E) (200 mL) with magnetic stirring. The mixture was filtered on a sintered glass filter and the solution was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (200 mL) and the solution was washed as above with aqueous $NaHCO_3$ (100 mL), then with H_2O (2×200 mL), dried ($MgSO_4$), filtered and evaporated in vacuo, to give 0.093 g (40%) of pure **5a** (vide infra). (3) By the EDC/HOAt method, to a suspension of **2b** (0.237 g; 0.46 mmol), HCl·H-Ala-OMe (0.194 g; 1.39 mmol) and HOAt (0.126 g; 0.93 mmol) in CH_2Cl_2 (5 mL), was added NMM (0.205 mL; 1.85 mmol) and then EDC (0.133 g; 0.69 mmol). The mixture was stirred at room temperature for 48 h and evaporated to dryness in vacuo. The residue was extracted as above, to give 0.257 g of a crude product which, by ^{1}H NMR, was constituted of a mixture of pure **5a** and traces (ca. 5% mol/mol) of the side product $ClCH_2OAt$. The crude product was purified by preparative TLC followed by the same extraction procedure as above, to give (i) 0.0041 g of pure 1-chloromethyloxy-7-aza-1,2,3-benzotriazole ($ClCH_2OAt$), R_f=0.90 (G), identified by ^{1}H NMR ($CDCl_3$): 8.79 [dd, J=4.5, 1.4 Hz, 1H, ArH^6], 8.43 [dd, J=8.4, 1.4 Hz, 1H, ArH^4], 7.47 [dd, J=8.4, 4.4 Hz, 1H, ArH^5], 6.28 [s, 2H, OCH_2Cl] and ^{1}H NMR (CD_3OD): 8.79 [dd, J=4.5, 1.4 Hz, 1H, ArH^6], 8.43 [dd, J=8.4, 1.4 Hz, 1H, ArH^4], 7.47 [dd, J=8.4, 4.4 Hz, 1H, ArH^5], 6.28 [s, 2H, OCH_2Cl], and (ii) 0.191 g (69%) of pure **5a** as a pale yellow glass. R_f=0.30 (G). ^{1}H NMR ($CDCl_3$): 6.84 [d (broad), J=6.6 Hz, 1H, NH Ala], 6.77 [d, J=8.6 Hz, 1H, ArH^5], 6.65 [dd, ≈J=8, 1.8 Hz, 1H, ArH^6], 6.64 [d, J=1.8 Hz, 1H, ArH^2], 4.80 [s (broad), 1H, NH Mdp], 4.57 [dq, ≈J=7.2, 7.2 Hz, 1H, H^{α} Ala], 4.11 [m, 4H, OCH_2], 3.89 [m, 4H, OCH_2], 3.74 [m (partly masked), 4H, OCH_2], 3.72 [s, 3H, OCH_3], 3.70 [m (partly masked), 4H, OCH_2], 3.66 [s, 4H, OCH_2], 3.32 [d, J=14.0 Hz, 1H] and 2.98 [d, J=13.8 Hz, 1H, $ArCH_2^{\beta}$ Mdp], 1.45 [s, 9H, $(CH_3)_3$ Boc], 1.38 [d, J=7.2 Hz, 3H, CH_3^{β} Ala], 1.35 [s, 3H, CH_3^{β} Mdp]. ^{13}C NMR ($CDCl_3$): 173.5, 173.4 [C=O Ala and Mdp], 154.4 [C=O Boc], 148.4, 147.8 [C^{Ar}–O], 129.2, 123.3, 116.4, 113.6 [C^{Ar}], 80.2 [O–C Boc], 70.7, 70.6, 69.5, 68.9, 68.8 [OCH_2], 59.8 [C^{α} Mdp], 52.3 [OCH_3], 48.1 [C^{α} Ala], 40.3 [$ArCH_2^{\beta}$ Mdp], 28.2 [$(CH_3)_3$ Boc], 24.0 [CH_3^{β} Mdp], 18.3 [CH_3^{β} Ala]. $[\alpha]_{589}^{25}$=−50.5°, $[\alpha]_{578}^{25}$=−52.0°, $[\alpha]_{546}^{25}$=−61.5°, $[\alpha]_{436}^{25}$=−109.0°, $[\alpha]_{365}^{25}$=−187.0° (*c* 0.2; MeOH). ESI^+ MS *m/z* (relative intensity): 1219 (2) $[2M,Na]^+$, 637 (4) $[M,K]^+$, 621 (100) $[M,Na]^+$. Anal. for $C_{29}H_{46}N_2O_{11}$: calcd C 58.18, H 7.74, N 4.68; found C 57.76, H 7.61, N 4.38. In a duplicate experiment, **2b** (0.340 g; 0.66 mmol) was coupled with HCl·H-Ala-OMe (0.277 g; 1.99 mmol) in the presence of NMM (0.300 mL; 2.73 mmol), by the EDC (0.190 g; 0.99 mmol)/HOAt (0.180 g; 1.32 mmol) method, in CH_2Cl_2 (5 mL), under the same experimental conditions

and work-up as above, to give 0.387 g (≈98%) of a crude mixture consisting in pure **5a** with traces (ca. 6% mol/mol by ^{1}H NMR) of the side product $ClCH_2OAt$. This mixture was used in the next coupling step without further purification (vide infra).

