

Article

Synthesis of New Optically Active 2-Pyrrolidinones

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Abstract: A new class of optically active 2-pyrrolidinones was synthesized, starting from *S*-pyroglutamic acid, a well known natural chiral synthon. The synthetic design followed led to the insertion of various substituents at positions 1 and 5 of the 2-pyrrolidinone ring, including the imidazole moiety. Some of them possess two or three stereogenic centers, the configuration of which was retained under the mild conditions used. The new compounds also carry an imidazole moiety, which, along with the 2-pyrrolidinone template, may prove pivotal to several biological processes.

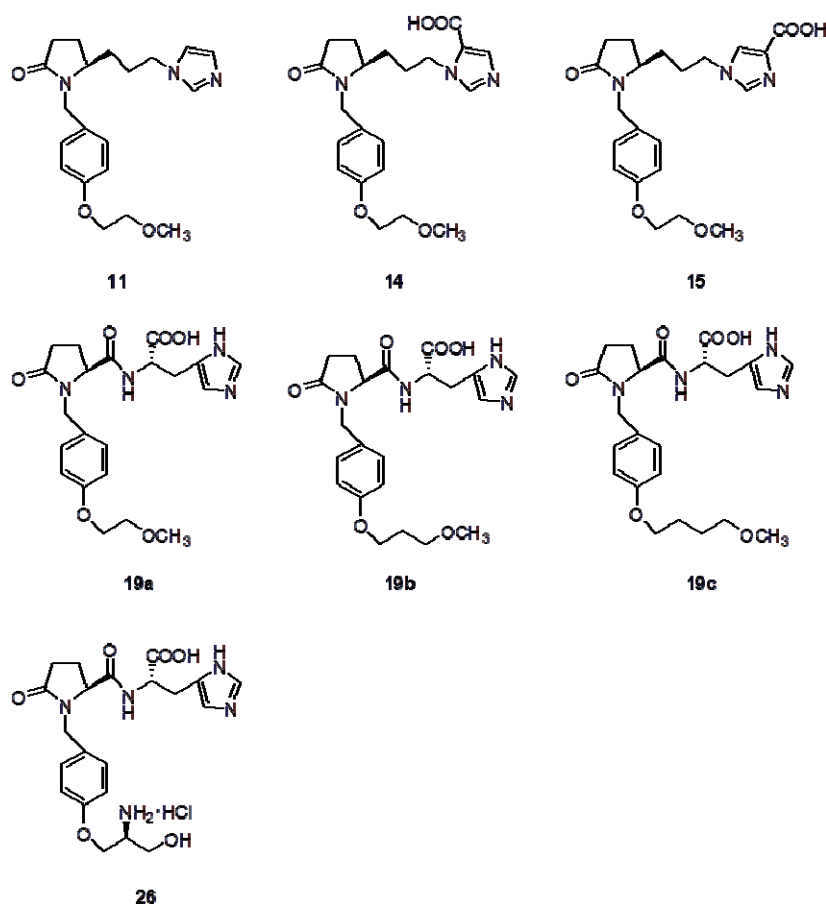
Keywords: *S*-pyroglutamic acid; 2-pyrrolidinone; imidazole

1. Introduction

Derivatives of 2-pyrrolidinone have shown significant biological and pharmacological activities. Some of them are well known medicines, e.g., 2-oxo-1-pyrrolidine acetamide (piracetam) for patients with seizures, Alzheimer's and senile dementia, concussion and other neurological problems [1], 1-ethyl-4-(2-morpholin-4-ylethyl)-3,3-diphenyl-pyrrolidin-2-one (doxapram) for patients with respiratory failure [2], *etc.* Moreover, the 2-pyrrolidinone template, considered as an essential pharmacophore group, is also aggregation-inhibiting effects [4], or properties related to the treatment of a variety of diseases incorporated in more complicated chemical structures with anticonvulsant activity [3], pharmacological properties like modulated by H3 receptors, including those associated with the central nervous system [5] and many others.

In recent years, we have designed and synthesized 2-pyrrolidinones, starting from the naturally derived *S*-pyroglutamic acid (2-oxotetrahydropyrrol-5*S*-carboxylic acid), which is considered as a unique chiral synthon. The asymmetric use of *S*-pyroglutamic acid is based on its two differentiated carbonyls, the properties of which allow an extended derivatization on the 5-membered ring of the starting compound leading to a plethora of natural products, e.g., (–) domoic acid [6], the neurotoxin anatoxin-a [7], biologically interesting compounds, e.g., an inhibitor of angiotensin-converting enzyme (ACE) [8] for the treatment of hypertension as well as to chemical auxiliaries in asymmetric synthesis [9]. The properties and applications of pyroglutamic acid as a versatile building block in asymmetric synthesis has extensively been reviewed in the literature [10–12]. As it was mentioned above, in recent years, we have synthesized optically active pyrrolidinones based on the *S*-pyroglutamic acid, in which an imidazole ring has also been inserted. Some of them exhibited antihypertensive and anti-inflammatory activity [13–16]. In this paper we present the synthesis of seven new compounds (Figure 1), containing up to three stereogenic centers, with predetermined absolute configuration derived from the natural amino acid *S*-pyroglutamic acid, *S*-histidine and *S*-serine.

Figure 1. The structure of the new synthesized 2-pyrrolidinones.

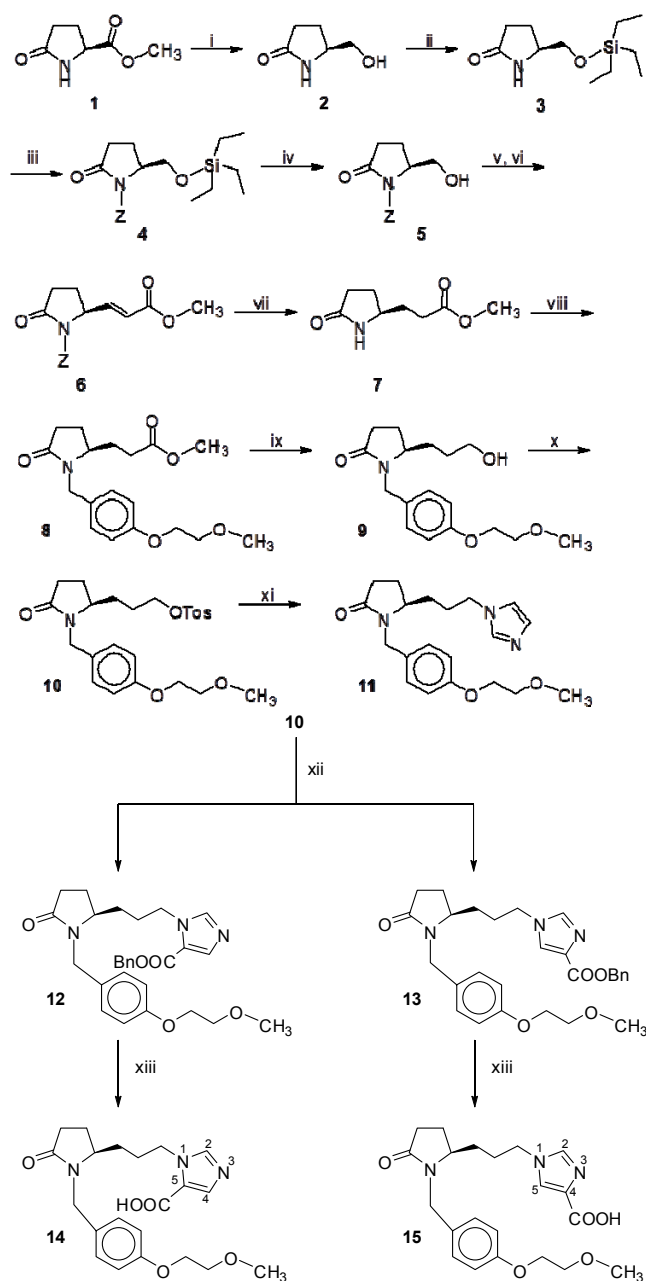


2. Results and Discussion

The 2-pyrrolidinones shown in Figure 1 possess an *N*-benzyl- type substituent, the 4-position of which is substituted by a methoxyalkoxy group. In the case of compound **26** the alkoxy substituent is a chiral α -amino alcohol moiety.

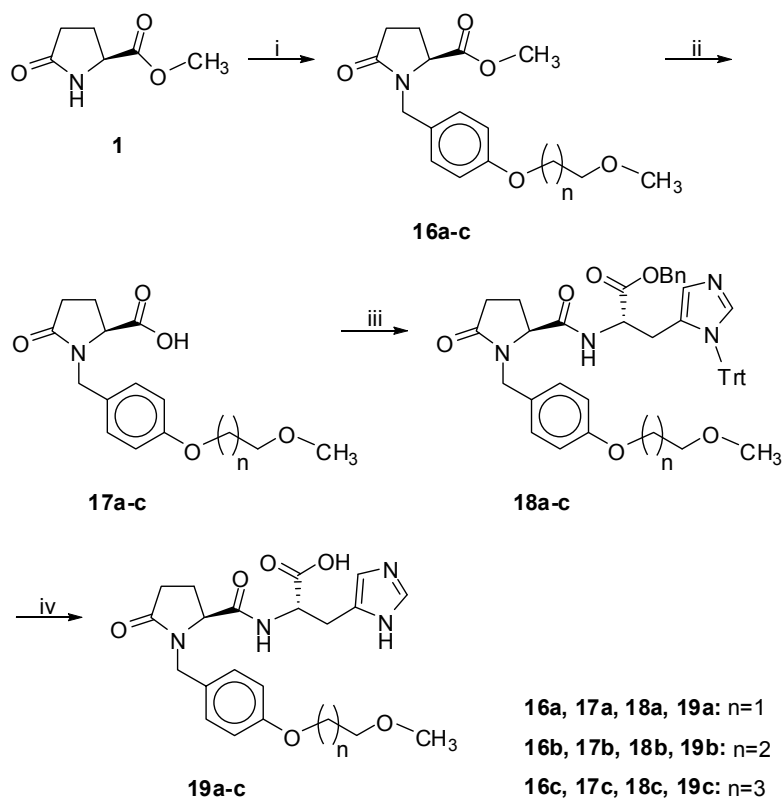
The 5-position of the 2-pyrrolidinone template has retained the absolute configuration of the initial *S*-pyroglutamic acid, regardless of whether the carbon chain is elongated or not. At the other end of this chain, an imidazole ring (with or without substitution) has been inserted (compounds **11**, **14**, **15**). In the case of compounds **19a–c** and **26**, the carboxyl group of the starting acid has been coupled to the amino acid *S*-histidine. Our approach for the synthesis of these 2-pyrrolidinones is depicted in Schemes 1–3.

Scheme 1. Synthesis of products **11**, **14**, **15**.



Reagents and Conditions: (i) NaBH_4 , dry EtOH; 94%; (ii) TES-Cl, Et_3N , DMAP in CH_2Cl_2 ; 83%; (iii) NaH, Z-Cl in dry THF; 50%; (iv) TFA in CH_2Cl_2 ; 86%; (v) Moffatt oxidation: EDC.HCl, Pyr, TFA drops in dry Tol and dry DMSO, under Ar; (vi) $\text{Ph}_3\text{P}=\text{CHCOOMe}$ in dry THF, 1h reflux under Ar; 60%; (vii) H_2 , 10% Pd/C in MeOH, overnight; 97%; (viii) **30**, NaH in dry DMF; 40%; (ix) LiBH_4 , dry THF; 87%; (x) TosCl, Et_3N in CH_2Cl_2 ; 72%; (xi) $\text{N}^1\text{-H-imidazole}$, Cs_2CO_3 in dry DMF; 58%; (xii) $\text{N}^1\text{-H-imidazole-COOBn}$, Cs_2CO_3 in dry DMF; 55% for **12**; 30% for **13**; (xiii) H_2 , 10% Pd/C in MeOH; 99% for **14**; 90% for **15**.

Scheme 2. Synthesis of products 19a–c.

