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An Access to 3,4-(Aminomethano)proline in Racemic and Enantiomerically Pure Form**

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Abstract: Protected racemic and enantiomerically pure 3,4-(aminomethano)prolines *rac*-**9** and (2*S*,2′*R*,3*R*,4*R*)-**9** have been prepared applying a titanium-mediated reductive cyclopropanation as a key step. Thus, cyclopropanations of *N*,*N*-dibenzylformamide with titanacyclopropanes generated in situ from racemic or enantiomerically pure *tert*-butyl *N*-Boc-3,4-dehydroprolinates *rac*-**8** or (*S*)-**8** proceed diastereoselectively, and furnish the protected racemic and enantiomerically pure diamino acid **9**. The latter was incorporated into three tripeptides containing glycyl, alanyl and phenylalanyl moieties.

Keywords: amino acids · cyclopropanes · enantiopure compounds · small ring systems · titanium

Introduction

Several important biologically active compounds contain amino acid and alkylamine fragments with a relatively rigid bicyclo[3.1.0]hexane skeleton. One of the longest known examples is 3,4-methanoproline (**1**) (Figure 1), a potent inhibitor of the proline metabolism and a potential chemical control agent in the production of hybrid wheats, which was first isolated from the American horse chestnut in 1968.[1a] Since then, numerous synthetic approaches to racemic and enantiomerically pure **1** have been developed.[1b–d] 2-Aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (**2**) which has been found to be an agonist for certain glutamate receptors,[2] is another interesting example of such bicyclic amino acids. The 3-azabicyclo[3.1.0]hexylamine (**3**) is not only an important constituent of the once popular antibiotic Trovafloxacin, which is, for example, effective against penicillin-resistant bacteria,[3] but has also been incorporated in synthetic analogues of the common antiinfectant Ciprofloxacin.[4]

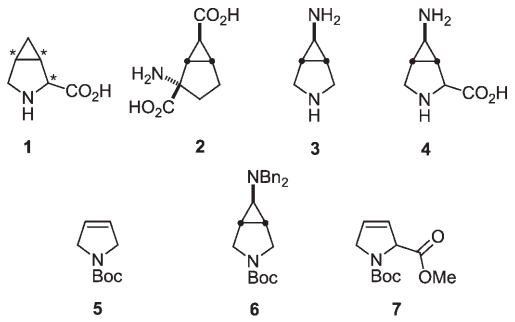

Figure 1. Examples of biologically active molecules or fragments thereof containing the bicyclo[3.1.0]hexane skeleton, **1**–**3**, the envisaged diamino acid **4** and potential starting materials **5**–**7**.

As a building block, 3,4-(aminomethano)proline (**4**) is essentially a superposition of 3,4-methanoproline (**1**) and 3-azabicyclo[3.1.0]hexylamine (**3**), and as such it might induce enhanced biological activity in comparison with those of the parent bicycles. In addition, **4** can be taken into consideration as a conformationally constrained analogue of lysine as well as of ornithine and, after guanidinylation of its γ-amino group, of arginine. Furthermore, it might serve as a scaffold for the preparation of new pharmaceutically rele-

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Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author: Structures of intermediates **A1**–**4** and **B1**–**4**.

vant compounds. Herewith we present a synthesis of the fully protected diamino acid **9** as well as the model tripeptides **17**–**23** containing the new building block **4**.

Results and Discussion

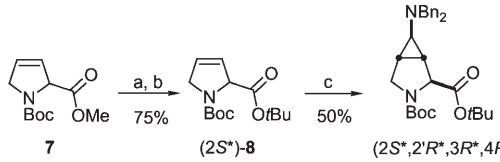
Synthesis of racemic 3,4-(aminomethano)proline: Until recently, only two rather complicated methods were commonly used for the realization of a 3-azabicyclo[3.1.0]hexylamine skeleton, the intramolecular Michael-initiated ring-closure-type cyclizations of 4-amino-substituted 3-chloro-3,6-dihydro-2*H*-pyridines[5] and cycloadditions of bromo-nitrocarbene onto *N*-benzylmaleimide followed by reduction.[3e] A new perspective was opened by the application of the reductive cyclopropanation of *N*,*N*-dialkylcarboxamides with 1,2-dicarbanionic organometallics in situ generated from organomagnesium (Grignard) reagents in the presence of stoichiometric or substoichiometric (semicatalytic) quantities of a titanium alkoxide derivative of the type $XTi(OR)_3$ (de Meijere's variant of the Kulinkovich reaction).[6] Thus, diamine **3**[7a] and its analogues[7b,c] can easily be obtained by reductive cyclopropanation of *N*,*N*-dibenzylformamide with titanacyclopropanes in situ generated from *N*-Boc-2,5-dihydropyrrole (**5**) (prepared by a ring-closing metathesis from *N*-Boc-protected diallylamine) in an orthogonally bisprotected form **6**, on an up to 0.6 mol scale in 61–87% yield.

The easiest access to the bicyclic diamino acid **4** would be by selective deprotonation of the diamine **6** (which was prepared as indicated above) in the 2-position, followed by reaction with any suitable electrophile (cf. ref. [8]). Unfortunately, this approach turned out to be unsuccessful: no selective deprotonation of **6** was observed, presumably because of the enhanced acidity of the benzylic and aminocyclopropyl protons.

Adopting a procedure developed by Helmchen et al.,[9] *N*-Boc-2,5-dihydropyrrole (**5**) was converted into the *N*-Boc-3,4-dihydroprolinate (**8**). Titanium-mediated aminocyclopropanation of the latter gave a complex mixture of products, mainly of oligomeric nature, indicating that the methoxycarbonyl function is not inert under such conditions.

Fortunately, the reactivities of both, ester as well as amide carbonyl groups can significantly be influenced by steric bulk around them. For example, the enhanced steric requirements of a *tert*-butoxy group can suppress the reaction of a carbonyl function with a titanacyclopropane.[10] Thus, in intermolecular competition reactions between *N*,*N*-dibenzylformamide and *tert*-butyl acetate with a titanacyclopropane intermediate, the former won to yield only the corresponding cyclopropylamine derivative, and only the aminocyclopropyl derivative was isolated from the reaction of succinic acid *tert*-butyl monoester monoamide while the *tert*-butyl ester stayed intact.[10]

Therefore, the methyl substituent in the ester **7** was replaced by a *tert*-butyl group, which actually acts as a protecting group: Basic hydrolysis of **7** followed by treatment with *tert*-butyl bromide under phase transfer conditions according to a published protocol (Scheme 1)[11] furnished the racemic *tert*-butyl ester (2*S**)-**8** in 75% yield over two steps. Indeed, the reductive cyclopropanation of (2*S**)-**8** yielded the target



Scheme 1. Synthesis of protected, racemic 3,4-(aminomethano)proline [(2*S**,2′*R**,3*R**,4*R**)-**9**]. a) KOH, EtOH/H_2O, 70 °C, 4 h, then citric acid to pH 4. b) $Et_3NBn^+Cl^-$, K_2CO_3, *t*BuBr, $MeCONMe_2$, 55 °C, 21 h. c) $MeTi(OiPr)_3$, Bn_2NCHO, *c*HexMgBr, THF, 25 °C, 16 h.

threefold orthogonally protected diamino acid (2*S**,2′*R**,3*R**,4*R**)-**9** in 50% yield after chromatographic purification. Fortunately, only one diastereomer of (2*S**,2′*R**,3*R**,4*R**)-**9** was formed in which the *tert*-butoxycarbonyl, the *N*,*N*-dibenzylamino group and the two cyclopropane bridgehead protons are *cis*-oriented with respect to each other, as disclosed by an NOE-NMR experiment. The high diastereoselectivity in the transformation of (2*S**)-**8** evidently must be due to the considerable steric bulk of the *tert*-butyl ester group. Indeed, according to the generally accepted mechanism of this reaction,[12] the intermediate **A1** (Figure 2, only two out of eight possible isomers are shown,

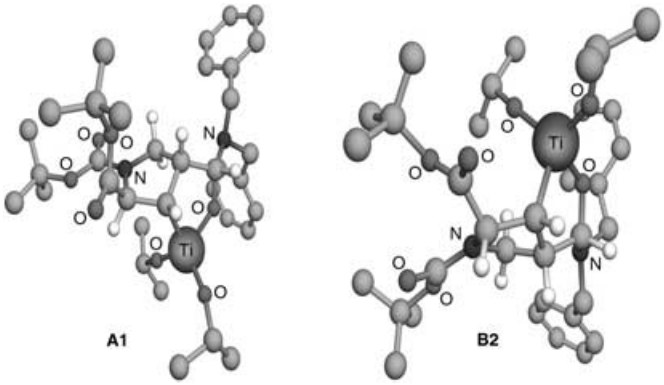


Figure 2. Structure of two out of eight conceivable sterioisomeric titanabicyclic intermediates formed en route to the aminocyclopropanated dehydroproline ester **8** (chosen as to show the smallest and the largest steric encumberance) as computed at the B3LYP/6-31G* level of theory with the Spartan program package.[13]

see Supporting Information for all structures) leading to the obtained (2*S**,2′*R**,3*R**,4*R**)-diastereomer, ought to be more stable than the intermediate **B2** which should give rise to another diastereomer. The results from calculations confirm this hypothesis. For the intermediates of type **A** (titanium and ester group in *trans* relationship) lower enthalpies of formation at the PM3 level of theory have been predicted than for those of type **B** (titanium and ester group on the same side, see Table 1). Because of the cyclic structure of the resulting imine moiety the attack of the titanium-bound

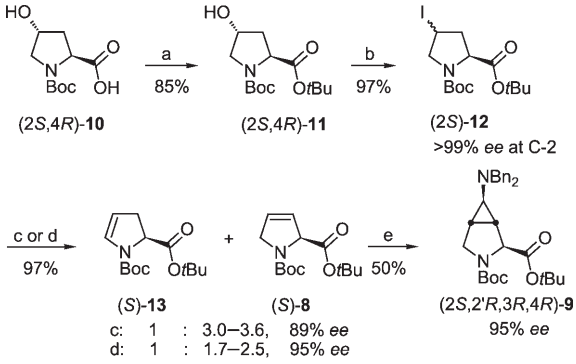
Table 1. Calculated enthalpies of formation ΔH_f for the azaoxatitanabicyclo[3.3.0] intermediates at the PM3-level of theory. Calculations were run on optimized (B3LYP/6-31G*) structures. See Supporting Information for the structures of **A1** to **B4**.