2.2.11. Fmoc-Ala-[18-C-6]-Mdp-Ala-OMe (6a). To an ice-cold solution of crude **5a** (0.175 g; ≈0.29 mmol), contaminated by $ClCH_2OAt$ (ca. 6% mol/mol by ^{1}H NMR) (vide supra) in CH_2Cl_2 (7.5 mL) was added TFA (2.5 mL). The solution was stirred from 0°C to room temperature for 4 h and evaporated in vacuo at 30°C. The residue was repeatedly dissolved in CH_2Cl_2 and the solution evaporated in vacuo. The residue was repeatedly triturated with Et_2O and the mixture evaporated in vacuo, to yield crude TFA·H-[18-C-6]-Mdp-Ala-OMe (**5c**) (not characterized). The crude dipeptide **5c** (≈0.29 mmol) was dissolved in THF (3 mL), the solution was magnetically stirred at 0°C and DIPEA (0.180 mL; 1.03 mmol) was added, followed by solid Fmoc Ala-NCA (0.296 g; 0.88 mmol). The solution was stirred from 0°C to room temperature for 64 h and evaporated in vacuo at 40°C. The residue was dissolved in CH_2Cl_2 (150 mL), the solution was washed with 0.5N HCl (2×75 mL), H_2O (2×100 mL), dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was chromatographed on preparative TLC plates of silica gel with eluent (G). The silica gel from the TLC zone containing the desired product was finely ground and extracted by the solvent mixture (E) (200 mL) with magnetic stirring. The mixture was filtered on sintered glass and the solution was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (200 mL) and the solution was washed as above with aqueous $NaHCO_3$ (2×100 mL), then with H_2O (2×200 mL), dried ($MgSO_4$), filtered and evaporated in vacuo, to give 0.160 g (69%) (67% overall yield from **2b**) of pure Fmoc-Ala^1-[18-C-6]-Mdp-Ala^2-OMe (**6a**). R_f=0.50 (G); 0.60 (D). ^{1}H NMR ($CDCl_3$): 7.75 [d, J=7.3 Hz, 2H, ArH Fmoc], 7.58 [m (t-like), 2H, ArH Fmoc], 7.39 [m (t-like), 2H, ArH Fmoc], 7.30 [m (split t-like), 2H, ArH Fmoc], 7.00 [d (broad), J=7.0 Hz, 1H, NH Ala^2], 6.69 [d, J=8.1 Hz, 1H, ArH^5], 6.61 [dd, J=8.1, 1.9 Hz, 1H, ArH^6], 6.64 [d, J=1.8 Hz, 1H, ArH^2], 6.54 [s (broad), 1H, NH Mdp], 5.52 [d (broad), J=6.1 Hz, 1H, NH Ala^1], 4.51 [dq, ≈J=7.1, 7.1 Hz, 1H, H$^\alpha$ Ala^2], 4.39 [dd, J=7.0, 10.3 Hz, 1H] and 4.28 [dd (broad), ≈J=7.0, 10.3 Hz, 1H, CH_2O Fmoc], 4.19 [m (t-like), ≈J=7.0 Hz, 1H, Ar–CH Fmoc], 4.06 [m, 4H, OCH_2], 4.03 [dq (partly masked), ≈J=7, 7 Hz, 1H, H$^\alpha$ Ala^1], 3.83 [m, 4H, OCH_2], 3.70 [m (partly masked), 4H, OCH_2], 3.69 [s, 3H, OCH_3], 3.66 [m (partly masked), 4H, OCH_2], 3.64 [s, 4H, OCH_2], 3.37 [d, J=13.8 Hz, 1H] and 3.11 [d, J=13.9 Hz, 1H, $ArCH_2^\beta$ Mdp], 1.53 [s, 3H, CH_3^β Mdp], 1.35 [d (broad, partly masked), ≈J=7 Hz, 3H, CH_3^β Ala^1], 1.33 [d, J=7.2 Hz, 3H, CH_3^β Ala^2]. ^{13}C NMR ($CDCl_3$): 173.2, 172.9, 171.8 [C=O Ala^1, Ala^2 and Mdp], 156.2 [C=O