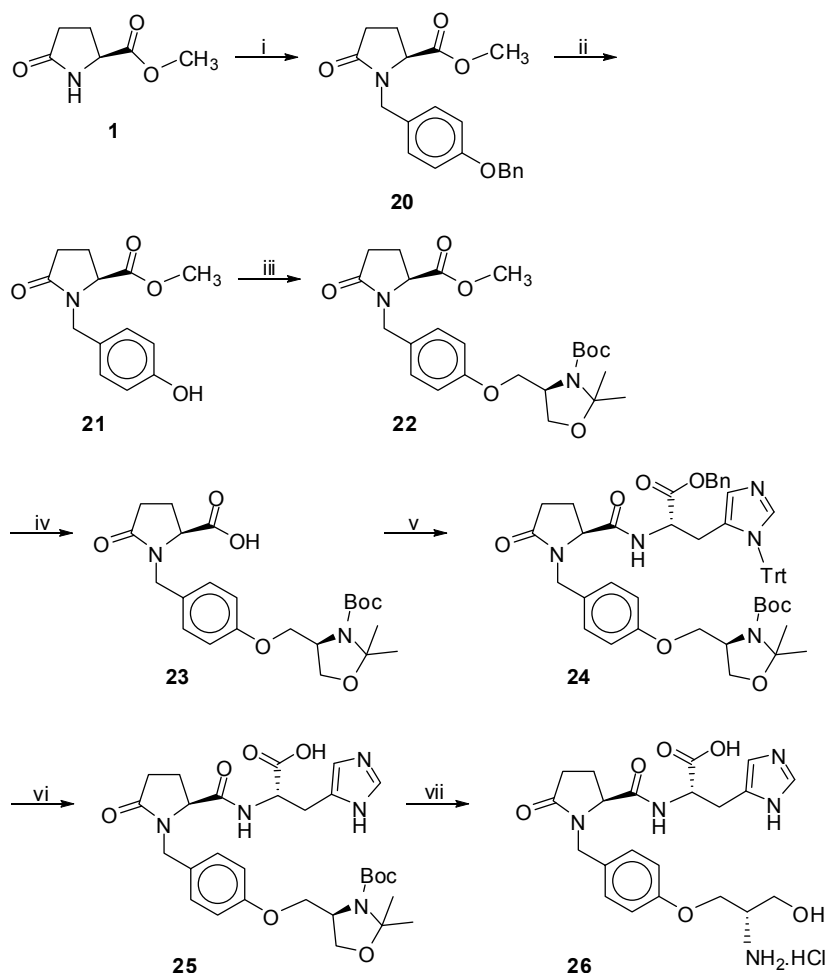


Reagents and Conditions: (i) **30**, **35**, **39**, NaH in dry DMF; 66–73%; (ii) 2N NaOH in MeOH; 94–99%; (iii) **42**, Et₃N, HOBT, EDC.HCl in CH₂Cl₂; 55–68%; (iv) H₂, 10% Pd/C; 92–99%.

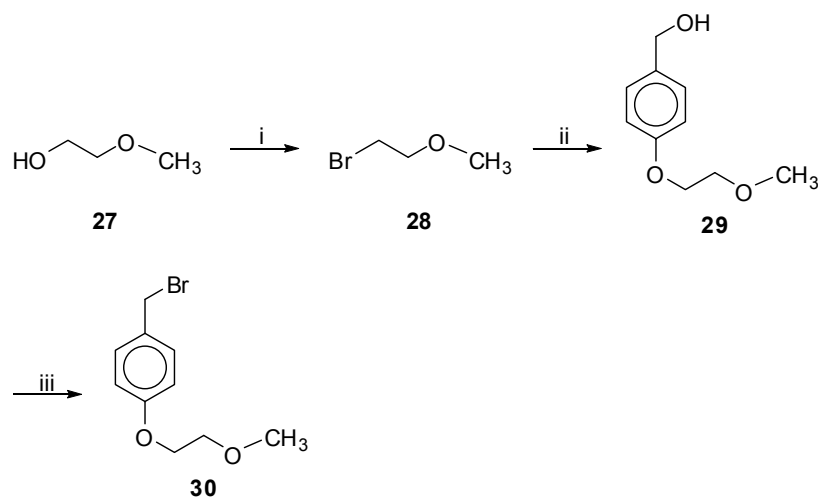
As shown in Scheme 1, the *S*-pyroglutaminol (**2**), derived from methyl *S*-pyroglutamate (**1**) using NaBH₄ in absolute alcohol [17], was protected as the TES ether using TESCl, Et₃N and DMAP [18] to yield compound **3**. *N*-benzyloxy-carbonylation of **3** with benzyloxycarbonylchloride using NaH in dry THF [19], afforded compound **4**. After deprotection of the TES group using TFA in CH₂Cl₂ [20], the resulting alcohol **5** was subjected to Moffatt oxidation [21] yielding the corresponding aldehyde, using DMSO, water soluble carbodiimide (EDC.HCl), pyridine and a trace of TFA. The aldehyde, without being isolated was immediately reacted with the stabilized ylide, phosphoranylidene methyl acetate [22], under the conditions of the Wittig reaction to give alkene **6**. After catalytic hydrogenation, the *N*-unprotected, saturated methylester **7** was obtained, and its NH group was alkylated by benzylbromide **30** (Scheme 4) using NaH in dry DMF [19], to afford compound **8**. The reduction of the ester group of **8** to the corresponding alcohol **9** was accomplished by LiBH₄ in dry THF [23] and the alcohol **9** was converted to the activated tosyl ester **10**. The desired products **11–13** were provided in higher yields (~60%) using imidazole or 1*H*-imidazole-4(5)-carboxylic acid phenylmethyl ester [16] together with Cs₂CO₃ in dry DMF at 50 °C. It is known that the nucleophilic strength of nitrogen is enhanced via complexes with Cs⁺, the so called “cesium effect” [24]. After catalytic hydrogenation the final products **14** and **15** were obtained. As shown in Scheme 1, compounds **14** and **15** as well as their precursors **12** and **13** are constitutional isomers in proportion 2:1, depending on which position (4 or 5) on the imidazole ring the substituent is located. In this case the separation of the two isomers was achieved by column chromatography, but we had to identify which isomer corresponds to each

isolated compound. In a previous work on similar constitutional isomers [16], we had used 2D NOESY NMR spectroscopy, in order to distinguish whether the carboxyl group is attached on the 4- or 5- carbon of the imidazole ring. According to the ^1H -NMR spectra of isomers **14** and **15** and taking into account the aforementioned studies, the H-4 of isomer **14** with the carboxylic group at the 5-position of the imidazole ring, resonates at lower field (ca. 7.80 ppm) in comparison to H-5 (ca. 7.68 ppm) of isomer **15** with the carboxylic group at the 4-position. In addition, the diastereotopic proton of the methylene group attached to nitrogen that points towards the carboxylate group in the isomer with substitution at 5-position resonates at lower field (ca. 4.71 ppm) in comparison to the corresponding diastereotopic proton that is not deshielded by the carboxylic group in the isomer with substitution at 4-position and resonates at ca. 4.60 ppm.

Scheme 3. Synthesis of product **26**.



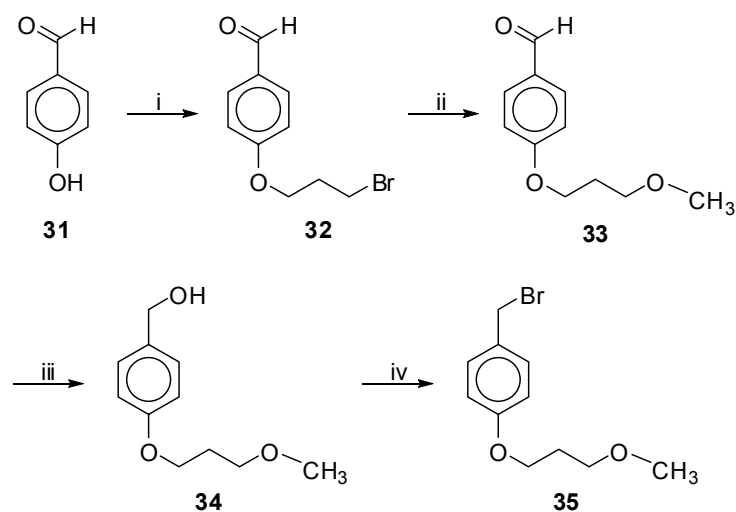
Reagents and Conditions: (i) , NaH in dry THF; 47%; (ii) H₂, 10% Pd/C in MeOH; 99%; (iii) , PPh₃, DEAD in dry Tol; 60%; (iv) 2N NaOH in MeOH; 94%; (v) **42**, Et₃N, HOBT, EDC.HCl in CH₂Cl₂; 48%; (vi) H₂, 10% Pd/C in MeOH; 97%; (vii) 4M HCl/dioxane; 90%.

Scheme 4. Synthesis of bromide **30**.

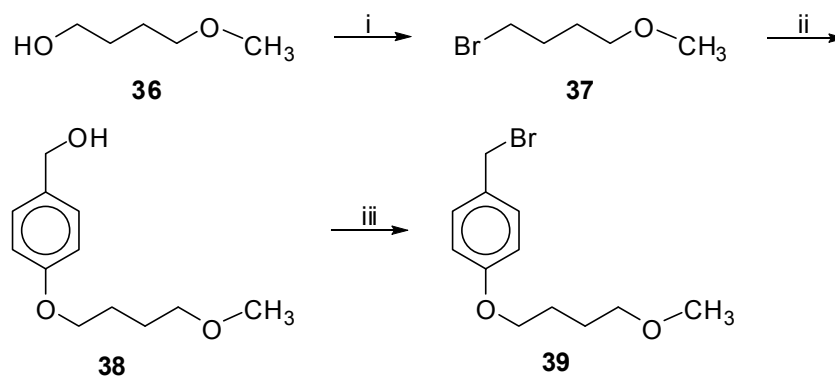
Reagents and Conditions: (i) PBr₃ in Et₂O; 58%; (ii) HO-C₆H₄-CH₂-OH, K₂CO₃, 18-Crown-6 in acetone; 76%; (iii) PBr₃ in Et₂O; 60%.

As shown in Scheme 2, methyl *S*-pyroglutamate was N-benzylated using bromides **30**, **35** and **39** (Schemes 4–6). After alkaline hydrolysis of the methyl ester of compounds **16a–c**, the resulting carboxylic group was coupled with properly protected *S*-histidine (**42**, Scheme 7) using the water soluble carbodiimide method [25]. The benzylester group and the N-trityl group of the protected amino acid were removed in the end under catalytic hydrogenation.

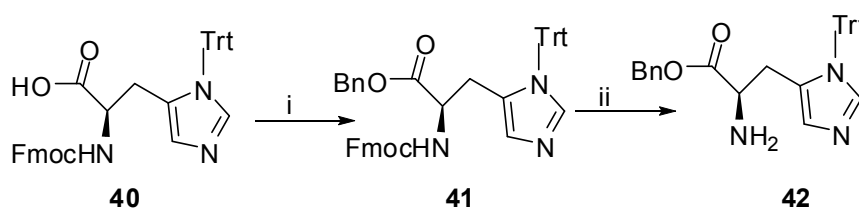
Bromides **30**, **35** and **39** were prepared under the conditions depicted in Schemes 4–6 respectively. Bromides **28** and **37** (Schemes 4 and 6), prepared from the commercially available alcohols **27** and **36** using PBr₃ in Et₂O, respectively [26], were used to convert 4-hydroxybenzyl alcohol to phenol ethers **29** and **38** using K₂CO₃ and 18-crown-6 in acetone [27]. Finally, using PBr₃ in Et₂O the bromide **30** was obtained in 60% yield, whereas bromide **39** was obtained in 42% yield only by the method of TMS-Cl, NaBr in CH₃CN [28]. We tried to prepare the desired bromide **39** using many other methods like PBr₃ in Et₂O, Tos-Cl/Et₃N and NaBr in acetone or DMF [29], MeSO₂Cl/Et₃N and NaBr in DMF or LiBr in THF [30], without any success. In the case of bromide **35**, we followed a different approach, depicted in Scheme 5, since 3-bromo-propanol was not commercially available. Compound **32** was obtained by the reaction of 4-hydroxy benzaldehyde (**31**) and 1,3-dibromo propane with K₂CO₃ in acetone [31]. After conversion of the bromide group of **32** to methyl ether by MeONa [31], the aldehyde **33** was readily subjected to reduction by NaBH₄ in dry THF to afford alcohol **34**. The relatively low yield of the preparation of compound **32** can be explained by the fact that a parallel Cannizzaro reaction had occurred, under the alkaline conditions of that synthetic step, as revealed from the characterization of the isolated by-products. Both benzaldehydes **32** and **33** were unstable even if they were stored at −4 °C for more than 2–3 h.