	ΔH_f [kcal^{-1}mol^{-1}]			
	1	**2**	**3**	**4**
A	−599.2	−596.5	−592.6	−599.4
B	–[a]	−589.1	−592.3	−595.5

[a] Geometry optimization failed to converge.

carbon atom on the imine unit is required to come from the front side as opposed to the course of the reaction in the case of acyclic imine intermediates. This leads to retention of the configuration at the titanium–carbon bond.[12]

Synthesis of protected 3,4-(aminomethano)proline 9 in enantiomerically pure form: As modern peptide chemistry deals almost exclusively with enantiomerically pure amino acids, a simple approach to the protected diamino acid **9** as well as to its synthetic precursor **7** in their enantiomerically pure forms was elaborated. Towards that end (2*S*,4*R*)-*N*-(*tert*-butoxycarbonyl)-4-hydroxyproline [(2*S*,4*R*)-**10**] [prepared from commercially available and inexpensive (2*S*,4*R*)-4-hydroxyproline according to a published procedure,[14] was converted to its *tert*-butyl ester (2*S*,4*R*)-**11** applying the method mentioned above.[11] The hydroxy function in (2*S*,4*R*)-**11** was transformed into the iodide by a Mitsunobu reaction[15] with methyl iodide (Scheme 2). Surprisingly, in contrast to the adopted original procedure for the analogous methyl ester,[16] racemization at C-4 occurred affording (2*S*)-**12** as a mixture of two diastereomers. However, the configuration at C-2 was retained with an *ee* $\geq$99%. Dehydroiodination of this mixture using diazabicyclo[5.4.0]undecene (DBU) proceeded virtually quantitatively and yielded the two regioisomers (*S*)-**8** and (*S*)-**13** which could be separated by column chromatography on silica gel. The composition of the reaction mixture as well as the enantiomeric purity of the product strongly depends on the conditions of this dehydroiodination. Thus, when DBU was added in one portion to a solution of (2*S*)-**12** in toluene, and the mixture then heated up to 85 °C, a ratio of the undesired (2*S*)-**13** to the desired regioisomer (2*S*)-**8** of 1:3.0 to 1:3.6[17] could be reached, but with an enantiomeric excess of only 89%.[18] On the other hand, slow addition of the base over a period of three hours to the solution of (*S*)-**12**, kept at 85 °C, gave a mixture of (*S*)-**13** and (*S*)-**8** in ratios of only 1:1.7 to 1:2.5,[17] but with an enantiomeric excess of $\geq$95% (Scheme 2). In analogy to the aminocyclopropanation of (2*S**)-**8**, that of (*S*)-**8** furnished only one enantiomer of the threefold orthogonally protected diamino acid (2*S*,2′*R*,3*R*,4*R*)-**9** in 50% yield (Scheme 2). To the best of our knowledge, apart from several moderately successful titanium-mediated reductive cyclopropanations with chirally modified titanium reagents,[6a,19] there is only one example in the literature for a cyclopropanation of a chiral amide with an achiral titanium reagent;[20] however, the enantiomeric excess in the obtained cyclopropanol was only 50%.



Scheme 2. Synthesis of trisprotected, enantiomerically pure 3,4-(aminomethano)proline (2*S*,2′*R*,3*R*,4*R*)-**9**. a) $Et_3NBn^+Cl^-$, K_2CO_3, *t*BuBr, $MeCONMe_2$, 55 °C, 21 h. b) PPh_3, DIAD, MeI, THF, 0 → 25 °C 17 h. c) DBU (in one portion), toluene, 25 → 85 °C, 8 h. d) 85 °C, DBU (added over 3 h). e) $MeTi(OiPr)_3$, Bn_2NCHO, *c*HexMgBr, THF, 25 °C, 16 h.

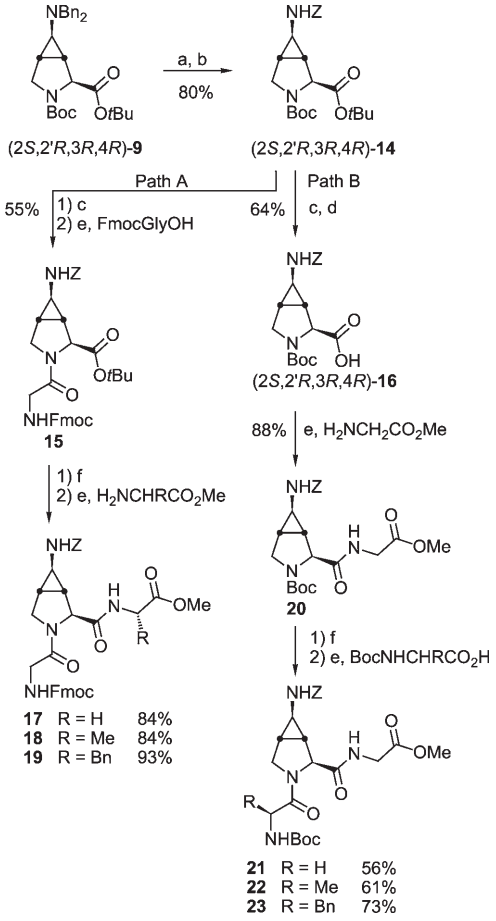
An attempted titanium-mediated cyclopropanation under the same conditions of the enamine (*S*)-**13** failed completely, and only unchanged starting material could be recovered.

Incorporation of 3,4-(aminomethano)proline moieties into tripeptides: In order to demonstrate the feasibility of incorporating the new proline analogue **4** into oligopeptides, the model tripeptides **17**–**23** were synthesized starting from the fully protected diamino acid **9**.

As the removal of *N*-benzyl protecting groups often may cause problems, the two in (2*S*,2′*R*,3*R*,4*R*)-**9** were replaced by the more easily hydrogenolytically cleavable benzyloxycarbonyl (*Z*-group). Thus, palladium-catalyzed hydrogenolysis of (2*S*,2′*R*,3*R*,4*R*)-**9** followed by treatment with Z-*O*-succinimide furnished (2*S*,2′*R*,3*R*,4*R*)-**14** in 80% yield (Scheme 3).

Two different approaches were examined for the preparation of tripeptides from (2*S*,2′*R*,3*R*,4*R*)-**14**. In the first one, the secondary amine function was coupled first, followed by a reaction on the acid group (Scheme 3, path A). This was realized by selective removal of the *N*-Boc-group in the presence of the *tert*-butyl ester function by treatment with hydrogen chloride in ethyl acetate. In contrast to the published procedure,[21] this deprotection of (2*S*,2′*R*,3*R*,4*R*)-**14** proceeded very slowly (11 h) and was accompanied by partial cleavage of the *tert*-butyl ester function. However, after peptide coupling of this crude product with *N*-Fmoc-glycine using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl), 7-aza-1-hydroxybenzotriazole (HOAt)[22] and 2,4,6-collidine, the dipeptide **15** was obtained in 55% yield over two steps. Cleavage of the *tert*-butyl ester in the latter with trifluoroacetic acid (TFA) followed by peptide coupling with glycine-, alanine- and phenylalanine methyl ester, respectively, furnished the tripeptides **17**, **18** and **19** in 84, 84 and 93% yield, respectively (Scheme 3, path A).

Along the second route, peptide coupling on the carboxylic acid group was envisaged prior to attaching an aminoacyl residue on the secondary amine function (Scheme 3, path



Scheme 3. Incorporation of 3,4-(aminomethano)proline into some model tripeptides. a) H_2, Pd/C, MeOH, 25 °C, 2 d. b) ZOSu, $NaHCO_3$, acetone/H_2O, 1 h. c) HCl in EtOAc, EtOAc, 0 → 25 °C, 11 h. d) Boc_2O, NaOH, $NaHCO_3$, H_2O, 0 → 25 °C, 18 h. e) EDC·HCl, HOAt, 2,4,6-collidine, CH_2Cl_2, 0 → 25 °C, 18 h. f) TFA, 25 °C, 45 min.