Fmoc], 148.4, 147.9 [C^{Ar}–O Mdp], 143.7, 143.6, 141.2 [C^{Ar} Fmoc], 128.9 [C^{Ar} Mdp], 127.7, 127.1, 127.0, 125.0, 124.9, 119.9 [C^{Ar} Fmoc], 123.0, 116.3, 113.3 [C^{Ar} Mdp], 70.5, 69.4, 68.8, 68.7 [OCH_2], 67.0 [O–CH_2 Fmoc], 60.4 [C$^\alpha$ Mdp], 52.3 [OCH_3], 51.4, 48.3 [C$^\alpha$ Ala^1 and Ala^2], 47.0 [Ar–CH Fmoc], 40.8 [$ArCH_2^\beta$ Mdp], 23.9 [CH_3^β Mdp], 17.9, 17.7 [CH_3^β Ala^1 and Ala^2]. $[\alpha]_{589}^{25}$=−68.3°, $[\alpha]_{578}^{25}$=−72.3°, $[\alpha]_{546}^{25}$=−79.2°, $[\alpha]_{436}^{25}$=−146.0°, $[\alpha]_{365}^{25}$=−242.6° (*c* 0.1; MeOH). ESI$^+$ MS *m/z* (relative intensity): 830 (2) [M,K]$^+$, 814 (100) [M,Na]$^+$. Anal. for $C_{42}H_{53}N_3O_{12}\cdot0.5H_2O$: calcd C 62.98, H 6.80, N 5.25; found C 62.77, H 6.47, N 5.15.

2.2.12. Diketopiperazine *c*([18-C-6]-Mdp-Ala) (7). Crude **5a** (0.467 g; ≈0.78 mmol), contaminated by $ClCH_2OAt$ (ca. 9% mol/mol by ^{1}H NMR) (vide supra) was *N*-deprotected in TFA (5 mL)/CH_2Cl_2 (15 mL), and then the obtained crude TFA·H-[18-C-6]-Mdp-Ala-OMe (**5c**) (not characterized) (≈0.78 mmol) was directly reacted with Boc-Aib-NCA (0.715 g; 3.12 mmol) and DIPEA (0.300 mL; 1.72 mmol) in THF (1 mL) at room temperature for 96 h, under the same experimental conditions as for the preparation of **6a**. The obtained THF suspension was filtered on a Büchner funnel (water aspirator), the precipitate was washed with 5 portions of 2 mL THF and air dried, to afford 0.155 g (43%) of crude **7** as a white powder. The filtrate was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (150 mL), the solution was washed with 0.5N HCl (2×100 mL), H_2O (2×100 mL), dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was chromatographed on a 2.3×34 cm column of silica gel with eluent (G) and the combined fractions containing the desired product were treated as in the preparation of **1a** to give 0.173 g (33%) of pure Boc-Aib-[18-C-6]-Mdp-Ala-OMe (**9a**) (vide infra). The crude diketopiperazine **7** was chromatographed on a 1.3×29 cm column of silica gel with eluent (G), the combined fractions containing the desired product being treated as in the preparation of **1a**, to give 0.083 g (23%) of pure **7** as a pale yellow solid. The solid was dissolved in CH_2Cl_2 (10 mL) and EtOAc (25 mL) was added. The clear solution was refluxed, concentrated to ca. 15 mL (CH_2Cl_2 off) and left at room temperature overnight, resulting in crystallization. The crystals were filtered on a Büchner funnel, abundantly washed with EtOAc and air dried, to afford 0.057 g of pure *c*([18-C-6]-Mdp-Ala) (**7**) as white crystals. Mp=228°C. R_f=0.15 (G). ^{1}H NMR ($CDCl_3$): 6.94 [s, 1H, NH Mdp], 6.81 [d, J=7.9 Hz, 1H, ArH^5], 6.75 [s (broad), 1H, ArH^2], 