Scheme 5. Synthesis of bromide **35**.

Reagents and Conditions: (i) BrCH₂CH₂CH₂Br, K₂CO₃ in acetone; 40%; (ii) 1N MeONa/MeOH; 38%; (iii) NaBH₄ in dry THF; 80%; (iv) PBr₃ in Et₂O; 70%.

Scheme 6. Synthesis of bromide **39**.

Reagents and Conditions: (i) PBr₃ in Et₂O; 60%; (ii) HO-CH₂-C₆H₄-CH₂-OH, K₂CO₃, 18-Crown-6 in acetone; 67%; (iii) TMS-Cl, NaBr in CH₃CN; 42%.

Scheme 7. Synthesis of compound **42**.

Reagents and Conditions: (i) Bn-Br, Cs₂CO₃ in DMF; 87%; (ii) Et₂NH in abs. EtOH, 82%.

As depicted in Scheme 3, a different approach was followed for the synthesis of product **26**. Methyl *S*-pyroglutamate was benzylated at the N-position by 1-(benzyloxy)-4-(bromomethyl) benzene [32] to

afford product **20**. After deprotection of the benzylether by catalytic hydrogenation, the phenol group of compound **21** reacted with the cyclic alcohol (*tert*-butyl (4*R*)-4-(hydroxymethyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate), a precursor of Garner aldehyde and derived from the methylester of *N*-Boc-*S*-serine [33], under Mitsunobu reaction conditions [34]. The resulting product **22**, was hydrolyzed and coupled with a properly protected derivative of *S*-histidine (**42**, Scheme 7). Catalytic hydrogenation, followed by acidic hydrolysis with 4 N HCl in dioxane, afforded the desired product **26** (Figure 1). Finally the synthesis of H-His(Trt)-OBn (**42**) is depicted in Scheme 7. The commercially available Fmoc-His(Trt)-OH (**40**) was converted to the corresponding benzyl ester (**41**) [35]. The desired, properly protected histidine (**42**) was obtained after Fmoc removal [36].

3. Experimental

3.1. General

All chemicals and solvents were reagent grade and used without purification. Dry THF and extra dry DMF (99.8%) over molecular sieves were purchased from Acros. Melting points were determined on a Büchi 530 apparatus and are uncorrected. Specific rotations were measured at 25 °C on a Perkin–Elmer polarimeter using a 10 cm cell. Nuclear magnetic resonance spectra were obtained on a Varian Mercury spectrometer (¹H-NMR recorded at 200 MHz and ¹³C-NMR recorded at 50 MHz and they are referenced in ppm relative to TMS as an internal standard). Mass spectra were recorded on a Finnigan Surveyor MSQ Plus with only molecular ions and major peaks being reported with intensities quoted as percentages of the base peak. TLC plates (Silica Gel 60 F254) were purchased from Merck. Visualization of spots was effected with UV light and/or phosphomolybdic acid in EtOH stain. All target compounds possessed 95% purity as determined by combustion analysis.

3.2. General Procedure for the Preparation of Compounds **28**, **30**, **35**, **37**

To an ice cooled solution of appropriate alcohol **27**, **29**, **34**, **36** (10 mmol) in Et₂O (25 mL), PBr₃ (1.41 mL, 15 mmol) was added dropwise under argon. The mixture was stirred at room temperature for 3–7 h and the reaction was quenched by the addition of H₂O (15 mL) in small portions at 0 °C. The aqueous phase was removed and the organic layer was washed with H₂O, dried over Na₂SO₄ and evaporated *in vacuo*. In the case of products **30** and **35**, purification was achieved by column chromatography using the appropriate solvent systems as it will be defined in each case below. In the case of bromides **28**, **37**, the oily products were not visible either in UV-light or in iodine stain. They were characterized by NMR and used in the next step without further purification. For this reason the yields of their preparation must be considered as crude yields.

1-Bromo-2-Methoxyethane (**28**). Prepared from the commercially available alcohol **27**; Yield: 58% (colorless oil). ¹H-NMR (CDCl₃): δ 3.69 (t, *J* = 6.0 Hz, 2H, OCH₂), 3.45 (t, *J* = 6.0 Hz, 2H, CH₂Br), 3.38 (s, 3H, CH₃); ¹³C-NMR: δ 72.3 (OCH₂), 58.8 (CH₃), 30.3 (CH₂Br). Anal. calcd for C₃H₇BrO: C, 25.92; H, 5.08; Found: C, 25.68; H, 5.12.

1-(Bromomethyl)-4-(2-Methoxyethoxy)benzene (**30**). Prepared from alcohol **18**. Eluent EtOAc–petroleum ether (bp. 40–60 °C), 3:7; white solid; yield 60%; mp. 47–49 °C; R_f 0.50 in

EtOAc–petroleum ether (bp. 40–60 °C), 3:7. $^1\text{H-NMR}$ (CDCl_3): δ 7.30 (d, J = 8.7 Hz, 2H, Ph), 6.87 (d, J = 8.7 Hz, 2H, Ph), 4.48 (s, 2H, CH_2Br), 4.09 (t, J = 4.5 Hz, 2H, PhOCH_2), 3.73 (t, J = 4.8 Hz, 2H, CH_2OCH_3), 3.43 (s, 3H, CH_3). $^{13}\text{C-NMR}$: δ 158.7, 130.3, 114.7, 70.8 (CH_2OCH_3), 67.2 (PhOCH_2), 59.1 (CH_3), 33.9 (CH_2Br). Anal. calcd for $\text{C}_{10}\text{H}_{13}\text{BrO}_2$: C, 49.00; H, 5.35; Found: C, 48.95; H, 5.25.

1-(Bromomethyl)-4-(3-Methoxypropoxy)benzene (35). Prepared from alcohol **34**. Eluent EtOAc–petroleum ether (bp. 40–60 °C), 3:7; yield: 70% (colorless oil); Rf 0.35 in EtOAc–petroleum ether (bp. 40–60 °C), 3:7. $^1\text{H-NMR}$ (CDCl_3): δ 7.31 (d, J = 8.7 Hz, 2H, Ph), 6.86 (d, J = 8.7 Hz, 2H, Ph), 4.50 (s, 2H, CH_2Br), 4.05 (t, J = 6.3 Hz, 2H, PhOCH_2), 3.55 (t, J = 6.2 Hz, 2H, CH_2OCH_3), 3.35 (s, 3H, CH_3), 2.11–1.98 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2$). $^{13}\text{C-NMR}$: δ 159.1, 130.4, 129.8, 114.7, 69.1 (CH_2OCH_3), 64.8 (PhOCH_2), 58.7 (CH_3), 34.1 (CH_2Br), 29.5 ($\text{CH}_2\text{CH}_2\text{CH}_2$). Anal. calcd for $\text{C}_{11}\text{H}_{15}\text{BrO}_2$: C, 50.98; H, 5.83; Found: C, 50.82; H, 5.93.

1-Bromo-4-Methoxybutane (37). Prepared from the commercially available alcohol **36**; Yield: 60% (colorless oil). $^1\text{H-NMR}$ (CDCl_3): δ 3.47–3.37 (m, 4H, OCH_2 , CH_2Br), 3.33 (s, 3H, CH_3), 2.02–1.88 (m, 2H, $\text{CH}_2\text{CH}_2\text{Br}$), 1.78–1.64 (m, 2H, $\text{CH}_2\text{CH}_2\text{O}$). $^{13}\text{C-NMR}$: δ 71.7 (OCH_2), 58.6 (CH_3), 33.7 (CH_2Br), 29.6 ($\text{CH}_2\text{CH}_2\text{Br}$), 28.2 ($\text{CH}_2\text{CH}_2\text{O}$). Anal. calcd for $\text{C}_5\text{H}_{11}\text{BrO}$: C, 35.95; H, 6.64; Found: C, 35.82; H, 6.59.

1-(Bromomethyl)-4-(4-Methoxybutoxy)benzene (39). To a stirred solution containing alcohol **38** (35 mg, 0.166 mmol) and NaBr (17 mg, 0.166 mmol) in CH_3CN (0.5 mL), TMS-Cl (21 μL , 0.166 mmol) was added under argon. After stirring for 1.5h at rt, the solvent was evaporated *in vacuo* and the residue dissolved in Et_2O was washed with brine and H_2O . The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. After purification by column chromatography using EtOAc–petroleum ether (bp. 40–60 °C) 1:9 as eluent, the product was obtained as a colorless oil in 42% yield (19 mg). Rf 0.35 in EtOAc–petroleum ether (bp. 40–60 °C) 1:9. $^1\text{H-NMR}$ (CDCl_3): δ 7.27 (d, J = 8.6 Hz, 2H, Ph), 6.84 (d, J = 8.6 Hz, 2H, Ph), 4.50 (d, J = 12.6 Hz, 2H, CH_2Br), 3.95 (t, J = 5.9 Hz, 2H, PhOCH_2), 3.42 (t, J = 6.2 Hz, 2H, CH_2OCH_3), 3.33 (s, 3H, CH_3), 1.87–1.68 (m, 4H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$). $^{13}\text{C-NMR}$: δ 159.0, 130.3, 114.5, 72.2 (CH_2OCH_3), 67.5 (PhOCH_2), 58.5 (CH_3), 34.0 (CH_2Br), 26.1, 25.9. Anal. calcd for $\text{C}_{12}\text{H}_{17}\text{BrO}_2$: C, 52.76; H, 6.27; Found: C, 52.82; H, 6.35.

3.3. General Procedure for the Preparation of Compounds **29**, **38**

To a stirred solution of 4-hydroxybenzylalcohol (1.24 g, 10 mmol) in acetone (45 mL), bromides **28** or **37** (10.5 mmol), K_2CO_3 (4.14 g, 30 mmol) and 18-crown-6 (0.020 g) were added consecutively. The mixture was refluxed for 3 days. After evaporation of the solvent, the residue was dissolved in EtOAc and washed with brine and H_2O . The organic layer was dried over Na_2SO_4 , filtered and evaporated under reduced pressure. Purification was achieved by column chromatography, eluting with the appropriate solvents as defined for each case below.

[4-(2-Methoxyethoxy)-phenyl]methanol (29). Prepared from bromide **28**. Eluent CHCl_3 –MeOH, 9.5:0.5; Yield: 76% (colorless oil); Rf 0.48 in CHCl_3 –MeOH, 9.5:0.5. $^1\text{H-NMR}$ (CDCl_3): δ 7.27 (d, J = 8.7 Hz, 2H, Ph), 6.90 (d, J = 8.7 Hz, 2H, Ph), 4.61 (s, 2H, CH_2OH), 4.11 (t, J = 4.6 Hz, 2H,

PhOCH₂), 3.75 (t, J = 4.9 Hz, 2H, CH₂OCH₃), 3.44 (s, 3H, CH₃); ¹³C-NMR: δ 158.2, 133.3, 128.5, 114.5, 70.9 (CH₂OCH₃), 67.2 (PhOCH₂), 64.8 (CH₂OH), 59.2 (CH₃). Anal. calcd for C₁₀H₁₄O₃: C, 65.91; H, 7.74; Found: C, 65.79; H, 7.68.