B). As a *tert*-butyl ester cannot be selectively cleaved in the presence of a Boc group, in (2*S*,2′*R*,3*R*,4*R*)-**14** both were removed with hydrogen chloride in ethyl acetate. Reprotection of the amino function with Boc_2O afforded (2*S*,2′*R*,3*R*,4*R*)-**16**, albeit in 64% yield only. This acid was subjected to peptide coupling under the conditions described above furnishing the dipeptide **20** in 88% yield. Boc-deprotection of **20** followed again by peptide coupling with *N*-Boc-glycine, -alanine and -phenylalanine, respectively, led to tripeptides **21**, **22** and **23** in 56, 61 and 73% yield, respectively (Scheme 3, path B).

Conclusion

A synthetic route to diastereomerically and enantiomerically pure 3,4-(aminomethano)proline **4** has been developed. This diamino acid **4** in its triprotected form (2*S*,2′*S*,3*R*,4*R*)-**9** with a distance of 4.24 Å between the two nitrogen atoms (Figure 3), can serve as a scaffold for pharmacophoric groups or as a proline analogue inducing a modified hairpin

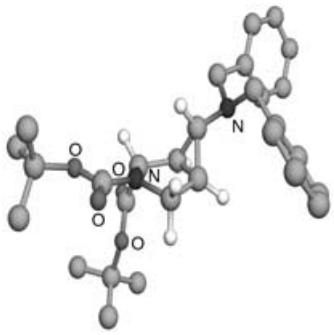


Figure 3. The structure of *tert*-butyl N_α-Boc-3,4-(*N*,*N*-dibenzylaminomethano)prolinate [(2*S*,2′*R*,3*R*,4*R*)-**9**] as computed at the B3LYP/6–31G* level of theory with the Spartan program package.[13]

motif in oligopeptides. The applicability of (2*S*,2′*S*,3*R*,4*R*)-**9** as a building block has been demonstrated by the synthesis of three simple model tripeptides.

Experimental Section

General remarks: $[\alpha]_D^{20}$ values: Polarimeter 241 Perkin–Elmer, IR: Bruker Vector 22 (FT-IR) spectrophotometer, measured as KBr pellets or oils between NaCl plates. NMR spectra were recorded on a Varian Mercury 200 (200 MHz for ^1H and 50.2 MHz for ^{13}C NMR), a Bruker AM 250 (250 MHz for ^1H and 62.9 MHz for ^{13}C NMR) or a Varian UNITY 300 (300 MHz for ^1H and 75.5 MHz for ^{13}C NMR) instrument. Proton chemical shifts are reported in ppm relative to residual peaks of deuterated solvents. Multiplicities were determined by DEPT (distortionless enhancement by polarisation transfer), APT (attached proton test), NOE (nuclear Overhauser effect) measurements or HMQC (heteronuclear multiple quantum coherence) measurements. MS (EI at 70 eV or DCI with NH_3): Finnigan MAT 95 spectrometer. MS (ESI): Finnigan LCQ. MS (HR-EI): Finnigan MAT 95 spectrometer, pre-selected ion peak matching at *R* ca. 10000 to be within ±2 ppm of the exact masses. MS (HR-ESI): APEX IV 7T FTICR, Bruker Daltonic spectrometer. Melting points: Büchi 510 capillary melting point apparatus, values are uncorrected. HPLC: Knauer Nucleosil-100 C18 (analytical, 5 μm, 3 mm × 250 mm). TLC: Macherey–Nagel precoated sheets, 0.25 mm Sil G/UV_{254}. Column chromatography: Merck silica gel, grade 60, 230–400 mesh. Elemental analyses: Mikroanalytisches Laboratorium des Instituts für Organische und Biomolekulare Chemie, Universität Göttingen. Starting materials: 3-*tert*-butoxycarbonyl-6-*exo*-(*N*,*N*-dibenzylamino)-3-azabicyclo-[3.1.0]hexane (**6**),[7a] *N*-Boc-pyrroline-2-carboxylic acid methylester **7**,[9] 7-aza-1-hydroxybenzotriazole[22] and methyltitanium triisopropoxide[23] were prepared according to published procedures. *N*-(Benzyloxycarbonyloxy)succinimide was recrystallized from hexane/EtOAc prior to use. Anhydrous THF and toluene were obtained by distillation from sodium/benzophenone, CH_2Cl_2 from P_4O_{10}. All other chemicals were used as commercially available. All operations in anhydrous solvents were performed under a nitrogen atmosphere in flame-dried glassware. Organic extracts were dried over $MgSO_4$.

General procedure for the titanium-mediated aminocyclopropanation of alkenes with dibenzylformamide (GP 1): *c*HexMgBr (1.2–2.2 equiv, 1.38 M solution in Et_2O) was added over a period of 1 h (syringe pump) to a solution of *N*,*N*-dibenzylformamide (1.1–1.5 equiv), $MeTi(OiPr)_3$ (1.2 equiv) and the respective alkene (1.0 equiv) in anhydrous THF (0.2–1.0 M) and the solution was stirred for 16 h. H_2O (1 mL) was added, and the reaction mixture was stirred until the resulting precipitate turned white (10 min–1 h). The suspension was filtered, and the solid components were washed with Et_2O. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography on silica gel.

General procedure for the transformation of a carboxylic acid into the corresponding *tert*-butyl ester (GP 2): A suspension of the carboxylic acid (1.0 equiv), benzyltriethylammonium chloride (1.0 equiv), K_2CO_3 (26 equiv) and *tert*-butyl bromide (40 equiv) in $MeCONMe_2$ (0.2 M) was vigorously stirred at 55 °C for 21 h. After cooling to ambient temperature, H_2O was added until a clear solution was obtained, and the reaction mixture was extracted with Et_2O (3×). The combined organic extracts were dried and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel and, if necessary, recrystallized.

General procedure for the peptide coupling of amino acids (GP 3): The respective *N*-protected amino acid or peptide, respectively (1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (0.05–0.3 M), and the solution cooled to 0 °C. EDC·HCl (1.05 equiv), HOAt (1.05 equiv), the respective *N*-deprotected amino acid hydrochloride or peptide hydrochloride, respectively (1.0–1.05 equiv) and 2,4,6-collidine (4.0 equiv) were added in this order. The resulting clear solution was slowly warmed to ambient temperature and stirred for an additional 18 h. The reaction mixture was washed with H_2O (2×), 1 M aq. $KHSO_4$ (2×), 3% aq. $NaHCO_3$ (2×) and H_2O (2×) and dried. The volatile compounds were evaporated in vacuo and the residue was purified by column chromatography on silica gel.

General procedure for the *N*-Boc or *tert*-butyl deprotection of dipeptides (GP 4): The corresponding dipeptide (250 μmol) was treated with TFA (0.5 mL) and stirred for 30 min. All volatile compounds were evaporated in vacuo. Toluene (2 mL) was added to the residue, and the mixture was concentrated under reduced pressure. This operation was repeated three times. The residual oily amine trifluoroacetate or acid, respectively, was used in the subsequent peptide coupling reaction without further purification.

***tert*-Butyl *N*-Boc-3,4-dehydroprolinate [(2*S**)-8]**: Methyl *N*-Boc-3,4-dehydroprolinate (**7**) (2.31 g, 10.2 mmol) in EtOH (10 mL) was added to a solution of KOH (2.00 g, 35.7 mmol) in H_2O (5 mL) and the resulting mixture was stirred at 70 °C for 4 h. After cooling to ambient temperature all volatile compounds were evaporated in vacuo. The residue was taken up in H_2O (10 mL) and acidified with 10% aq. citric acid up to pH 4. The reaction mixture was extracted with Et_2O (5×25 mL). The combined organic extracts were dried and evaporated under reduced pressure to yield crude *N*-Boc-2,5-dihydropyrrole-2-carboxylic acid (1.78 g). ^{1}H NMR (250 MHz, $CDCl_3$, rotamers): δ = 1.44, 1.49 [s, 9H, $C(CH_3)_3$], 4.01–4.38 (m, 2H, 5-H), 4.91–5.00, 5.02–5.13 (m, 1H, 2-H), 5.69–5.80, 5.80–5.89 (m, 1H, 4-H), 5.91–6.07 (m, 1H, 3-H), 10.93 (brs, 1H, COOH); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT, rotamers): δ = 28.2, 28.3 [+, $C(CH_3)_3$], 53.3, 53.6 (−, C-5), 66.1, 66.3 (+, C-2), 80.7, 81.1 [C_{quat}, $C(CH_3)_3$], 124.3, 124.6 (+, C-4), 128.9, 129.7 (+, C-3), 153.5, 154.9 (C_{quat}, NCO_2), 174.3, 175.7 (C_{quat}, C-1).