6.73 [dd, ≈J=8, 1.9 Hz, 1H, ArH^6], 6.66 [d (broad), 1H, NH Ala], 4.11 [m, 4H, OCH_2], 3.94 [dq, J=7.2, 1.8 Hz, 1H, H$^\alpha$ Ala], 3.88 [m, 4H, OCH_2], 3.74 [m, 4H, OCH_2], 3.70 [m, 4H, OCH_2], 3.67 [s, 4H, OCH_2], 3.21 [d, J=13.6 Hz, 1H] and 2.72 [d, J=13.6 Hz, 1H, $ArCH_2^\beta$ Mdp], 1.56 [s, 3H, CH_3^β Mdp], 0.84 [d, J=7.1 Hz, 3H, CH_3^β Ala]. ^{13}C NMR ($CDCl_3$): 169.7, 168.2 [C=O Ala and Mdp], 148.8, 148.3 [C^{Ar}–O], 128.1, 123.5, 116.7, 114.0 [C^{Ar}], 70.7, 70.6, 70.5, 69.5, 69.4, 69.1, 69.0 [OCH_2], 60.6 [C$^\alpha$ Mdp], 51.0 [C$^\alpha$ Ala], 46.6 [$ArCH_2^\beta$ Mdp], 27.6 [CH_3^β Mdp], 20.3 [CH_3^β Ala]. $[\alpha]_{589}^{25}$=+35.9°, $[\alpha]_{578}^{25}$=+36.3°, $[\alpha]_{546}^{25}$=+42.6°, $[\alpha]_{436}^{25}$=+83.0°, $[\alpha]_{365}^{25}$=+156.3° (*c* 0.22; MeOH). Anal. for $C_{23}H_{34}N_2O_8\cdot0.5H_2O$: calcd C 58.08, H 7.42, N 5.89; found C 57.84, H 7.31, N 5.71.

2.2.13. Boc-Aib-[18-C-6]-Mdp-OH (8b). A solution of **2b** (0.529 g; 1.03 mmol) in CH_2Cl_2 (15 mL) was treated with TFA (5 mL) under the same experimental conditions and work-up as for the *N*-deprotection of **5a** (see preparation of **6a**), to afford crude TFA·H-[18-C-6]-Mdp-OH (**2d**) (not characterized) (1.03 mmol) which was directly reacted with Boc-Aib-NCA (0.945 g; 4.12 mmol) and DIPEA (0.720 mL; 4.12 mmol) in THF (7.5 mL) at 55°C for 30 h. Extraction followed by preparative TLC of the crude

product on silica gel with eluent (G) and then product extraction from silica gel, using the same work-up procedure as in the preparation of **6a**, gave 0.481 g (78%) of pure Boc-Aib-[18-C-6]-Mdp-OH (**8b**). R_f=0.25 (G). ^{1}H NMR ($CDCl_3$): 7.39 [s (broad), 1H, COOH], 7.03 [s, 1H, NH Mdp], 6.69 [s (broad), 1H, ArH^2], 6.68 [d (partly masked), J=8.4 Hz, 1H, ArH^5], 6.64 [d (broad), J=8.4 Hz, 1H, ArH^6], 5.29 [s (broad), 1H, NH Aib], 4.06 [m, 4H, OCH_2], 3.83 [m, 4H, OCH_2], 3.69 [m, 8H, OCH_2], 3.64 [s, 4H, OCH_2], 3.38 [d, J=13.8 Hz, 1H] and 3.16 [d, J=13.8 Hz, 1H, $ArCH_2^{\beta}$ Mdp], 1.61 [s, 3H, CH_3^{β} Mdp], 1.40 [s, 3H] and 1.36 [s (masked), 3H, CH_3^{β} Aib], 1.36 [s, 9H, $(CH_3)_3$ Boc]. ^{13}C NMR ($CDCl_3$): 175.9, 174.2 [COOH Mdp and C=O Aib], 154.7 [C=O Boc], 148.2, 147.6 [C^{Ar}–O], 129.4, 122.7, 115.7, 113.2 [C^{Ar}], 79.9 [O–C Boc], 70.4, 69.42, 69.39, 68.63, 68.58 [OCH_2], 60.8 [C^{α} Mdp], 56.7 [C^{α} Aib], 40.8 [$ArCH_2^{\beta}$ Mdp], 28.1 [$(CH_3)_3$ Boc], 25.8 [CH_3^{β} Mdp], 24.9, 23.0 [CH_3^{β} Aib]. $[\alpha]_{589}^{25}$=+8.8°, $[\alpha]_{578}^{25}$=+9.7°, $[\alpha]_{546}^{25}$=+11.9°, $[\alpha]_{436}^{25}$=+26.9°, $[\alpha]_{365}^{25}$=+62.1° (*c* 0.23; MeOH). Anal. for $C_{29}H_{46}N_2O_{11}\cdot 0.5H_2O$: calcd C 57.31, H 7.80, N 4.61; found C 57.28, H 7.73, N 4.19.