[4-(4-Methoxybutoxy) Phenyl]methanol (**38**). Prepared from bromide **37**. Eluent CHCl₃–MeOH, 9:1; Yield: 67% (colorless oil); R_f 0.35 in CHCl₃–MeOH, 9:1. ¹H-NMR (CDCl₃): δ 7.26 (d, J = 8.7 Hz, 2H, Ph), 6.86 (d, J = 8.7 Hz, 2H, Ph), 4.60 (s, 2H, CH₂OH), 3.97 (t, J = 6.1 Hz, 2H, PhOCH₂), 3.43 (t, J = 6.2 Hz, 2H, CH₂OCH₃), 3.34 (s, 3H, CH₃), 1.88–1.69 (m, 4H, CH₂CH₂CH₂CH₂). ¹³C-NMR: δ 158.6, 132.9, 128.6, 114.5, 72.3 (CH₂OCH₃), 67.6 (PhOCH₂), 65.0 (CH₂OH), 58.5 (CH₃), 26.2, 26.0. Anal. calcd for C₁₂H₁₈O₃: C, 68.54; H, 8.63; Found: C, 68.62; H, 8.59.

4-(3-Bromopropoxy) Benzaldehyde (**32**). To a stirred solution of 4-hydroxy-benzaldehyde (1 g, 8.2 mmol) in CH₃CN (15 mL), K₂CO₃ (1.70 g, 12.3 mmol) and 1,3-dibromopropane (8.3 mL, 81.9 mmol) were added consecutively. A tube filled with CaCl₂ was fixed on the condenser and the mixture was refluxed overnight. After evaporation of the solvent, the residue was dissolved in EtOAc and washed with brine and H₂O. The organic layer was dried over Na₂SO₄, filtered and evaporated under reduced pressure. Purification was achieved by column chromatography using EtOAc–petroleum ether (bp. 40–60 °C) 1:4 as eluent. The product was obtained as colorless oil in 40% yield (0.8 g) and stored at –4 °C, only for a short time. R_f 0.36 in EtOAc–petroleum ether (bp. 40–60 °C) 1:4. ¹H-NMR (CDCl₃): δ 9.88 (s, 1H, CHO), 7.83 (d, J = 8.9 Hz, 2H, Ph), 7.00 (d, J = 8.9 Hz, 2H, Ph), 4.19 (t, J = 5.8 Hz, 2H, PhOCH₂), 3.60 (t, J = 6.3 Hz, 2H, CH₂Br), 2.41–2.29 (m, 2H, CH₂CH₂CH₂). ¹³C-NMR: δ 190.7 (CHO), 163.6, 131.9, 130.1, 114.7, 65.6 (PhOCH₂), 32.0 (CH₂Br), 29.6 (CH₂CH₂CH₂). Anal. calcd for C₁₀H₁₁BrO₃: C, 49.41; H, 4.56; Found: C, 49.56; H, 4.39.

4-(3-Methoxypropoxy)benzaldehyde (**33**). To a stirred solution of bromide **32** (46 mg, 0.19 mmol) in MeOH (2 mL), a freshly prepared solution of 1N CH₃ONa/MeOH (200 μ L) was added and the mixture was left stirring at rt for 2 days. The reaction was quenched by the addition of H₂O and the mixture was acidified with aq. 1 N HCl. After evaporation of the solvent, the residue was dissolved in EtOAc and washed with brine and H₂O. The organic layer was dried over Na₂SO₄, filtered and evaporated under reduced pressure. Purification was achieved by column chromatography using EtOAc–petroleum ether (bp. 40–60 °C) 2:3 as eluent. The product was obtained as a colorless oil in 38% yield (14 mg) and was immediately subjected to the following reaction. R_f 0.38 in EtOAc–petroleum ether (bp. 40–60 °C) 2:3. ¹H-NMR (CDCl₃): δ 9.87 (s, 1H, CHO), 7.82 (d, J = 8.8 Hz, 2H, Ph), 7.00 (d, J = 8.8 Hz, 2H, Ph), 4.14 (t, J = 6.3 Hz, 2H, PhOCH₂), 3.56 (t, J = 6.0 Hz, 2H, CH₂O), 3.35 (s, 3H, CH₃), 2.14–2.01 (m, 2H, CH₂CH₂CH₂). ¹³C-NMR: δ 190.8 (CHO), 164.0, 131.9, 129.8, 114.7, 68.8 (CH₂OCH₃), 65.2 (PhOCH₂), 58.7 (CH₃), 29.4 (CH₂CH₂CH₂). MS (ESI): m/z = 195 (100) (M+H⁺). Anal. calcd for C₁₁H₁₄O₃: C, 68.02; H, 7.27; Found: C, 68.18; H, 7.15.

[4-(3-Methoxypropoxy) Phenyl]methanol (**34**). To a stirred solution of aldehyde **33** (63 mg, 0.324 mmol) in dry THF (2 mL) at 0 °C NaBH₄ (18 mg, 0.487 mmol) was added under argon. The reaction mixture was left stirring at rt overnight. The reaction was quenched by the addition of a 20% solution of AcOH at 0 °C, until the production of the gas was ceased. The organic solvent was evaporated under reduced pressure and the residue was dissolved in EtOAc. The organic phase was washed with 5% aq.

NaHCO₃, brine and H₂O, dried over Na₂SO₄ and evaporated under reduced pressure. After purification with column chromatography using EtOAc–petroleum ether (bp. 40–60 °C) 2:3 as eluent, the product was obtained as a colorless oil in 75% yield (47 mg). Rf 0.25 in EtOAc–petroleum ether (bp. 40–60 °C) 2:3. ¹H-NMR (CDCl₃): δ 7.28 (d, *J* = 8.6 Hz, 2H, Ph), 6.89 (d, *J* = 8.6 Hz, 2H, Ph), 4.61 (s, 2H, CH₂OH), 4.05 (t, *J* = 6.3 Hz, 2H, PhOCH₂), 3.55 (t, *J* = 6.2 Hz, 2H, CH₂OCH₃), 3.35 (s, 3H, CH₃), 2.11–1.98 (m, 2H, CH₂CH₂CH₂). ¹³C-NMR: δ 158.6, 133.0, 114.5, 69.2 (CH₂OCH₃), 65.0 (CH₂OH), 64.8 (PhOCH₂), 58.7 (CH₃), 29.5 (CH₂CH₂CH₂). MS (ESI): *m/z* = 197 (100) (M+H⁺). Anal. calcd for C₁₁H₁₆O₃: C, 67.32; H, 8.22; Found: C, 67.53; H, 8.09.

(5*S*)-(Hydroxymethyl)-2-Pyrrolidinone (**2**). See reference [17].

5-[[*(Triethylsilyl)oxy*] Methyl]-2-Pyrrolidinone (**3**). See reference [18].

3.4. General Procedure of for the Preparation of Compounds **4**, **8**, **16a–c**, **20**

To a cooled solution of methyl (S)-pyroglutamate (**1**), *O*-protected-S-pyroglutaminol (**3**), or methylester **7** (1 mmol) in dry THF (5 mL) NaH (60% in paraffin oil, 1.5 mmol) was added in small portions, followed by the addition of the appropriate benzyl bromide (or benzyloxycarbonylchloride in case of compound **4**) (1.1 mmol). The stirring was continued for 15 min at 0 °C, and for 24 h at rt under argon. The reaction was quenched by the addition of a saturated solution of NH₄Cl at 0 °C, the organic solvent was evaporated and the residue was dissolved in ethyl acetate. The organic layer was washed with brine, dried over Na₂SO₄ and evaporated under reduced pressure. The product was purified by column chromatography (Silica Gel 60) using the appropriate solvent systems as defined in each case below.

Benzyl (5S)-2-oxo-5-[[(triethylsilyl)oxy*]methyl]pyrrolidine-1-carboxylate* (**4**). Prepared from compound **3** and benzyloxycarbonyl chloride. Eluent EtOAc–petroleum ether (bp. 40–60 °C), 4:6. The product was obtained as colorless oil in 50% yield. Rf 0.53 in EtOAc–petroleum ether (bp. 40–60 °C), 4:6; [α]_D –68.2 (c 1.1, CHCl₃). ¹H-NMR (CDCl₃): δ 7.46–7.32 (m, 5H, Ph), 5.28 (dd, *J*₁ = 12.4 Hz, *J*₂ = 18.4 Hz, 2H, COOCH₂), 4.28–4.20 (m, 1H, NCH), 3.88 (dd, *J*₁ = 4.0 Hz, *J*₂ = 10.6 Hz, 1H, CHHOSi), 3.67 (dd, *J*₁ = 2.5 Hz, *J*₂ = 10.7 Hz, 1H, CHHOSi), 2.84–2.03 (m, 4H, 2xCH₂), 0.88 (t, *J* = 7.6 Hz, 9H, 3 × CH₃), 0.51 (q, *J* = 7.6 Hz, 6H, 3 × (CH₂CH₃)). ¹³C-NMR: δ 174.7 (CON), 151.3 (COO), 135.2, 128.5, 128.3, 128.2, 67.8 (CH₂OSi), 63.7 (OCH₂Ph), 58.8 (NCH), 32.1, 21.2, 6.6 (CH₂CH₃), 4.1 (CH₂CH₃). MS (ESI): *m/z* = 364 (100) (M+H⁺). Anal. calcd for C₁₉H₂₉NO₄Si: C, 62.78; H, 8.04; N, 3.85 Found: C, 62.83; H, 7.95; N, 3.92.

*Methyl 3-[(2*S*)-1-[4-(2-Methoxyethoxy)benzyl]-5-oxopyrrolidin-2-yl] propanoate* (**8**). Prepared from compound **7** and bromide **30**. Eluent EtOAc–petroleum ether (bp. 40–60 °C), 9:1. The product was obtained as colorless oil in 40% yield. Rf 0.23 in EtOAc–petroleum ether (bp. 40–60 °C), 1:9; [α]_D +5.2 (c 0.92, CHCl₃). ¹H-NMR (CDCl₃): δ 7.13 (d, *J* = 8.6 Hz, 2H, Ph), 6.83 (d, *J* = 8.6 Hz, 2H, Ph), 4.90 (d, *J* = 14.8 Hz, 1H, NCHHPh), 4.09–4.04 (m, 2H, PhOCH₂), 3.85 (d, *J* = 14.8 Hz, 1H, NCHHPh), 3.73–3.68 (m, 2H, CH₂OCH₃), 3.62 (s, 3H, COOCH₃), 3.42–3.38 (m, 1H, NCH), 3.41 (s, 3H, OCH₃), 2.45–1.54 (m, 8H, 4 × CH₂). ¹³C-NMR: δ 174.8 (NCO), 173.0 (COO), 158.1, 129.2,

128.7, 114.6, 70.7 (CH₂OCH₃), 67.1 (PhOCH₂), 59.1 (OCH₃), 55.7 (NCH), 51.7 (COOCH₃), 43.3 (NCH₂Ph), 30.0, 29.0, 27.6, 23.3. MS (ESI): m/z = 358 (100) (M+Na⁺). Anal. calcd for C₁₈H₂₅NO₅: C, 64.46; H, 7.51; N, 4.18 Found: C, 64.51; H, 7.62; N, 4.05.

Methyl 1-[4-(2-Methoxyethoxy)benzyl]-5-oxo-L-prolinate (16a). Prepared from methyl-S-pyroglutamate (1) and bromide 30. Eluent EtOAc. The product was obtained as a colorless oil in 73% yield. Rf 0.42 in EtOAc; [α]_D +20.2 (c 1.0, CHCl₃). ¹H-NMR (CDCl₃): δ 7.07 (d, J = 8.5 Hz, 2H, Ph), 6.82 (d, J = 8.5 Hz, 2H, Ph), 4.87 (d, J = 14.7 Hz, 1H, CHHPh), 4.07–4.02 (m, 2H, PhOCH₂), 3.93–3.86 (m, 2H, CHHPh, NCHCOO), 3.71–3.66 (m, 2H, CH₂OCH₃), 3.62 (s, 3H, COOCH₃), 3.39 (s, 3H, OCH₃), 2.61–1.92 (m, 4H, 2 × CH₂). ¹³C-NMR: δ 174.8 (NCO), 172.1 (COO), 158.2, 129.7, 127.8, 114.6, 70.8 (CH₂OCH₃), 67.1 (OCH₂), 59.0 (NCH), 58.4 (OCH₃), 52.2 (COOCH₃), 44.8 (CH₂Ph), 29.5, 22.6. MS (ESI): m/z = 308 (100) (M+H⁺). Anal. calcd for C₁₆H₂₁NO₅: C, 62.53; H, 6.89; N, 4.56 Found: C, 62.58; H, 6.75; N, 4.61.