This acid was treated with benzyltriethylammonium chloride (1.90 g, 8.35 mmol), K_2CO_3 (30.0 g. 217 mmol) and *tert*-butyl bromide (38.8 mL, 334 mmol) in $MeCONMe_2$ (40 mL) according to GP 2. Column chromatography of the residue (40 g silica gel, 2×20 cm column, hexane/Et_2O 1:1, R_f = 0.70) furnished (2*S**)-**8** (2.06 g, 75%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, rotamers): δ = 1.41, 1.42, 1.44 [s, 18H, $C(CH_3)_3$], 4.04–4.16, 4.16–4.26 (m, 2H, 5-H), 4.74–4.80, 4.82–4.88 (m, 1H, 2-H), 5.63–5.73 (m, 1H, 4-H), 5.84–5.94 (m, 1H, 3-H); ^{13}C NMR (50.3 MHz, $CDCl_3$, APT, rotamers): δ = 28.0, 28.3, 28.4 [+, $C(CH_3)_3$], 53.3, 53.5 (−, C-5), 67.1, 67.2 (+, C-2), 79.7, 79.9, 81.3, 81.4 [−, $C(CH_3)_3$], 125.2, 125.3 (+, C-4), 128.89, 128.93 (+, C-3), 153.5 (−, NCO_2), 169.5 (−, C-1); IR (film): $\tilde{\nu}$ = 2980 (C-H), 2933 (C-H), 2868 (C-H), 1750 (C=O), 1719 (C=O), 1394 (*t*Bu), 1369 (*t*Bu), 1318, 1283, 1161, 1096 cm^{-1}; MS (EI): *m*/*z* (%): 269 (2) [M^+], 213 (3) [$M^+-C_4H_8$], 196 (2) [M^+-OtBu], 168 (34) [M^+-CO_2tBu], 140 (8), 112 (100) [$M^+-CO_2tBu-C_4H_8$], 68 (76) [M^+-2CO_2tBu+H], 57 (98) [tBu$^+$]; HRMS (EI): *m*/*z*: calcd for $C_{14}H_{23}NO_4$: 269.1627 [M^+], correct mass; elemental analysis calcd (%) for $C_{14}H_{23}NO_4$ (269.34): C 62.43, H 8.61, N 5.20; found C 62.29, H 8.48, N 5.03.

***tert*-Butyl N_α-Boc-3,4-(*N*,*N*-dibenzylaminomethano)prolinate [(2*S**,2′*R**,3*R**,4*R**)-9]**: According to GP 1, *tert*-butyl *N*-Boc-3,4-dehydroprolinate [(2*S**)-**8**] (2.69 g, 10.0 mmol) was treated with $MeTi(OiPr)_3$ (2.88 mL, 12.0 mmol), Bn_2NCHO (2.93 g, 13.0 mmol) and *c*HexMgBr (14.5 mL, 20.0 mmol, 1.38 M solution in Et_2O) in anhydrous THF (10 mL). Column chromatography of the residue (300 g silica gel, 4× 35 cm column, hexane/Et_2O 5:1, R_f = 0.25) yielded (2*S**,2′*R**,3*R**,4*R**)-**9** (2.37 g, 50%) as a pale yellow, highly viscous oil. ^{1}H NMR (250 MHz, $CDCl_3$, rotamers): δ = 1.27–1.53 (m, 2H, 3,4-H), 1.40, 1.42, 1.43 [s, 18H, $C(CH_3)_3$], 1.65–1.75 (m, 1H, 1′-H), 3.35–3.50 (m, 2H, 5-H), 3.56–3.75 (m, 4H, NCH_2Ph), 3.96, 4.07 (s, 1H, 2-H), 7.18–7.40 (m, 10H, Ph-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT, rotamers): δ = 24.4, 25.0 (+, C-4*), 27.9, 28.3, 28.4 [+, $C(CH_3)_3$], 29.0, 29.6 (+, C-3*), 46.5, 46.6 (+, C-1′), 48.0, 48.2 (−, C-5), 59.0, 59.1 (−, NCH_2Ph), 61.5, 61.7 (+, C-2), 79.8, 79.9, 81.1 [C_{quat}, $C(CH_3)_3$], 127.1, 128.2, 129.3 (+, Ph-C), 138.38, 138.44 (C_{quat}, Ph-C), 154.1 (C_{quat}, NCO_2), 170.9 (C_{quat}, C-1); IR (KBr): $\tilde{\nu}$ = 2976 (C-H), 2930 (C-H), 1741 (C=O), 1700 (C=O), 1455, 1392 (*t*Bu), 1366 (*t*Bu), 1249, 1155, 1113, 902, 751, 701 cm^{-1}; MS (EI): *m*/*z* (%): 478 (5) [M^+], 421 (1) [M^+-tBu], 387 (5) [M^+−Bn], 377 (6) [M^+-CO_2tBu], 331 (5) [M^+−Bn−C_4H_8], 321 (15) [M^+-CO_2tBu−C_4H_8], 275 (29) [M^+−Bn−2C_4H_8], 231 (18) [M^+−Bn−CO_2−2C_4H_8], 91 (100) [Bn$^+$], 57 (35) [tBu$^+$]; HRMS (EI): *m*/*z*: calcd for $C_{29}H_{38}N_2O_4$: 478.2832 [M^+], correct mass; elemental analysis calcd (%) for $C_{29}H_{38}N_2O_4$ (478.63): C 72.77, H 8.00, N 5.85; found C 72.87, H 7.85, N 5.74.

***tert*-Butyl (2*S*,4*R*)-*N*-Boc-4-hydroxyprolinate [(2*S*,4*R*)-11]**: (2*S*,4*R*)-*N*-Boc-4-Hydroxy-proline [(2*S*,4*R*)-**10**] (8.09 g, 35.0 mmol) was treated with benzyltriethylammonium chloride (7.97 g, 35.0 mmol), K_2CO_3 (126 g, 910 mmol) and *tert*-butyl bromide (163 mL, 1.40 mol) in $MeCONMe_2$ (175 mL) according to GP 2. The residue was purified by column chromatography (250 g silica gel, 5×15 cm column, EtOAc/hexane 1:1, R_f = 0.33) and then recrystallized from pentane yielding (2*S*,4*R*)-**11** (8.53 g, 85%) as a colorless, voluminous solid. M.p. 66–68 °C; $[\alpha]_D^{20}$ = −60.0° (*c* = 0.5, $CDCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, rotamers): δ = 1.46, 1.50 [s, 18H, $C(CH_3)_3$], 1.94–2.10 (m, 1H, 3-H), 2.18–2.40 (m, 1H, 3-H), 3.40–3.74 (m, 2H, 5-H), 4.11–4.25 (m, 1H, 4-H*), 4.25–4.36 (m, 1H, 2-H*); ^{13}C NMR (50.3 MHz, $CDCl_3$, APT, rotamers): δ = 27.8, 27.9, 28.3 [+, $C(CH_3)_3$], 37.7, 38.7 (−, C-3), 55.7, 56.1 (−, C-5), 58.8 (+, C-4), 70.4, 71.4 (+, C-2), 80.2, 80.3, 82.4, 82.5 [−, $C(CH_3)_3$], 153.8, 154.5 (−, NCO_2), 174.4, 174.5 (−, C-1); IR (KBr): $\tilde{\nu}$ = 3433 (br, O-H), 3001 (C-H), 2979 (C-H), 2933 (C-H), 2880 (C-H), 1740 (C=O), 1673 (C=O), 1415 (*t*Bu), 1367 (*t*Bu), 1344, 1302, 1180, 1130, 1090, 1006, 974, 906, 853, 773 cm^{-1}; MS (EI): *m*/*z* (%): 287 (2) [M^+], 269 (5) [M^+-H_2O], 214 (2) [M^+-OtBu], 186 (50) [M^+-CO_2tBu], 158 (12) [$M^+-OtBu-C_4H_8$], 130 (100) [$M^+-CO_2tBu-C_4H_8$], 86 (73) [$M^+-2CO_2-tBu-C_4H_8$], 68 (10) [$M^+-2CO_2-tBu-C_4H_8-H_2O$], 57 (75) [$tBu^+$]; elemental analysis calcd (%) for $C_{14}H_{25}NO_5$ (287.36): C 58.52, H 8.77, N 4.87; found C 58.35, H 8.77, N 4.87.

***tert*-Butyl (2*S*)-*N*-Boc-4-iodoprolinate [(2*S*)-12]**: A solution of *tert*-butyl (2*S*,4*R*)-*N*-Boc-4-hydroxyprolinate [(2*S*,4*R*)-**11**] (5.03 g, 17.5 mmol) in anhydrous THF (100 mL) was cooled to 0 °C. After addition of triphenylphosphane (6.42 g, 24.5 mmol) and diisopropyl azodicarboxylate (4.07 mL, 21.0 mmol), methyl iodide (1.31 mL, 21.0 mmol) was added dropwise. The resulting mixture was slowly warmed to ambient temperature and stirred for an additional 17 h. The volatile compounds were evaporated in vacuo. Column chromatography of the residue (250 g silica gel, 5×15 cm column, EtOAc/hexane 1:7, R_f = 0.39, crude product dissolved in CH_2Cl_2) furnished (2*S*)-**12** (6.70 g, 16.9 mmol, 97%) as a colorless solid. M.p. 86–88 °C; $[\alpha]_D^{20}$ = −36.3° (*c* = 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, rotamers): δ = 1.42, 1.44, 1.46, 1.48 [s, 18H, $C(CH_3)_3$], 2.20–2.42, 2.47–2.63, 2.78–2.93 (m, 2H, 3-H), 3.57–3.71, 3.74–3.82, 3.88–3.96, 3.96–4.37 (m, 4H, 2,4,5-H); ^{13}C NMR (50.3 MHz, $CDCl_3$, APT, rotamers): δ = 12.1, 13.0, 15.9 (+, C-4), 27.9, 28.0, 28.3 [+, $C(CH_3)_3$], 41.9, 42.2, 42.9, 43.2 (−, C-3), 56.7, 57.0, 57.4, 57.6 (−, C-5), 59.3, 59.4, 59.6 (+, C-2), 80.5, 81.5, 81.6 [−, $C(CH_3)_3$], 153.2 (−, NCO_2), 170.4, 171.3 (−, C-1); IR (KBr): $\tilde{\nu}$ = 2985 (C-H), 2975 (C-H), 2935 (C-H), 2886 (C-H), 1725 (C=O), 1688 (C=O), 1412 (*t*Bu), 1367 (*t*Bu), 1299, 1259, 1161, 1143, 996, 905, 844, 764, 590 cm^{-1} (C-I); MS (DCI): *m*/*z* (%): 415 (20) [M^++NH_4], 398 (29) [M^++H], 359 (25) [M^++$NH_4-C_4H_8$], 289 (32) [M^++NH_3−I], 272 (100) [M^+−I], 233 (41) [M^++NH_3−I−C_4H_8]; elemental analysis calcd (%) for $C_{14}H_{24}INO_4$ (397.25): C 42.33, H 6.09, N 3.53; found C 42.17, H 5.98, N 3.50.