2.2.14. Boc-Aib-[18-C-6]-Mdp-Ala-OMe (9a). (1) To a suspension of **8b** (0.092 g; 0.15 mmol), HCl·H-Ala-OMe (0.065 g; 0.46 mmol) and HOAt (0.042 g; 0.0.30 mmol) in CH_2Cl_2 (2 mL), was added NMM (0.070 mL; 0.62 mmol) and then EDC (0.044 g; 0.23 mmol). The mixture was stirred at room temperature for 72 h, and then diluted with CH_2Cl_2 (150 mL) and 0.5N HCl (100 mL). The separated organic phase was extracted with 0.5N HCl (100 mL), H_2O (100 mL), 5% $NaHCO_3$ (2×100 mL), H_2O (2×100 mL), dried ($MgSO_4$), filtered and evaporated in vacuo, to give 0.091 g (≈86%) of a crude product which, by ^{1}H NMR, consisted of a mixture of **9a** and traces (ca. 6% mol/mol) of the side product $ClCH_2OAt$. This mixture could be directly used in further experiments. (2) From **5a**, a sample of pure **9a** was obtained after separation of the side product **7** (vide supra). R_f=0.25 (G). ^{1}H NMR ($CDCl_3$): 7.72 [d (broad), J=6.2 Hz, 1H, NH Ala], 6.74 [d, J=7.9 Hz, 1H, ArH^5], 6.65 [d (broad), ≈J=2 Hz, 1H, ArH^2], 6.62 [dd (broad), J=8.1 Hz and ≈J=2 Hz, 1H, ArH^6], 6.20 [s, 1H, NH Mdp], 4.95 [s, 1H, NH Aib], 4.53 [dq, ≈J=7.2, 7.2 Hz, 1H, H^{α} Ala], 4.11 [m, 4H, OCH_2], 3.89 [m, 4H, OCH_2], 3.77–3.67 [m, 8H, OCH_2], 3.70 [s, 3H, OCH_3], 3.67 [s, 4H, OCH_2], 3.54 [d, J=13.8 Hz, 1H] and 3.06 [d, J=13.9 Hz, 1H, $ArCH_2^{\beta}$ Mdp], 1.47 [s, 3H, CH_3^{β} Mdp], 1.43 [d, J=7.2 Hz, 3H, CH_3^{β} Ala], 1.40 [s, 9H, $(CH_3)_3$ Boc], 1.38 [s, 3H] and 1.34 [s, 3H, CH_3^{β} Aib]. ^{13}C NMR ($CDCl_3$): 173.8, 173.6, 172.8 [C=O Aib, Mdp and Ala], 155.5 [C=O Boc], 148.2, 147.8 [C^{Ar}–O], 129.8, 123.6, 117.1, 113.3 [C^{Ar}], 81.0 [O–C Boc], 70.6, 70.5, 69.5, 69.0, 68.8 [OCH_2], 59.6 [C^{α} Mdp], 57.1 [C^{α} Aib], 52.0 [OCH_3], 48.4 [C^{α} Ala], 39.1 [$ArCH_2^{\beta}$ Mdp], 28.1 [$(CH_3)_3$ Boc], 26.8 [CH_3^{β} Mdp], 24.9, 23.9 [CH_3^{β} Aib], 17.0 [CH_3^{β} Ala]. $[\alpha]_{589}^{25}$=−26.8°, $[\alpha]_{578}^{25}$=−28.8°, $[\alpha]_{546}^{25}$=−36.2°, $[\alpha]_{436}^{25}$=−59.1° (*c* 0.15; MeOH). Anal. for $C_{33}H_{53}N_3O_{12}$: calcd C 57.96, H 7.81, N 6.15; found C 58.09, H 7.82, N 5.53.

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