Methyl 1-[4-(3-Methoxypropoxy)benzyl]-5-oxo-L-prolinate (16b). Prepared from methyl-S-pyroglutamate (1) and bromide 35. Eluent EtOAc. The product was obtained as a colorless oil in 72% yield. Rf 0.44 in EtOAc; [α]_D +13.5 (c 1.0, CHCl₃). ¹H-NMR (CDCl₃): δ 7.08 (d, J = 8.6 Hz, 2H, Ph), 6.80 (d, J = 8.6 Hz, 2H, Ph), 4.90 (d, J = 14.6 Hz, 1H, NCHHPh), 3.99 (t, J = 6.3 Hz, 2H, PhOCH₂), 3.95–3.90 (m, 1H, NCHCOO), 3.89 (d, J = 4.6 Hz, 1H, NCHHPh), 3.65 (s, 3H, COOCH₃), 3.51 (t, J = 6.2 Hz, 2H, CH₂OCH₃), 3.31 (s, 3H, OCH₃), 2.57–1.93 (m, 6H, 3 × CH₂). ¹³C-NMR: δ 174.8 (NCO), 172.2 (COO), 158.5, 129.7, 127.5, 114.5, 69.0 (CH₂OCH₃), 64.7 (PhOCH₂), 58.6 (NCH), 58.4 (OCH₃), 44.8 (CH₂Ph), 29.5, 29.4, 22.6. MS (ESI): m/z = 322 (100) (M+H⁺). Anal. calcd for C₁₇H₂₃NO₅: C, 63.54; H, 7.21; N, 4.36 Found: C, 63.48; H, 7.28; N, 4.18.

Methyl 1-[4-(4-Methoxybutoxy)benzyl]-5-oxo-L-prolinate (16c). Prepared from methyl-S-pyroglutamate (1) and bromide 39. Eluent EtOAc. The product was obtained as a colorless oil in 66% yield. Rf 0.47 in EtOAc; [α]_D +11.7 (c 1.0, CHCl₃). ¹H-NMR (CDCl₃): δ 7.08 (d, J = 8.6 Hz, 2H, Ph), 6.79 (d, J = 8.6 Hz, 2H, Ph), 4.90 (d, J = 14.7 Hz, 1H, NCHHPh), 3.97–3.89 (m, 1H, NCHCOO), 3.92 (t, J = 6.30 Hz, 2H, PhOCH₂), 3.90 (d, J = 14.7 Hz, 1H, NCHHPh), 3.65 (s, 3H, COOCH₃), 3.40 (t, J = 6.2 Hz, 2H, CH₂OCH₃), 3.31 (s, 3H, OCH₃), 2.58–1.96 (m, 4H, 2 × CH₂), 1.84–1.67 (m, 4H, (OCH₂CH₂)₂). ¹³C-NMR: δ 174.8 (NCO), 172.2 (COO), 158.6, 129.7, 127.5, 114.5, 72.2 (CH₂OCH₃), 67.5 (PhOCH₂), 58.5 (NCH), 58.4 (OCH₃), 52.2 (COOCH₃), 44.9 (NCH₂Ph), 29.5, 26.1, 25.9, 22.7. MS (ESI): m/z = 336 (100) (M+H⁺). Anal. calcd for C₁₈H₂₅NO₅: C, 64.46; H, 7.51; N, 4.18 Found: C, 64.38; H, 7.48; N, 4.27.

Methyl 1-[4-(Benzyloxy)benzyl]-5-oxo-L-prolinate (20). Prepared from methyl-S-pyroglutamate (1) and 1-(benzyloxy)-4-(bromomethyl) benzene [32]. Eluent EtOAc–petroleum ether (bp. 40–60 °C), 7:3. The product was obtained as a colorless oil in 47% yield. Rf 0.35 in EtOAc–petroleum ether (bp. 40–60 °C), 7:3; [α]_D +22.5 (c 1, CHCl₃). ¹H-NMR (CDCl₃): δ 7.44–7.28 (m, 5H, Ph), 7.14 (d, J = 8.5 Hz, 2H, Ph), 6.92 (d, J = 8.5 Hz, 2H, Ph), 5.05 (s, 2H, OCH₂Ph), 4.93 (d, J = 14.7 Hz, 1H, NCHHPh), 4.00–3.92 (m, 2H, NCHHPh, NCH), 3.66 (s, 3H, CH₃), 2.53–2.04 (m, 4H, 2 × CH₂). ¹³C-NMR: δ 174.8 (NCO), 172.1 (COOCH₃), 158.2, 136.7, 129.7, 128.4, 127.9, 127.8, 127.3, 114.8, 69.8

(OCH₂Ph), 58.5 (NCH), 52.2 (CH₃), 44.8 (NCHPh), 29.4, 22.6. MS (ESI): m/z = 340 (100) (M+H⁺). Anal. calcd for C₂₀H₂₁NO₄: C, 70.78; H, 6.24; N, 4.13 Found: C, 70.62; H, 6.27; N, 4.22.

Benzyl (2S)-2-(Hydroxymethyl)-5-oxopyrrolidine-1-carboxylate (5). To a stirred solution of compound **4** (1.20 g, 3.30 mmol) in DCM (20 mL), TFA was added (2.02 mL, 26.4 mmol) at room temperature. Once the reaction was finished (45 min), the solvent was evaporated to dryness. The residue was dissolved in toluene and the solvent was evaporated (twice) for the removal of the acid. Finally the residue was dissolved in ethyl acetate and the organic phase was washed with brine to neutral pH. After drying over Na₂SO₄ and evaporation of the solvent under reduced pressure, the product was obtained as a pure white solid. Yield: 0.710 g (86%); R_f 0.37 in EtOAc; mp. 83–86 °C; [α]_D −54.2 (c 1.0, CHCl₃). ¹H-NMR (CDCl₃): δ 7.37–7.33 (m, 5H, Ph), 5.23 (s, 2H, OCH₂Ph), 4.29–4.23 (m, 1H, NCH), 3.95 (dd, J_1 = 3.2 Hz, J_2 = 11.8 Hz, 1H, CHHOH), 3.66 (dd, J_1 = 3.2 Hz, J_2 = 11.8 Hz, 1H, CHHOH), 3.09 (bs, 1H, OH), 3.86–1.95 (m, 4H, 2 × CH₂). ¹³C-NMR: δ 175.5 (CON), 151.7 (COO), 135.0, 128.6, 128.4, 128.1, 68.0 (OCH₂Ph), 64.1 (CH₂OH), 59.4 (NCH), 32.1, 20.9. MS (ESI): m/z = 250 (100) (M+H⁺). Anal. calcd for C₁₃H₁₅NO₄: C, 62.64; H, 6.07; N, 5.62 Found: C, 62.59; H, 6.12; N, 5.59.

Benzyl (2S)-2-[(1E)-3-Methoxy-3-oxoprop-1-en-1-yl]-5-oxopyrrolidine-1-carboxylate (6). Alcohol **5** (0.22 g, 0.882 mmol) was dissolved in a mixture of dry toluene (5 mL) and dry DMSO (2.5 mL), followed by the addition of EDC·HCl (0.51 g, 2.64 mmol), the dropwise addition of dry pyridine (0.25 mL, 3.04 mmol) and finally TFA (33.2 μL, 0.441 mmol) under argon. After stirring at rt for 1.5 h the reaction was quenched by the addition of CHCl₃ and the solution was washed with brine and H₂O. The organic layer was dried over Na₂SO₄, filtered and evaporated under reduced pressure. The resulting crude aldehyde was subjected to Wittig reaction without further purification. More specifically, it was dissolved in dry THF (6 mL), methyl (triphenylphosphoranylidene)acetate (0.32 g, 0.95 mmol) was added and the mixture was refluxed under argon for 1 h. The reaction was quenched by the addition of saturated solution of NH₄Cl. The solvent was evaporated under reduced pressure and the residue dissolved in EtOAc was successively washed with NH₄Cl, H₂O and brine. The organic layer was dried over Na₂SO₄, filtered and evaporated under reduced pressure. After purification by column chromatography using EtOAc as eluent, the product was obtained in 60% yield (0.16 g) as a colorless oil. R_f 0.63 in EtOAc; [α]_D −71.1 (c 1.0, CHCl₃). ¹H-NMR (CDCl₃): δ 7.38–7.31 (m, 5H, Ph), 6.89 (dd, J_1 = 6.3 Hz, J_2 = 6.2 Hz, 1H, CHCHCOOCH₃), 5.25 (dd, J_1 = 12.3 Hz, J_2 = 12.2 Hz, 2H, CH₂Ph), 4.87–4.81 (m, 1H, NCH), 3.73 (s, 3H, OCH₃), 2.64–1.82 (m, 4H, 2 × CH₂). ¹³C-NMR: δ 173.0 (NCOCH₂), 166.0 (COOCH₃), 150.8 (COOCH₂), 145.1, 134.8, 128.5, 128.4, 128.2, 121.5 (CHCOOCH₃), 68.2 (OCH₂Ph), 57.8 (NCH), 51.7 (CH₃), 30.7, 23.8. MS (ESI): m/z = 326 (100) (M+Na⁺). Anal. calcd for C₁₇H₁₇NO₅: C, 63.36; H, 5.65; N, 4.62 Found: C, 63.29; H, 5.48; N, 4.75.

(5R)-5-(3-Hydroxypropyl)-1-[4-(2-methoxyethoxy)benzyl]-pyrrolidin-2-one (9). To a two necked flask, LiBH₄ (14 mg, 0.656 mmol) was suspended in dry THF (0.5 mL) under argon at rt. A solution of compound **8** (0.110g, 0.656 mmol) in dry THF (1.5 mL) was added dropwise and the reaction mixture was stirred for 10 h. The reaction was quenched by the addition of a 20% aq. solution of AcOH at 0 °C until gas production ceased. The excess of acetic acid was neutralized by the addition of a small quantity of Na₂CO₃. The organic solvent was evaporated under reduced pressure and the residue was

dissolved in EtOAc. The organic phase was then washed with brine, dried over Na₂SO₄ and evaporated under reduced pressure. After purification with column chromatography using EtOAc–MeOH 9:1 as eluent, the product was obtained as a colorless oil in 87% yield (87 mg). R_f 0.34 in EtOAc–MeOH 9:1; [α]_D +7.6 (c 0.95, CHCl₃). ¹H-NMR (CDCl₃): δ 7.13 (d, *J* = 8.6 Hz, 2H, Ph), 6.84 (d, *J* = 8.6 Hz, 2H, Ph), 4.89 (d, *J* = 14.8 Hz, 1H, NCHHPh), 4.10–4.05 (m, 2H, PhOCH₂), 3.88 (d, *J* = 14.8 Hz, 1H, NCHHPh), 3.74–3.70 (m, 2H, CH₂OCH₃), 3.64–3.54 (m, 2H, CH₂OH), 3.42 (s, 4H, NCH, CH₃), 2.47–1.36 (m, 8H, 4 × CH₂). ¹³C-NMR: δ 175.1 (NCO), 158.1, 129.2, 128.8, 114.6, 70.9 (CH₂OCH₃), 67.1 (PhOCH₂), 62.2 (CH₂OH), 59.2 (CH₃), 56.6 (NCH), 43.4 (NCH₂Ph), 30.2, 28.9, 27.3, 23.7. MS (ESI): *m/z* = 308 (90) (M+H⁺). Anal. calcd for C₁₇H₂₅NO₄: C, 66.43; H, 8.20; N, 4.56 Found: C, 66.38; H, 8.26; N, 4.42.