***tert*-Butyl (*S*)-*N*-Boc-3,4-dehydroprolinate [(*S*)-8] and *tert*-butyl (*S*)-*N*-Boc-4,5-dehydroprolinate [(*S*)-13]**: A solution of *tert*-butyl (2*S*)-*N*-Boc-4-

iodoprolinate [(2*S*)-**12**] (14.9 g, 37.5 mmol) in anhydrous toluene (200 mL) was warmed to 85 °C. A solution of DBU (5.65 mL, 37.5 mmol) in anhydrous toluene (175 mL) was added dropwise over a period of 3 h, and the resulting solution was stirred at 85 °C for an additional 3 h. After cooling to ambient temperature, the mixture was filtered through Celite and the solvent evaporated in vacuo. The residue was taken up in a minimal amount of hexane/EtOAc 20:1, again filtered through Celite and concentrated under reduced pressure. The residue was purified by column chromatography (400 g silica gel, 5×25 cm hexane/EtOAc 20:1). The obtained mixed fraction of (*S*)-**8** and (*S*)-**13** was again separated by column chromatography (75 g silica gel, 3×15 cm, hexane/EtOAc 20:1). The product (*S*)-**8** (6.98 g, 69%) and its regioisomer (*S*)-**13** (2.82 g, 28%) were obtained as colorless, viscous oils. (*S*)-**8**: R_f (hexane/EtOAc 2:1) = 0.34; $[\alpha]_D^{20} = -75.5°$ ($c = 1.00$, $CHCl_3$); the spectroscopic data were consistent with those described above for (*S**)-**8**. (*S*)-**13**: R_f (hexane/EtOAc 2:1) = 0.55; ^{1}H NMR (300 MHz, $CDCl_3$, rotamers): $\delta = 2.47$, 2.48, 2.50 [s, 18H, $C(CH_3)_3$], 2.54–2.68 (m, 1H, 3-H), 2.94–3.14 (m, 1H, 3-H), 4.45, 4.52 (dd, $^3J = 11.7$, 4.7 Hz, 1H, 2-H), 4.84–4.90, 4.90–4.96 (m, 1H, 4-H), 6.47–6.52, 6.62–6.67 (m, 1H, 5-H); ^{13}C NMR (50.3 MHz, $CDCl_3$, APT, rotamers): $\delta = 27.9$, 28.2, 28.4 [+, $C(CH_3)_3$], 34.3, 35.6 (−, C-3), 58.5, 58.7 (+, C-2), 80.5, 80.9, 81.3 [−, $C(CH_3)_3$], 104.9 (+, C-4), 130.0 (+, C-5), 151.3, 151.6 (−, NCO_2), 170.9 (−, C-1); IR (film): $\tilde{\nu} = 2978$ (C-H), 2933 (C-H), 1742 (C=O), 1708 (C=O), 1391 (*t*Bu), 1368 (*t*Bu), 1156 cm^{-1}; MS (EI): *m*/*z* (%): 269 (4) [M^+], 169 (6) [$M^+ - CO_2 - C_4H_8$], 140 (2), 113 (28) [$M^+ - CO_2 - 2C_4H_8$], 68 (74) [$M^+ - 2CO_2 - C_4H_8$], 57 (100) [tBu$^+$]; HRMS (EI): *m*/*z*: calcd for $C_{14}H_{23}NO_4$: 269.1627 [M^+], correct mass.

***tert*-Butyl (2*S*,2′*R*,3*R*,4*R*)-*N*$_\alpha$-Boc-3,4-(dibenzylaminomethano)prolinate [(2*S*,2′*R*,3*R*,4*R*)-9]**: $[\alpha]_D^{20} = -36.6°$ ($c = 0.95$, $CHCl_3$); the spectroscopic data were identical with those described above for (2*S**,2′*R**,3*R**,4*R**)-**9**.

***tert*-Butyl (2*S*,2′*R*,3*R*,4*R*)-*N*$_\alpha$-Boc-3,4-(Z-aminomethano)prolinate [(2*S*,2′*R*,3*R*,4*R*)-14]**: A suspension of Pd (248 mg, 5 mol%, 10% on charcoal) in MeOH (20 mL) was stirred under an atmosphere of H_2 for 15 min. A solution of (2*S*,2′*R*,3*R*,4*R*)-**9** (2.31 g, 4.83 mmol) in MeOH (30 mL) was added and the resulting mixture was shaken under an atmosphere of H_2 for 2 d. The reaction mixture was filtered through Celite, and the solvent evaporated in vacuo. The residue was dissolved in acetone/H_2O (15 mL/10 mL), treated with $NaHCO_3$ (812 mg, 9.66 mmol) and ZOSu (1.32 g, 5.31 mmol), and the mixture stirred for 1 h. The volatile compounds were evaporated in vacuo. The residual fraction was diluted with H_2O (10 mL) and extracted with Et_2O (3×20 mL). 3-Dimethylamino-1-propylamine (302 μL, 2.42 mmol) was added to the combined organic phases, and the resulting solution was stirred for 10 min. The reaction mixture was washed with 1 M $KHSO_4$ (20 mL), sat. $NaHCO_3$ solution (20 mL) and H_2O (20 mL), dried and evaporated in vacuo. Column chromatography of the residue (70 g silica gel, 3×15 cm, hexane/Et_2O 1:1, $R_f = 0.16$) furnished (2*S*,2′*R*,3*R*,4*R*)-**14** (1.68 g, 80%) as a colorless, highly viscous oil. $[\alpha]_D^{20} = -34.5°$ ($c = 1.09$, $CHCl_3$); ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): $\delta = 1.44$, 1.51 [s, 18H, $C(CH_3)_3$], 1.70–1.82 (m, 2H, 3,4-H), 2.45–2.50 (m, 1H, 1′-H), 3.56 (dd, $^2J = 11.7$, $^3J = 4.5$ Hz, 1H, 5-H), 3.66–3.74 (m, 1H, 5-H), 4.31 (s, 1H, 2-H), 4.87 (br s, 1H, NH), 5.33 (s, 2H, OCH_2Ph), 7.28–7.42 (m, 5H, Ph-H); ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, APT, 100 °C): $\delta = 27.9$, 28.1 [+, $C(CH_3)_3$, C-4*], 28.3 (+, C-3*), 32.7 (+, C-1′), 47.7 (−, C-5), 61.4 (+, C-2), 66.6 (−, OCH_2Ph), 79.7, 81.3 [−, $C(CH_3)_3$], 127.5, 127.8, 128.2 (+, Ph-C), 136.3 (−, Ph-C), 156.1 (−, NCO_2), 170.0 (−, C-1); IR (KBr): $\tilde{\nu} = 3326$ (br, N-H), 2978 (C-H), 2935 (C-H), 2884 (C-H), 1741 (C=O), 1707 (C=O), 1524, 1478, 1456, 1394 (*t*Bu), 1368 (*t*Bu), 1253, 1177, 1155, 1121, 1069, 775, 698 cm^{-1}; MS (ESI): positive mode: *m*/*z* (%): 887 (100) [$2M^+$+Na], 455 (9) [M^++Na]; HRMS (ESI): *m*/*z*: calcd for $C_{23}H_{32}N_2O_6Na$: 455.21526, found 455.21562 [M^++Na]; elemental analysis calcd (%) for $C_{23}H_{32}N_2O_6$ (432.52): C 63.87, H 7.46, N 6.48; found C 63.67, H 7.19, N 6.29.

***tert*-Butyl (2*S*,2′*R*,3*R*,4*R*)-*N*-Fmoc-glycyl-3,4-(Z-aminomethano)prolinate (15)**: A 2 M solution of HCl in EtOAc (4.3 mL) was added to a solution of (2*S*,2′*R*,3*R*,4*R*)-**14** (738 mg, 1.71 mmol) in EtOAc (4.3 mL), and the resulting mixture was stirred for 11 h. The volatile compounds were evaporated in vacuo, and the residue was treated according to GP 3 with Fmoc-GlyOH (508 mg, 1.71 mmol) to yield, after column chromatography (30 g silica gel, 2×20 cm, hexane/EtOAc 1:1, $R_f = 0.24$), **15** (575 mg, 55%) as a pale yellow foam. M.p. 81–86 °C; $[\alpha]_D^{20} = -32.8°$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, HMQC): $\delta = 1.47$ [s, 9H, $C(CH_3)_3$], 1.77–2.02 (m, 2H, 3,4-H), 2.32–2.42 (m, 1H, 1′-H), 3.50–3.75, 3.80–4.08 (m, 2H, 2-H, *Gly*), 3.60–4.02 (m, 2H, 5-H), 4.20 (t, $^3J = 7.5$ Hz, 1H, 9-H, *Fmoc*), 4.34 (d, $^3J = 7.5$ Hz, 2H, 1′-H, *Fmoc*), 4.61 (s, 1H, 2-H), 4.98 (br s, 1H, NH, *Z*), 5.08 (s, 2H, OCH_2Ph), 5.66–5.73 (m, 1H, NH, *Fmoc*), 7.24–7.42 (m, 9H, Ph-H, *Fmoc*, *Z*), 7.58 (d, $^3J = 7.5$ Hz, 2H, Ph-H, *Fmoc*), 7.74 (d, $^3J = 7.5$ Hz, 2H, Ph-H, *Fmoc*); ^{13}C NMR (50.3 MHz, $CDCl_3$, APT, HMQC): $\delta = 24.5$ (+, C-4*), 27.0 (+, C-3*), 27.95, 27.99 [+, $C(CH_3)_3$], 32.4, 32.6 (+, C-1′*), 43.3, 43.4 (−, C-2, *Gly*), 47.1 (+, C-9, *Fmoc*), 47.4, 47.8 (−, C-5), 60.8, 61.4 (+, C-2), 67.1 (−, OCH_2Ph, C-1′, *Fmoc*), 82.5, 83.5 [−, $C(CH_3)_3$], 119.9, 125.1, 127.0, 127.7, 128.1, 128.3, 128.6 (+, Ph-C, *Fmoc*, *Z*), 136.1 (−, Ph-C, *Z*), 141.3, 143.9 (−, Ph-C, *Fmoc*), 156.1, 156.4 (−, NCO_2), 167.5, 169.2 (−, C-1, C-1, *Gly*); IR (KBr): $\tilde{\nu} = 3325$ (br, N-H), 2977 (C-H), 2936 (C-H), 2883 (C-H), 1730 (C=O), 1663 (C=O), 1518, 1451, 1370, 1250, 1154, 1048, 759, 741, 698 cm^{-1}; MS (ESI): positive mode: *m*/*z* (%): 1856 (47) [$3M^+$+Na], 1245 (100) [$2M^+$+Na], 634 (88) [M^++Na]; negative mode: *m*/*z* (%): 1267 (100) [$2M^-$+COOH], 656 (71) [M^-+COOH].

Methyl (2*S*,2′*R*,3*R*,4*R*)-*N*-Fmoc-glycyl-3,4-(Z-aminomethano)prolylglycinate (17): According to GP 4, the *tert*-butyl ester group in **15** (153 mg, 250 μmol) was cleaved and the resulting acid then coupled with glycine methyl ester hydrochloride (31.4 mg, 250 μmol) according to GP 3. After column chromatography (10 g silica gel, 1×5 cm, hexane/EtOAc 4:1, $R_f = 0.10$), **17** (131 mg, 84%) was obtained as a colorless amorphous solid. M.p. 155–156 °C; $[\alpha]_D^{20} = -47.4°$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): $\delta = 1.90–2.02$ (m, 1H, 4-H), 2.09–2.20 (m, 1H, 3-H), 2.38–2.44 (m, 1H, 1′-H), 3.66–3.80 (m, 2H, 2-H, *Gly*), 3.77 (s, 3H, OMe), 3.85–3.98 (m, 2H, 5-H), 4.04 (d, $^2J = 7.5$ Hz, 2H, 2-H, *Gly*), 4.27 (t, $^3J = 7.5$ Hz, 1H, 9-H, *Fmoc*), 4.44 (d, $^3J = 7.5$ Hz, 2H, 1′-H, *Fmoc*), 4.78 (s, 1H, NH, *Gly*), 4.97 (s, 1H, 2-H), 5.16 (s, 2H, OCH_2Ph), 5.51–5.60 (m, 1H, NH, *Fmoc*), 6.85 (br s, 1H, NH, *Z*), 7.30–7.48 (m, 9H, Ph-H, *Fmoc*, *Z*), 7.63 (d, $^3J = 7.5$ Hz, 2H, Ph-H, *Fmoc*), 7.79 (d, $^3J = 7.5$ Hz, 2H, Ph-H, *Fmoc*); ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, APT, 100 °C): $\delta = 24.4$ (+, C-4*), 26.1 (+, C-3*), 32.4 (+, C-1′), 41.0 (−, C-2, *Gly*), 43.5 (−, C-2, *Gly*), 47.2 (+, C-9, *Fmoc*), 47.6 (−, C-5), 52.0 (+, OCH_3), 61.4 (+, C-2), 66.8 (−, OCH_2Ph*), 67.1 (−, C-1′*, *Fmoc*), 119.7, 124.8, 126.9, 127.5, 127.6, 127.9, 128.3 (+, Ph-C, *Fmoc*, *Z*), 136.2 (−, Ph-C, *Z*), 141.0, 143.7 (−, Ph-C, *Fmoc*), 155.9, 156.0 (−, NCO_2), 168.0, 169.3, 169.5 (−, C-1, C-1, *Gly*); IR (KBr): $\tilde{\nu} = 3322$ (N-H), 2952 (C-H), 1723 (C=O), 1663 (C=O), 1526, 1451, 1248, 1215, 1182, 1048, 760, 742, 699 cm^{-1}; MS (ESI): positive mode: *m*/*z* (%): 1275 (100) [$2M^+$+Na], 649 (26) [M^++Na]; negative mode: *m*/*z* (%): 1297 (20) [$2M^-$+COOH], 671 (36) [M^-+COOH]; HRMS (ESI): *m*/*z*: calcd for $C_{34}H_{34}N_4O_8Na$: 649.22689, found 649.22719 [M^++Na].

Methyl (2*S*,2′*R*,3*R*,4*R*)-*N*-Fmoc-glycyl-3,4-(Z-aminomethano)prolyl-L-alaninate (18): According to GP 4, the *tert*-butyl ester group in **15** (153 mg, 250 μmol) was cleaved and the acid then coupled with alanine methyl ester hydrochloride (34.9 mg, 250 μmol) according to GP 3. After column chromatography (10 g silica gel, 1×5 cm, hexane/EtOAc 4:1, $R_f = 0.20$), **18** (134 mg, 84%) was obtained as a colorless amorphous solid. M.p. 86–89 °C; $[\alpha]_D^{20} = -43.4°$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): $\delta = 1.44$ (d, $^3J = 7.5$ Hz, 3H, 1′-H, *Ala*), 1.89–2.00 (m, 1H, 4-H), 2.07–2.14 (m, 1H, 3-H), 2.37–2.42 (m, 1H, 1′-H), 3.64–3.80 (m, 2H, 2-H, *Gly*), 3.79 (s, 3H, OMe), 3.83–3.96 (m, 2H, 5-H), 4.25 (t, $^3J = 7.5$ Hz, 1H, 9-H, *Fmoc*), 4.43 (d, $^3J = 7.5$ Hz, 2H, 1′-H, *Fmoc*), 4.55 (t, $^3J = 7.5$ Hz, 1H, 2-H, *Ala*), 4.69 (s, 1H, NH, *Ala*), 4.92 (s, 1H, 2-H), 5.14 (s, 2H, OCH_2Ph), 5.46–5.56 (m, 1H, NH, *Fmoc*), 6.68 (br s, 1H, NH, *Z*), 7.29–7.47 (m, 9H, Ph-H, *Fmoc*, *Z*), 7.62 (d, $^3J = 7.5$ Hz, 2H, Ph-H, *Fmoc*), 7.78 (d, $^3J = 7.5$ Hz, 2H, Ph-H, *Fmoc*); ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, APT, 100 °C): $\delta = 17.7$ (+, C-1′, *Ala*), 24.5 (+, C-4*), 26.3 (+, C-3*), 32.5 (+, C-1′), 43.5 (−, C-2, *Gly*), 47.2 (+, C-9, *Fmoc*), 47.7 (−, C-5), 48.1 (+, C-2, *Ala*), 52.0 (+, OCH_3), 61.6 (+, C-2), 66.8 (−, OCH_2Ph*), 67.1 (−, C-1′, *Fmoc*), 119.7, 124.8, 126.9, 127.5, 127.6, 127.9, 128.3 (+, Ph-C, *Fmoc*, *Z*), 136.2 (−, Ph-C, *Z*), 141.1, 143.7 (−, Ph-C, *Fmoc*), 155.8, 156.0 (−, NCO_2), 167.8, 168.6, 172.5 (−, C-1, C-1, *Ala*, C-1, *Gly*); IR (KBr): $\tilde{\nu} = 3319$ (N-H), 2951 (C-H), 2885 (C-H), 1725 (C=O), 1662 (C=O), 1526, 1451, 1248, 1218, 1050, 742, 699, 621 cm^{-1}; MS (ESI): positive mode: *m*/*z* (%): 1942 (21) [$3M^+$+Na], 1303 (100) [$2M^+$+Na], 663 (13) [M^++Na]; negative mode: *m*/*z* (%): 685 (46) [M^-+COOH];

HRMS (ESI): *m/z*: calcd for $C_{35}H_{36}N_4O_8Na$: 663.24254, found 663.24312 [M^++Na].