3-{(2R)-1-[4-(2-Methoxyethoxy)benzyl]-5-oxopyrrolidin-2-yl}propyl 4-Methylbenzenesulfonate (10). To an ice cooled stirred solution of alcohol **9** (35 mg 0.114 mmol) in DCM (2 mL), p-toluenesulfonylchloride (43 mg, 0.228 mmol) was added, followed by the addition of Et₃N (17.5 μL). The reaction mixture was stirred at 0 °C for 10 min and overnight at room temperature. The organic layer was subsequently washed with a 1N HCl aq. solution, brine, 5% aq. solution of NaHCO₃ and brine. After drying over Na₂SO₄ and evaporation in vacuo, the residue was purified by column chromatography using EtOAc as eluent, and the product was obtained as a yellowish oil in 72% yield (37 mg). R_f 0.35 in EtOAc; [α]_D +5.6 (c 1, CHCl₃). ¹H-NMR (CDCl₃): δ 7.75 (d, *J* = 8.3 Hz, 2H, Ph), 7.34 (d, *J* = 8.0 Hz, 2H, Ph), 7.10 (d, *J* = 8.6 Hz, 2H, Ph), 6.85 (d, *J* = 8.6 Hz, 2H, Ph), 4.83 (d, *J* = 14.9 Hz, 1H, NCHHPh), 4.11–4.06 (m, 2H, PhOCH₂), 3.95 (t, *J* = 5.9 Hz, 2H, CH₂OSO₂), 3.83 (d, *J* = 14.9 Hz, 1H, NCHHPh), 3.75–3.71 (m, 2H, CH₂OCH₃), 3.43 (s, 3H, OCH₃), 3.39–3.31 (m, 1H, NCH), 2.44 (s, 3H, CH₃), 2.41–1.50 (m, 8H, 4 × CH₂). ¹³C-NMR: δ 174.9 (NCO), 158.1, 144.9, 132.8, 129.9, 129.2, 128.7, 127.8, 114.7, 70.9 (CH₂OCH₃), 69.9 (CH₂OSO₂), 67.2 (PhOCH₂), 59.2 (CH₃), 56.1 (NCH), 43.5 (NCH₂Ph), 30.1, 28.7, 23.9, 23.5, 21.6 (PhCH₃). MS (ESI): *m/z* = 462 (100) (M+H⁺). Anal. calcd for C₂₄H₃₁NO₆S: C, 62.45; H, 6.77; N, 3.03 Found: C, 62.32; H, 6.82; N, 3.18.

3.5. General Procedure of for the Preparation of Compounds 11–13

Imidazole or 1*H*-imidazole-4(5)-carboxylic acid phenylmethyl ester [16], (1.2 mmol) and cesium carbonate (0.39 g, 1.2 mmol) were dissolved in dry DMF (3 mL) under argon. After stirring of the mixture for 30 min at 50 °C, a solution of tosyl ester **10** (1 mmol) dissolved in dry DMF (3 mL) was added and the stirring was continued overnight at 50 °C under argon. After evaporation of DMF in high vacuo, the residue was dissolved in EtOAc and the organic phase was washed with brine to neutral pH, dried over Na₂SO₄ and evaporated under reduced pressure. The residual product was purified by column chromatography (silica gel) using the appropriate solvent systems as it will be defined, in each case, below.

(5R)-5-[3-(1H-Imidazol-1-yl)propyl]-1-[4-(2-methoxyethoxy)benzyl]-pyrrolidin-2-one (11). Prepared from tosyl ester **10** and imidazole as a colorless oil. Eluent EtOAc–MeOH, 7:3. Yield: 58%. R_f 0.29 in EtOAc–MeOH, 7:3. [α]_D +4.1 (c 0.8, MeOH). ¹H-NMR (CD₃OD): δ 7.61 (s, 1H, NCHN), 7.11 (d, *J* = 8.6 Hz, 2H, Ph), 7.07 (s, 1H, CH₂NCHCHN), 6.98 (s, 1H, CH = NCH = CHN), 6.89 (d, *J* = 8.6 Hz, 2H, Ph), 4.69 (d, *J* = 14.9 Hz, 1H, NCHHPh), 4.12–4.07 (m, 2H, PhOCH₂), 4.03–3.93 (m,

3H, NCHPh, CH₂N), 3.75–3.71 (m, 2H, CH₂OCH₃), 3.52–3.42 (m, 1H, NCH), 3.41 (s, 3H, CH₃), 2.47–1.30 (m, 8H, 4 × CH₂). ¹³C-NMR: δ 177.8 (NCO), 159.8, 138.5, 130.4, 130.1, 129.1, 120.6, 115.8, 72.2 (CH₂OCH₃), 68.5 (PhOCH₂), 59.3 (CH₃), 58.7 (CONCH), 47.7 (CH₂N), 44.7 (NCH₂Ph), 31.2, 30.6, 26.9, 24.5. MS (ESI): *m/z* = 358 (100) (M+H⁺). Anal. calcd for C₂₀H₂₇N₃O₃: C, 67.20; H, 7.61; N, 11.76 Found: C, 67.28; H, 7.52; N, 11.82.

Benzyl 1-(3-((2R)-1-[4-(2-Methoxyethoxy)benzyl]-5-oxopyrrolidin-2-yl)propyl)-1H-imidazole-5-carboxylate (12). Prepared from tosyl ester **10** and 1H-imidazole-4(5)-carboxylic acid phenylmethyl ester [16], as a mixture with its constitutional isomer **13**. Eluent EtOAc–MeOH, 9:1. Yield: 55% (colorless oil). R_f 0.42 in EtOAc–MeOH, 7:3. [α]_D +2.8 (c 1, CHCl₃). ¹H-NMR (CDCl₃): δ 7.78 (s, 1H, NCHN), 7.58 (s, 1H, NCHCOO), 7.40–7.34 (m, 5H, Ph), 7.08 (d, *J* = 8.6 Hz, 2H, Ph), 6.85 (d, *J* = 8.6 Hz, 2H, Ph), 5.28 (s, 2H, OCH₂Ph), 4.78 (d, *J* = 14.9 Hz, 1H, NCHHPh), 4.20 (t, *J* = 6.7 Hz, 2H, CH₂N), 4.10–4.06 (m, 2H, PhOCH₂), 3.87 (d, *J* = 14.9 Hz, 1H, NCHHPh), 3.74–3.70 (m, 2H, CH₂OCH₃), 3.42 (s, 3H, CH₃), 3.41–3.33 (m, 1H, NCH), 2.43–1.24 (m, 8H, 4 × CH₂). ¹³C-NMR: δ 174.9 (NCO), 159.8 (COO), 158.1, 141.8, 137.9, 135.5, 129.1, 128.8, 128.6, 128.5, 128.3, 128.0, 114.7, 70.9 (CH₂OCH₃), 67.2 (PhOCH₂), 66.2 (COOCH₂Ph), 59.1 (CH₃), 56.3 (NCH), 46.6 (CH₂NCCOO), 43.6 (NCH₂Ph), 30.1, 29.6, 26.0, 23.6. MS (ESI): *m/z* = 492 (100) (M+H⁺). Anal. calcd for C₂₈H₃₃N₃O₅: C, 68.41; H, 6.77; N, 8.55 Found: C, 68.32; H, 6.60; N, 8.57.

Benzyl 1-(3-((2R)-1-[4-(2-Methoxyethoxy)benzyl]-5-oxopyrrolidin-2-yl)propyl)-1H-imidazole-4-carboxylate (13). Prepared from tosyl ester **10** and 1H-imidazole-4(5)-carboxylic acid, phenylmethyl ester [16], as a mixture with its constitutional isomer **12**. After the separation of isomer **12**, the elution system (EtOAc–MeOH, 9:1) was gradually changed to the more polar EtOAc–MeOH, 3:2 in order to recover isomer **13**. Yield: 30% (colorless oil). R_f 0.56 in EtOAc–MeOH, 3:2. [α]_D +9.9 (c 1, CHCl₃). ¹H-NMR (CDCl₃): δ 7.53 (s, 1H, NCHN), 7.51 (s, 1H, NCHCOO), 7.46–7.31 (m, 5H, Ph), 7.07 (d, *J* = 8.7 Hz, 2H, Ph), 6.84 (d, *J* = 8.7 Hz, 2H, Ph), 6.34 (s, 2H, COOCH₂Ph), 4.73 (d, *J* = 14.9 Hz, 1H, NCHHPh), 4.09–4.05 (m, 2H, PhOCH₂), 3.97–3.82 (m, 3H, NCHHPh, CH₂N), 3.74–3.69 (m, 2H, CH₂OCH₃), 3.43 (s, 3H, CH₃), 3.41–3.36 (m, 1H, NCH), 2.45–1.24 (m, 8H, 4 × CH₂). ¹³C-NMR: δ 174.9 (NCO), 162.2 (COO), 158.2, 137.9, 136.0, 133.6, 129.1, 128.7, 128.5, 128.4, 128.2, 124.9, 114.7, 70.9 (CH₂OCH₃), 67.2 (PhOCH₂), 66.2 (COOCH₂Ph), 59.2 (CH₃), 56.4 (NCH), 47.3 (CH₂NCHN), 43.9 (NCH₂Ph), 30.1, 29.7, 25.8, 23.6. MS (ESI): *m/z* = 492 (100) (M+H⁺). Anal. calcd for C₂₈H₃₃N₃O₅: C, 68.41; H, 6.77; N, 8.55 Found: C, 68.38; H, 6.82; N, 8.45.

3.6. General Procedure for the Preparation of Compounds **7**, **14**, **15**, **19a–c**, **21**, **25**

A mixture of a compound possessing a double bond and also the *N*-benzyloxycarbonyl group (compound **6**), benzyl ester (compounds **12,13**), benzyl ether (compound **20**) or benzyl ester and *N*-trityl imidazole group (compounds **18a–c**, **24**) (1 mmol) in MeOH (10 mL) and 10% palladium on activated carbon (0.02 g or 0.04 g for compounds **6**, **18a–c**, **24**) was hydrogenated for 1.5–3 h (overnight for compound **6**) under atmospheric conditions. After filtration through a pad of Celite, the solvent was removed *in vacuo* to give the deprotected final compound in almost quantitative yield and high purity. In the case of compounds **18a–c** and **24** the triphenylmethane produced from the

hydrogenation of trityl protecting group was completely removed by adding a small quantity of CHCl_3 and discounting the supernatant where the polar products (**19a–c**, **25**) were insoluble.

Methyl 3-[(2S)-5-Oxopyrrolidin-2-yl] propanoate (7). Prepared from alkene **6**. The product was obtained as a yellowish solid in 94% yield and high purity. R_f 0.14 in EtOAc; mp. 72–75 °C; $[\alpha]_D^{25} +14.3$ (c 0.95, CHCl_3). $^1\text{H-NMR}$ (CDCl_3): δ 7.01 (bs, 1H, NH), 3.73–3.64 (m, 1H, NCH), 3.66 (s, 3H, CH_3), 2.41–1.60 (m, 8H, $4 \times \text{CH}_2$). $^{13}\text{C-NMR}$: δ 178.6 (NCO), 173.1 (COOCH_3), 53.7 (NCH), 51.4 (CH_3), 31.3, 30.1, 26.5. MS (ESI): $m/z = 172$ (100) ($\text{M}+\text{H}^+$). Anal. calcd for $\text{C}_8\text{H}_{13}\text{NO}_3$: C, 56.13; H, 7.65; N, 8.18 Found: C, 56.22; H, 7.58; N, 8.22.