Methyl (2*S*,2′*R*,3*R*,4*R*)-*N*-Fmoc-glycyl-3,4-(*Z*-aminomethano)prolyl-L-phenylalaninate (19): According to GP 4, the *tert*-butyl ester group in **15** (153 mg, 250 μmol) was cleaved and the acid then coupled with phenylalanine methyl ester hydrochloride (53.9 mg, 250 μmol) according to GP 3. After column chromatography (10 g silica gel, 1×5 cm, hexane/EtOAc 4:1, R_f=0.25), **19** (166 mg, 93 %) was obtained as a colorless amorphous solid. M.p. 76–83 °C; $[\alpha]_D^{20}=-18.8°$ (c=0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): δ=1.80–1.92 (m, 1H, 4-H), 2.00–2.15 (m, 1H, 3-H), 2.30–2.36 (m, 1H, 1′-H), 3.04 (dd, ^2J=14.0, ^3J=7.5 Hz, 1H, 1′-H, *Phe*), 3.22 (dd, ^2J=14.0, ^3J=7.5 Hz, 1H, 1′-H, *Phe*), 3.41–3.51 (m, 1H, 5-H), 3.54–3.96 (m, 3H, 5-H, 2-H, *Gly*), 3.76 (s, 3H, OMe), 4.27 (t, ^3J=7.5 Hz, 1H, 9-H, *Fmoc*), 4.46 (d, ^3J=7.5 Hz, 2H, 1′-H, *Fmoc*), 4.69 (s, 1H, NH, *Phe*), 4.81–4.92 (m, 2H, 2-H, 2-H, *Phe*), 5.14 (s, 2H, OCH_2Ph), 5.39–5.48 (m, 1H, NH, *Fmoc*), 6.80 (brs, 1H, NH, *Z*), 7.09–7.18 (m, 2H, Ph-H, *Phe*), 7.18–7.48 (m, 12H, Ph-H, *Phe*, *Fmoc*, *Z*), 7.62 (d, ^3J=7.5 Hz, 2H, Ph-H, *Fmoc*), 7.79 (d, ^3J=7.5 Hz, 2H, Ph-H, *Fmoc*); ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, APT, 100 °C): δ=24.2 (+, C-4*), 25.7 (+, C-3*), 32.2 (+, C-1′), 37.5 (−, C-1′, *Phe*), 43.4 (−, C-2, *Gly*), 47.2 (+, C-9, *Fmoc*), 47.4 (-, C-5), 52.0 (+, C-2, *Phe*), 52.8 (+, OCH_3), 61.3 (+, C-2), 66.7 (−, OCH_2Ph*), 67.0 (−, C-1′, *Fmoc*), 119.7, 124.8, 126.9, 127.5, 127.6, 127.9, 128.2, 128.3, 128.9 (+, Ph-C, *Phe*, *Fmoc*, *Z*), 135.8 (−, Ph-C, *Phe*), 136.2 (− Ph-C, *Z*), 141.1, 143.7 (−, Ph-C, *Fmoc*), 155.7, 156.0 (−, NCO_2), 167.7, 168.4, 171.2 (−, C-1, C-1, *Phe*, C-1, *Gly*); IR (KBr): $\tilde{\nu}$=3316 (N-H), 2951 (C-H), 1726 (C=O), 1664, 1524, 1451, 1247, 1217, 759, 741, 700 cm^{-1}; MS (ESI): positive mode: *m/z* (%): 1455 (100) [2M^++Na], 739 (22) [M^++Na]; negative mode: *m/z* (%): 1477 (16) [2M^-+COOH], 761 (33) [M^-+COOH]; HRMS (ESI): *m/z*: calcd for $C_{41}H_{40}N_4O_8Na$: 739.27384, found 739.27447 [M^++Na].

(2*S*,2′*R*,3*R*,4*R*)-*N*$_\alpha$-Boc-3,4-(*Z*-aminomethano)proline [(2*S*,2′*R*,3*R*,4*R*)-16]: A 2 M solution of HCl in EtOAc (5 mL) was added to a solution of (2*S*,2′*R*,3*R*,4*R*)-**14** (1.68 g, 3.88 mmol) in EtOAc (10 mL) and the resulting mixture was stirred for 11 h. All volatile compounds were removed in vacuo. The residue was taken up in H_2O (4 mL), the mixture cooled to 0 °C and treated with a 1 M aq. solution of NaOH (7.76 mL, 7.76 mmol) and $NaHCO_3$ (48.9 mg, 582 μmol). A solution of Boc_2O (932 mg, 4.27 mmol) in THF (5 mL) was added, the solution was warmed to ambient temperature and stirred for an additional 18 h. The reaction mixture was saturated with NaCl and then acidified with $KHSO_4$ up to pH 1–2. The reaction mixture was extracted with EtOAc (5×10 mL). The combined organic extracts were dried and concentrated in vacuo. Column chromatography of the residue (30 g silica gel, 1×20 cm, hexane/EtOAc 2:1 + 1.5 vol.% HOAc, R_f=0.14, furnished (2*S*,2′*R*,3*R*,4*R*)-**16** (936 mg, 64 %) as a colorless foam. M.p. 69–73 °C; $[\alpha]_D^{20}=-54.6°$ (c=0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, rotamers): δ=1.40, 1.43 [s, 9H, $C(CH_3)_3$], 1.68–1.82 (m, 1H, 4-H*), 1.85–2.00 (m, 1H, 3-H*), 2.42–2.51 (m, 1H, 1′-H), 3.48–3.63 (m, 1H, 5-H), 3.63–3.78 (m, 1H, 5-H), 4.37–4.54 (m, 1H, 2-H), 5.02–5.23 (m, 2H, OCH_2Ph), 6.14 (brs, 1H, NH, *Z*), 7.26–7.42 (m, 5H, Ph-H), 8.40 (brs, 1H, COOH); ^{13}C NMR (50.3 MHz, $CDCl_3$, APT, rotamers): δ=24.6 (+, C-4*), 28.2, 28.3 [+, $C(CH_3)_3$, C-3*], 32.6 (+, C-1′), 47.7, 47.9 (−, C-5), 60.4, 60.5 (+, C-2), 67.1 (−, OCH_2Ph), 80.7, 81.3 [−, $C(CH_3)_3$], 128.3, 128.6 (+, 3×Ph-C), 136.0 (−, Ph-C), 154.0, 155.1 (−, NCO_2), 175.7 (−, C-1); IR (KBr): $\tilde{\nu}$=3324 (br, N-H), 2978 (C-H), 2937 (C-H), 2887 (C-H), 1705 (br, C=O), 1526, 1396 (*t*Bu), 1369 (*t*Bu), 1256, 1173, 1127, 1070, 871, 776, 698 cm^{-1}; MS (ESI): positive mode: *m/z* (%): 775 (100) [2M^++Na], 399 (34) [M^++Na]; negative mode: *m/z* (%): 751 (69) [2M^-−H], 375 (61) [M^-−H]; HRMS (ESI): *m/z*: calcd for $C_{19}H_{24}N_2O_6Na$: 399.15266, found 399.15295 [M^++Na].

Methyl (2*S*,2′*R*,3*R*,4*R*)-*N*$_\alpha$-Boc-3,4-(*Z*-aminomethano)prolylglycinate (20): According to GP 3 (2*S*,2′*R*,3*R*,4*R*)-**16** (188 mg, 500 μmol) was treated with GlyOMe·HCl (62.8 mg, 500 μmol) to yield after column chromatography (10 g silica gel, 1×5 cm, hexane/EtOAc 3:2, R_f=0.20), **20** (198 mg, 88 %) as a colorless amorphous solid. M.p. 60–63 °C; $[\alpha]_D^{20}=-65.6°$ (c=0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): δ=1.50 [s, 9H, $C(CH_3)_3$], 1.74–1.83 (m, 1H, 4-H*), 2.04–2.12 (m, 1H, 3-H*), 2.37–2.42 (m, 1H, 1′-H), 3.52 (dd, ^2J=11.0, ^3J=4.5 Hz, 1H, 5-H), 3.68 (s, 3H, OCH_3), 3.68–3.78 (m, 1H, 5-H), 4.05 (d, ^2J=6.0 Hz, 2H, 2-H, *Gly*), 4.46 (s, 1H, NH, *Gly*), 4.92 (s, 1H, 2-H), 5.15 (s, 2H, OCH_2Ph), 6.69 (brs, 1H, NH, *Z*), 7.30–7.44 (m, 5H, Ph-H); ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, APT, 100 °C): δ=24.1 (+, C-4*), 28.1 [+, $C(CH_3)_3$, C-3*], 32.7 (+, C-1′), 41.0 (−, C-2, *Gly*), 47.8 (−, C-5), 51.9 (+, OCH_3), 61.6 (+, C-2), 66.6 (−, OCH_2Ph), 80.8 [−, $C(CH_3)_3$], 127.6, 127.8, 128.2 (+, Ph-C), 136.3 (−, Ph-C), 156.2 (−, 2×NCO_2), 169.5, 170.5 (−, C-1, C-1, *Gly*); IR (KBr): $\tilde{\nu}$=3320 (br, N-H), 2977 (C-H), 1702 (br, C=O), 1528, 1394 (*t*Bu), 1368 (*t*Bu), 1254, 1178, 1123, 872, 775, 699 cm^{-1}; MS (ESI): positive mode: *m/z* (%):917 (100) [2M^++Na], 470 (24) [M^++Na]; negative mode: *m/z* (%): 893 (67) [2M^-−H], 492 (49) [M^-+COOH], 446 (100) [M^-−H].

Methyl (2*S*,2′*R*,3*R*,4*R*)-*N*-Boc-glycyl-3,4-(*Z*-aminomethano)prolylglycinate (21): According to GP 4, the Boc group in **20** (112 mg, 250 μmol) was cleaved and the free amine then coupled with *N*-Boc-glycine (43.8 mg, 250 μmol) according to GP 3. After column chromatography (10 g silica gel, 1×5 cm, hexane/EtOAc 5:1, R_f=0.18) **21** (71 mg, 56 %) was obtained as a colorless amorphous solid. M.p. 67–70 °C; $[\alpha]_D^{20}=-63.2°$ (c=0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): δ=1.46 [s, 9H, $C(CH_3)_3$], 1.88–1.98 (m, 1H, 4-H*), 2.08–2.17 (m, 1H, 3-H*), 2.35–2.40 (m, 1H, 1′-H), 3.66–3.75 (m, 2H, 5-H*), 3.76 (s, 3H, OCH_3), 3.80–3.90 (m, 2H, 2-H*, *Gly*), 3.97–4.06 (m, 2H, 2-H, *Gly*), 4.94 (s, 1H, 2-H), 5.02 (s, 1H, NH, *Gly*), 5.12 (s, 2H, OCH_2Ph), 5.24 (s, 1H, NH, *Boc*), 6.92 (brs, 1H, NH, *Z*), 7.28–7.42 (m, 5H, Ph-H); ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, APT, 100 °C): δ=24.4 (+, C-4*), 26.0 (+, C-3*), 28.1 [+, C-(CH_3)$_3$], 32.4 (+, C-1′), 41.0 (−, C-2, *Gly*), 43.3 (−, C-2, *Gly*), 47.6 (−, C-5), 51.9 (+, OCH_3), 61.3 (+, C-2), 66.7 (−, OCH_2Ph), 79.7 [−, $C(CH_3)_3$], 127.6, 127.9, 128.3 (+, Ph-C), 136.2 (−, Ph-C), 155.3, 156.1 (−, NCO_2), 168.4, 169.4, 169.5 (−, C-1, C-1, *Gly*, C-1, *Gly*); IR (KBr): $\tilde{\nu}$=3324 (N-H), 2977 (C-H), 2937 (C-H), 1716 (C=O), 1659 (C=O), 1528, 1454, 1439, 1394 (*t*Bu), 1367 (*t*Bu), 1251, 1213, 1175, 1050, 741, 699 cm^{-1}; MS (ESI): positive mode: *m/z* (%): 1535 (7) [3M^++Na], 1031 (100) [2M^++Na], 527 (64) [M^++Na]; negative mode: *m/z* (%): 1007 (20) [2M^-−H], 549 (69) [M^-+COOH], 503 (64) [M^-−H]; HRMS (ESI): *m/z*: calcd for $C_{24}H_{32}N_4O_8Na$: 527.21124, found 527.21137 [M^++Na].

Methyl (2*S*,2′*R*,3*R*,4*R*)-*N*-Boc-L-alaninyl-3,4-(*Z*-aminomethano)prolylglycinate (22): According to GP 4, the Boc group in **20** (112 mg, 250 μmol) was cleaved and the free amine then coupled with *N*-Boc-alanine (47.3 mg, 250 μmol) according to GP 3. After column chromatography (10 g silica gel, 1×5 cm, hexane/EtOAc 3:1, R_f=0.19) **22** (79 mg, 61 %) was obtained as a colorless amorphous solid. M.p. 63–65 °C; $[\alpha]_D^{20}=-65.3°$ (c=0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): δ=1.25–1.38 (m, 3H, CH_3, *Ala*), 1.45 [s, 9H, $C(CH_3)_3$], 1.87–1.98 (m, 1H, 4-H*), 2.11–2.23 (m, 1H, 3-H*), 2.34–2.45 (m, 1H, 1′-H), 3.60–3.75 (m, 1H, 5-H*), 3.74 (s, 3H, OCH_3), 3.90–4.11 (m, 1H, 5-H*), 3.96 (dd, ^2J=18.0, ^3J=6.0 Hz, 1H, 2-H*, *Gly*), 4.05 (dd, ^2J=18.0, ^3J=6.0 Hz, 1H, 2-H*, *Gly*), 4.25–4.46 (m, 1H, 2-H, *Ala*), 4.80 (s, 1H, NH, *Gly*), 4.98 (s, 1H, 2-H), 5.13 (s, 2H, OCH_2Ph), 5.17 (s, 1H, NH, *Boc*), 6.91 (brs, 1H, NH, *Z*), 7.28–7.43 (m, 5H, Ph-H); ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, APT, 100 °C): δ=17.8 (+, CH_3, *Ala*), 24.4 (+, C-4*), 25.6 (+, C-3*), 28.1 [+, $C(CH_3)_3$], 32.1 (+, C-1′), 41.0 (−, C-2*, *Gly*), 48.0 (−, C-5), 48.4 (+, C-2, *Ala*), 51.8 (+, OCH_3), 61.0 (+, C-2), 66.7 (−, OCH_2Ph), 79.6 [−, $C(CH_3)_3$], 127.5, 127.8, 128.2 (+, Ph-C), 136.3 (−, Ph-C), 154.7, 156.0 (−, NCO_2), 169.4, 172.5 (−, C-1, C-1, *Ala*, C-1, *Gly*); IR (KBr): $\tilde{\nu}$=3322 (N-H), 2979 (C-H), 2936 (C-H), 2884 (C-H), 1711 (C=O), 1646 (C=O), 1526, 1455, 1393 (*t*Bu), 1368 (*t*Bu), 1252, 1212, 1170, 742, 699 cm^{-1}; MS (ESI): positive mode: *m/z* (%): 1059 (100) [2M^++Na], 541 (37) [M^+−Na]; negative mode: *m/z* (%): 563 (69) [M^-+COOH], 517 (100) [M^-−H]; HRMS (ESI): *m/z*: calcd for $C_{25}H_{34}N_4O_8Na$: 541.22689, found 541.22682 [M^++Na].

Methyl (2*S*,2′*R*,3*R*,4*R*)-*N*-Boc-L-phenylalaninyl-3,4-(*Z*-aminomethano)prolylglycinate (23): According to GP 4, the Boc group in **20** (112 mg, 250 μmol) was cleaved and the free amine then coupled with *N*-Boc-phenylalanine (66.3 mg, 250 μmol) according to GP 3. After column chromatography (10 g silica gel, 1×5 cm, hexane/EtOAc 2:1, R_f=0.20) **23** (108 mg, 73 %) was obtained as a colorless amorphous solid. M.p. 72–75 °C; $[\alpha]_D^{20}=-41.2°$ (c=0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): δ=1.44 [s, 9H, $C(CH_3)_3$], 1.78–1.89 (m, 1H, 4-H*), 2.06–2.16 (m, 1H, 3-H*), 2.29–2.41 (m, 1H, 1′-H), 2.94 (dd, ^2J=14.0, ^3J=7.5 Hz, 1H, CH_2Ph, *Phe*), 2.98–3.11 (m, 1H, CH_2Ph, *Phe*), 3.18–3.31 (m, 1H, 5-H*),

3.78 (s, 3H, OCH_3), 3.92–4.08 (m, 3H, 5-H*, 2-H*, *Gly*), 4.50–4.65 (m, 1H, 2-H, *Phe*), 4.78 (s, 1H, NH, *Gly*), 4.88 (s, 1H, 2-H), 5.12 (s, 3H, OCH_2Ph, NH, *Boc*), 6.78 (brs, 1H, NH, *Z*), 7.14–7.33 (m, 10H, Ph-H); ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, APT, 100 °C): $\delta = 24.3$ (+, C-4*), 25.6 (+, C-3*), 28.1 [+, $C(CH_3)_3$], 31.9 (+, C-1′), 38.7 (−, C-1′*, *Phe*), 41.0 (−, C-2*, *Gly*), 48.2 (−, C-5), 51.9 (+, OCH_3), 53.7 (+, C-2, *Phe*), 61.0 (+, C-2), 66.6 (−, OCH_2Ph), 79.8 [−, $C(CH_3)_3$], 126.8, 127.6, 127.8, 128.2, 129.1 (+, Ph-C), 135.9, 136.3 (−, Ph-C), 154.6, 156.0 (−, NCO_2), 169.1, 169.4, 172.5 (−, C-1, C-1, *Phe*, C-1, *Gly*); IR (KBr): $\tilde{\nu} = 3320$ (N-H), 2978 (C-H), 2953 (C-H), 2935 (C-H), 1707 (C=O), 1645 (C=O), 1523, 1439, 1393 (*t*Bu), 1367 (*t*Bu), 1250, 1211, 1173, 1050, 748, 700 cm^{-1}; MS (ESI): positive mode: *m*/*z* (%): 1805 (7) [$3M^+$+Na], 1211 (100) [$2M^+$+Na], 617 (34) [M^++Na]; negative mode: *m*/*z* (%): 639 (56) [M^-+COOH], 593 (34) [M^-−H]; HRMS (ESI): *m*/*z*: calcd for $C_{31}H_{38}N_4O_8Na$: 617.25819, found 617.25827 [M^++Na].

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