1-(3-{(2R)-1-[4-(2-Methoxyethoxy)benzyl]-5-oxopyrrolidin-2-yl}propyl)-1H-imidazole-5-carboxylic acid (14). Catalytic hydrogenation of compound **12** afforded product **14** as a pure colorless oil in 99% yield. R_f 0.18 in EtOAc–MeOH, 3:2. $[\alpha]_D^{25} +2.1$ (c 1, MeOH). $^1\text{H-NMR}$ (CD_3OD): δ 8.09 (s, 1H, NCHN), 7.80 (s, 1H, NCHCCOO), 7.12 (d, $J = 8.5$ Hz, 2H, Ph), 6.88 (d, $J = 8.5$ Hz, 2H, Ph), 4.71 (d, $J = 15.0$ Hz, 1H, NCHHPh), 4.41–4.34 (m, 2H, CH_2NCHCOO), 4.11–3.98 (m, 3H, NCHHPh, PhOCH_2), 3.75–3.71 (m, 2H, CH_2OCH_3), 3.55–3.48 (m, 1H, NCHCH₂), 3.41 (s, 3H, OCH_3), 2.46–1.28 (m, 8H, $4 \times \text{CH}_2$). $^{13}\text{C-NMR}$: δ 177.7 (NCO), 162.8 (COOH), 159.8, 142.0, 134.2, 130.4, 130.0, 126.5, 115.8, 72.2 (CH_2OCH_3), 68.4 (PhOCH_2), 59.3 (CH_3), 58.6 (NCH), 48.1 (CH_2NCCOOH), 44.5 (NCH₂Ph), 31.2, 30.5, 27.0, 24.5. MS (ESI): $m/z = 402$ (100) ($\text{M}+\text{H}^+$). Anal. calcd for $\text{C}_{21}\text{H}_{27}\text{N}_3\text{O}_5$: C, 62.83; H, 6.78; N, 10.47 Found: C, 62.88; H, 6.73; N, 10.38.

1-(3-{(2R)-1-[4-(2-Methoxyethoxy)benzyl]-5-oxopyrrolidin-2-yl}propyl)-1H-imidazole-4-carboxylic acid (15). Catalytic hydrogenation of compound **13** afforded product **15** as a pure colorless oil in 90% yield. R_f 0.15 in EtOAc–MeOH, 1:1. $[\alpha]_D^{25} +0.9$ (c 1, MeOH). $^1\text{H-NMR}$ (CD_3OD): δ 7.83 (s, 1H, NCHN), 7.68 (s, 1H, NCHCOO), 7.10 (d, $J = 8.2$ Hz, 2H, Ph), 6.88 (d, $J = 8.2$ Hz, 2H, Ph), 4.60 (d, $J = 14.9$ Hz, 1H, NCHHPh), 4.11–3.99 (m, 5H, PhOCH_2 , NCHHPh, CH_2NCHCOO), 3.75–3.71 (m, 2H, CH_2OCH_3), 3.51–3.47 (m, 1H, NCH), 3.41 (s, 3H, OCH_3), 2.47–1.21 (m, 8H, $4 \times \text{CH}_2$). $^{13}\text{C-NMR}$: δ 177.8 (NCO), 165.6 (COOH), 159.8, 139.5, 136.0, 134.7, 130.4, 130.0, 126.4, 115.8, 72.3 (CH_2OCH_3), 68.4 (PhOCH_2), 59.3 (CH_3), 58.5 (NCH), 48.4 (CH_2NCHN), 44.7 (NCH₂Ph), 31.2, 30.6, 26.8, 24.6. MS (ESI): $m/z = 402$ (100) ($\text{M}+\text{H}^+$). Anal. calcd for $\text{C}_{21}\text{H}_{27}\text{N}_3\text{O}_5$: C, 62.83; H, 6.78; N, 10.47 Found: C, 62.74; H, 6.84; N, 10.35.

1-[4-(2-Methoxyethoxy)benzyl]-5-oxo-L-prolyl-L-histidine (19a). Prepared from compound **18a** as a colorless oil in 97% yield. R_f 0.1 in EtOAc–MeOH, 1:1. $[\alpha]_D^{25} +3.0$ (c 1, MeOH). $^1\text{H-NMR}$ (CD_3OD): δ 8.85 (s, 1H, NCHN), 7.34 (s, 1H, NCHNCH), 7.05 (d, $J = 8.5$ Hz, 2H, Ph), 6.88 (d, $J = 8.5$ Hz, 2H, Ph), 4.84–4.72 (m, 2H, NHCHCOO , NCHHPh), 4.10–4.06 (m, 2H, PhOCH_2), 4.01–3.95 (m, 1H, NCHCON), 3.75–3.62 (m, 3H, CH_2OCH_3 , NCHHPh), 3.42 (s, 3H, CH_3), 3.15–3.02 (m, 2H, CH_2CHN), 2.57–1.96 (m, 4H, $2 \times \text{CH}_2$). $^{13}\text{C-NMR}$: δ 178.3 (NCO), 173.9, 173.2, 160.0, 135.3, 131.7, 130.8, 129.1, 118.3, 115.9, 72.2 (CH_2OCH_3), 68.5 (OCH_2), 61.1 (NCHCON), 59.3 (OCH_3), 52.7 (HNCHCO), 45.8 (CH_2Ph), 30.8 (CH_2CHN), 28.0, 24.2. MS (ESI): $m/z = 431$ (100) ($\text{M}+\text{H}^+$). Anal. calcd for $\text{C}_{21}\text{H}_{26}\text{N}_4\text{O}_6$: C, 58.59; H, 6.09; N, 13.02 Found: C, 58.65; H, 5.98; N, 13.14.

1-[4-(3-Methoxypropoxy)benzyl]-5-oxo-L-prolyl-L-histidine (19b). Prepared from compound **18b** as a colorless oil in 99% yield. R_f 0.11 in EtOAc–MeOH, 1:1. $[\alpha]_D^{+11.5}$ (c 1, MeOH). $^1\text{H-NMR}$ (CD_3OD): δ 8.75 (s, 1H, NCHN), 7.32 (s, 1H, NCHNC), 7.04 (d, $J = 8.5$ Hz, 2H, Ph), 6.85 (d, $J = 8.5$ Hz, 2H, Ph), 4.88 (d, $J = 14.8$ Hz, 1H, NCHHPh), 4.75–4.65 (m, 1H, NHCHCOO), 4.04–3.98 (m, 1H, NCHCO), 4.01 (t, $J = 6.3$ Hz, 2H, PhOCH_2), 3.63 (d, $J = 14.8$ Hz, 1H, NCHHPh), 3.54 (t, $J = 6.2$ Hz, 2H, CH_2OCH_3), 3.33 (s, 3H, OCH_3), 3.28–3.03 (m, 2H, CH_2CN), 2.53–1.93 (m, 6H, $3 \times \text{CH}_2$). $^{13}\text{C-NMR}$: δ 178.3 (NCO), 173.7, 160.2, 135.2, 132.1, 131.0, 130.7, 128.9, 118.2, 115.8, 70.3 (CH_2OCH_3), 65.9 (PhOCH_2), 61.2 (NCH), 58.9 (OCH_3), 53.4 (CHCOOH), 45.8 (NCH_2Ph), 30.9, 30.6, 28.4, 24.2. MS (ESI): $m/z = 445$ (100) ($\text{M}+\text{H}^+$). Anal. calcd for $\text{C}_{22}\text{H}_{28}\text{N}_4\text{O}_6$: C, 59.45; H, 6.35; N, 12.61 Found: C, 59.52; H, 6.37; N, 12.50.

1-[4-(4-Methoxybutoxy)benzyl]-5-oxo-L-prolyl-L-histidine (19c). Prepared from compound **18c** as a colorless oil in 92% yield. R_f 0.16 in EtOAc–MeOH, 1:1. $[\alpha]_D^{+6.9}$ (c 1, MeOH). $^1\text{H-NMR}$ (CD_3OD): δ 8.84 (s, 1H, HNCHN), 7.36 (s, 1H, NCCHN), 7.04 (d, $J = 8.5$ Hz, 2H, Ph), 6.85 (d, $J = 8.5$ Hz, 2H, Ph), 4.89 (d, $J = 14.7$ Hz, 1H, NCHHPh), 4.80–4.73 (m, 1H, NHCHCOO), 4.02–3.96 (m, 1H, NCH), 3.95 (t, $J = 5.4$ Hz, 2H, PhOCH_2), 3.63 (d, $J = 14.7$ Hz, 1H, NCHHPh), 3.45 (t, $J = 6.1$ Hz, 2H, CH_2OCH_3), 3.33 (s, 3H, CH_3), 3.17–3.05 (m, 2H, CH_2CNH), 2.49–1.96 (m, 4H, $2 \times \text{CH}_2$), 1.84–1.65 (m, 4H, $(\text{OCH}_2\text{CH}_2)_2$). $^{13}\text{C-NMR}$: δ 178.2 (NCO), 173.9, 160.3, 135.2, 131.8, 131.1, 130.7, 128.8, 118.3, 115.8, 73.5 (CH_2OCH_3), 68.9 (PhOCH_2), 61.1 (NCH), 58.8 (OCH_3), 52.9 (CHCOOH), 45.8 (NCH_2Ph), 30.8, 28.0, 27.3, 27.2, 24.1. MS (ESI): $m/z = 459$ (100) ($\text{M}+\text{H}^+$). Anal. calcd for $\text{C}_{23}\text{H}_{30}\text{N}_4\text{O}_6$: C, 60.25; H, 6.59; N, 12.12 Found: C, 60.32; H, 6.47; N, 12.30.

Methyl 1-(4-Hydroxybenzyl)-5-oxo-L-prolinate (21). Prepared from compound **20** as a colorless oil in 99% yield. R_f 0.69 in EtOAc. $[\alpha]_D^{+35.5}$ (c 1.1, CHCl_3). $^1\text{H-NMR}$ (CDCl_3): δ 7.03 (d, $J = 7.5$ Hz, 2H, Ph), 6.80 (d, $J = 7.5$ Hz, 2H, Ph), 4.89 (d, $J = 14.5$ Hz, 1H, NCHHPh), 4.02–3.91 (m, 2H, NCHHPh, NCH), 3.67 (s, 3H, CH_3), 2.55–2.04 (m, 4H, $2 \times \text{CH}_2$). $^{13}\text{C-NMR}$: δ 175.7 (NCO), 172.2 (COOCH_3), 156.3, 130.0, 126.5, 115.7, 58.9 (NCH), 52.5 (COOCH_3), 45.3 (NCHPh), 29.8, 22.7. MS (ESI): $m/z = 250$ (97) ($\text{M}+\text{H}^+$). Anal. calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_4$: C, 62.64; H, 6.07; N, 5.62 Found: C, 62.59; H, 6.17; N, 5.54.

1-(4-{[(4R)-3-(tert-Butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidin-4-yl]methoxy}benzyl)-5-oxo-L-prolyl-L-histidine (25). Prepared from compound **24** as a colorless oil in 97% yield. R_f 0.18 in EtOAc–MeOH, 1:1. $[\alpha]_D^{-24.9}$ (c 0.8, MeOH). $^1\text{H-NMR}$ (CD_3OD): δ 8.90 (s, 1H, HNCHN), 7.40 (s, 1H, HNCHNCH), 7.05 (d, $J = 8.3$ Hz, 2H, Ph), 6.93 (d, $J = 8.3$ Hz, 2H, Ph), 4.87–4.75 (m, 2H, CHCOOH , NCHHPh), 4.17–3.81 (m, 6H, NCHCO, $\text{PhOCH}_2\text{CHCH}_2\text{O}$), 3.64 (d, $J = 15.0$ Hz, 1H, NCHHPh), 3.41–3.06 (m, 2H, HOOCCHCH_2), 2.58–1.94 (m, 4H, $2 \times \text{CH}_2$), 1.58–1.45 (m, 15H, $5 \times \text{CH}_3$). $^{13}\text{C-NMR}$: δ 173.9 (NCO), 172.8, 159.8, 153.4 (NCOO), 135.3, 131.5, 130.8, 129.5, 129.3, 118.4, 115.9, 95.0 ($\text{NC}(\text{CH}_3)_2\text{O}$), 82.2 ($\text{C}(\text{CH}_3)_3$), 67.3, 66.2, 61.1 (NCHCO), 57.5 (PhOCH_2), 52.5 (NHCHCOOH), 45.8 (NCH_2Ph), 30.8, 28.8 (CH_3), 27.9, 27.7, 24.5, 24.2. MS (ESI): $m/z = 586$ (100) ($\text{M}+\text{H}^+$). Anal. calcd for $\text{C}_{29}\text{H}_{39}\text{N}_5\text{O}_8$: C, 59.47; H, 6.71; N, 11.96 Found: C, 59.52; H, 6.68; N, 12.05.

3.7. General Procedure for the Preparation of Compounds 17a–c, 23

To a stirred solution of methylester (compounds **16a–c**, **22**) (1 mmol), in MeOH (3 mL), an aq. solution of 2N NaOH (0.5 mL, 1 mmol) was added and the reaction mixture was left stirring at rt for 2–3 h. Upon completion of the reaction, the MeOH was evaporated under reduced pressure and the residual product was diluted with H₂O and extracted with Et₂O (1 × 10 mL). The aqueous phase was acidified with 1 N HCl aq. solution at pH 2 and extracted with EtOAc (2 × 10 mL). The combined organic phases were neutralized by washing with brine and H₂O, dried over Na₂SO₄ and evaporated under reduced pressure to afford the carboxylic products in quantitative yield and high purity.

1-[4-(2-Methoxyethoxy)benzyl]-5-oxo-L-proline (17a). Prepared from methylester **16a** as a colorless oil in 94% yield. R_f 0.36 in EtOAc–MeOH, 3:2. [α]_D +43.8 (c 1, CHCl₃). ¹H-NMR (CDCl₃): δ 8.77 (bs, 1H, COOH), 7.13 (d, *J* = 8.6 Hz, 2H, Ph), 6.85 (d, *J* = 8.6 Hz, 2H, Ph), 5.02 (d, *J* = 14.7 Hz, 1H, CHHPh), 4.11–4.06 (m, 2H, PhOCH₂), 3.99–3.93 (m, 1H, NCHCOO), 3.91 (d, *J* = 4.7 Hz, 1H, CHHPh), 3.77–3.72 (m, 2H, CH₂OCH₃), 3.44 (s, 3H, OCH₃), 2.68–2.09 (m, 4H, 2 × CH₂). ¹³C-NMR: δ 176.2 (NCO), 174.1 (COOH), 158.4, 129.9, 127.6, 114.7, 70.9 (CH₂OCH₃), 67.1 (OCH₂), 59.1 (NCH), 58.5 (OCH₃), 45.0 (CH₂Ph), 29.6, 22.8. MS (ESI): *m/z* = 292 (100) (M–H⁺). Anal. calcd for C₁₅H₁₉NO₅: C, 61.42; H, 6.53; N, 4.78 Found: C, 61.38; H, 6.57; N, 4.82.

1-[4-(3-Methoxypropoxy)benzyl]-5-oxo-L-proline (17b). Prepared from methylester **16b**, as a colorless oil in 99% yield. R_f 0.24 in EtOAc–MeOH, 3:2. [α]_D +17.2 (c 1, CHCl₃). ¹H-NMR (CDCl₃): δ 9.62 (bs, 1H, COOH), 7.13 (d, *J* = 8.6 Hz, 2H, Ph), 6.83 (d, *J* = 8.6 Hz, 2H, Ph), 5.05 (d, *J* = 4.7 Hz, 1H, CHHPh), 4.04–3.94 (m, 3H, NCHCOO, PhOCH₂), 3.91 (d, *J* = 14.7 Hz, 1H, CHHPh), 3.56 (t, *J* = 6.2 Hz, 2H, CH₂OCH₃), 3.35 (s, 3H, OCH₃), 2.66–2.09 (m, 4H, 2 × CH₂), 2.09–1.96 (m, 2H, CH₂CH₂CH₂). ¹³C NMR: δ 176.2 (NCO), 174.2 (COOH), 158.6, 129.9, 127.2, 114.6, 69.2 (CH₂OCH₃), 64.7 (PhOCH₂), 58.6 (NCH), 58.5 (OCH₃), 45.0 (CH₂Ph), 29.7, 29.4, 22.8. MS (ESI): *m/z* = 306 (100) (M–H⁺). Anal. calcd for C₁₆H₂₁NO₅: C, 62.53; H, 6.89; N, 4.56 Found: C, 62.58; H, 6.77; N, 4.53.

1-[4-(4-Methoxybutoxy)benzyl]-5-oxo-L-proline (17c). Prepared from methylester **16c**, as a colorless oil in 96% yield. R_f 0.30 in EtOAc–MeOH, 3:2. [α]_D +13.3 (c 1, CHCl₃). ¹H-NMR (CDCl₃): δ 9.98 (bs, 1H, COOH), 7.12 (d, *J* = 8.6 Hz, 2H, Ph), 6.81 (d, *J* = 8.6 Hz, 2H, Ph), 5.03 (d, *J* = 14.7 Hz, 1H, NCHHPh), 4.00–3.88 (m, 4H, NCHHPh, NCH, PhOCH₂), 3.44 (t, *J* = 6.2 Hz, 2H, CH₂OCH₃), 3.34 (s, 3H, OCH₃), 2.65–2.08 (m, 4H, 2 × CH₂), 1.85–1.68 (m, 4H, (OCH₂CH₂)₂). ¹³C-NMR: δ 176.2 (NCO), 173.8 (COO), 158.6, 129.9, 127.1, 114.6, 72.3 (CH₂OCH₃), 67.5 (PhOCH₂), 58.4 (NCH), 58.3 (OCH₃), 45.0 (CH₂Ph), 29.6, 26.0, 25.8, 22.8. MS (ESI): *m/z* = 320 (100) (M–H⁺). Anal. calcd for C₁₇H₂₃NO₅: C, 63.54; H, 7.21; N, 4.36 Found: C, 63.38; H, 7.19; N, 4.42.

1-(4-{[(4R)-3-(tert-Butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidin-4-yl]methoxy}benzyl)-5-oxo-L-proline (23). Prepared from methylester **22**, as a colorless oil in 94% yield. R_f 0.43 in EtOAc–MeOH, 1:1. [α]_D –11.5 (c 1, CHCl₃). ¹H-NMR (CDCl₃): δ 7.62 (bs, 1H, COOH), 7.13 (d, *J* = 7.4 Hz, 2H, Ph), 6.88 (d, *J* = 4 Hz, 2H, Ph), 5.03 (dd, *J*₁ = 14.6 Hz, *J*₂ = 3.1 Hz, 1H, NCHHPh), 4.28–3.80 (m, 7H, NCHHPh, NCHCOOH, OCH₂CHCH₂O), 4.68–2.15 (m, 4H, 2 × CH₂), 1.64–1.52 (m, 15H, 5 × CH₃). ¹³C-NMR: δ

176.1 (NCO), 173.9 (COOH), 158.1, 152.4 (NCOO), 129.9, 127.6, 114.8, 93.6 (OC(CH₃)₂N), 80.9 (C(CH₃)₃), 66.0, 65.1, 58.4 (NCHCOOH), 55.9 (PhOCH₂), 45.0 (NCH₂Ph), 29.6, 28.3 (CH₃), 27.4, 24.2, 22.8. MS (ESI): m/z = 447 (100) (M-H⁺). Anal. calcd for C₂₃H₃₂N₂O₇: C, 61.59; H, 7.19; N, 6.25 Found: C, 61.53; H, 7.24; N, 6.32.

3.8. General Procedure for the Preparation of Compounds 18a–c, 24

To a stirred solution of carboxylic acids (compounds **17a–c**, **23**) (1 mmol) in CH₂Cl₂ (10 mL) at 0 °C, 1-hydroxybenzotriazole (HOBt) (0.135 g, 1 mmol), freshly prepared benzyl 3-trityl-L-histidinate (**42**) (0.537 g, 1.1 mmol), Et₃N (0.154 mL, 1.1 mmol) and *N*-ethyl-*N*-dimethylaminopropylcarbodiimide hydrochloride (EDC.HCl) (0.210 g, 1.1 mmol) were added consecutively. The reaction mixture was left stirring at 0 °C for 1 h and then warmed to room temperature and left stirring for 18 h. The solvents were evaporated under reduced pressure and the crude product was dissolved in EtOAc (20 mL). The organic layer was washed with 5% aq. H₂SO₄, H₂O, 5% aq. NaHCO₃, and brine. After drying over Na₂SO₄ and evaporation of the solvent *in vacuo*, the crude ester was purified using column chromatography with the appropriate solvent systems as it will be defined in each case below.

Benzyl 1-[4-(2-Methoxyethoxy)benzyl]-5-oxo-L-prolyl-3-trityl-L-histidinate (18a). Prepared from compound **17a**. Eluent EtOAc–MeOH 9:1. Yield: 55% (colorless oil); R_f 0.55 in EtOAc–MeOH 9:1; [α]_D +3.8 (c 1, CHCl₃). ¹H-NMR (CDCl₃): δ 8.22 (d, *J* = 7.8 Hz, 1H, NH), 7.39 (d, *J* = 1.3 Hz, 1H, NCHN), 7.33–7.03 (m, 22H, Ph), 6.80 (d, *J* = 8.6 Hz, 2H, Ph), 6.47 (s, 1H, NCHNCHC), 5.01 (d, *J* = 14.3 Hz, 1H, CHHPh), 5.00 (s, 2H, OCH₂Ph), 4.86–4.77 (m, 1H, NHCHCOO), 4.12–4.04 (m, 2H, PhOCH₂), 3.89–3.83 (m, 1H, NCHCON), 3.75 (d, *J* = 14.3 Hz, 1H, CHHPh), 3.74–3.69 (m, 2H, CH₂OCH₃), 3.43 (s, 3H, OCH₃), 3.13–2.91 (m, 2H, COCHCH₂CHN), 2.68–1.98 (m, 4H, 2 × CH₂). ¹³C-NMR: δ 175.5 (NCO), 171.6, 170.6, 158.2, 142.0, 138.7, 135.9, 135.2, 129.9, 129.6, 128.5, 128.4, 128.3, 128.2, 128.1, 119.5, 119.4, 114.6, 75.4 (NCPh), 70.9 (CH₂OCH₃), 67.1 (OCH₂), 67.0 (OCH₂Ph), 60.0 (NCH), 59.2 (OCH₃), 52.5 (HNCHCO), 44.5 (CH₂Ph), 29.7, 28.8 (NHCHCH₂C), 23.2. MS (ESI): m/z = 763 (100) (M+H⁺). Anal. calcd for C₄₇H₄₆N₄O₆: C, 74.00; H, 6.08; N, 7.34 Found: C, 74.15; H, 6.16; N, 7.27.

Benzyl 1-[4-(3-Methoxypropoxy)benzyl]-5-oxo-L-prolyl-3-trityl-L-histidinate (18b). Prepared from compound **17b**. Eluent EtOAc–MeOH 9:1. Yield: 68% (colorless oil); R_f 0.63 in EtOAc–MeOH 9:1; [α]_D +8.5 (c 1, CHCl₃). ¹H-NMR (CDCl₃): δ 8.19 (d, *J* = 7.8 Hz, 1H, NH), 7.40 (d, *J* = 1.3 Hz, 1H, NCHN), 7.34–7.04 (m, 22H, Ph), 6.78 (d, *J* = 8.7 Hz, 2H, Ph), 6.48 (d, *J* = 1.2 Hz, 1H, NCHCN), 5.02 (d, *J* = 14.5 Hz, 1H, NCHHPh), 5.01 (s, 2H, CH₂Ph), 4.00 (t, *J* = 6.3 Hz, 2H, PhOCH₂), 3.89–3.83 (m, 1H, NCHCO), 3.76 (d, *J* = 14.5 Hz, 1H, NCHHPh), 3.53 (t, *J* = 6.2 Hz, 2H, CH₂OCH₃), 3.34 (s, 3H, OCH₃), 3.14–2.92 (m, 2H, HNCHCH₂), 2.69–2.08 (m, 4H, 2 × CH₂), 2.05–1.95 (m, 2H, CH₂CH₂CH₂). ¹³C-NMR: δ 175.5 (NCO), 171.6, 170.6, 158.4, 142.1, 138.7, 136.0, 135.2, 130.0, 129.6, 128.5, 128.3, 128.2, 128.1, 128.0, 119.5, 114.5, 75.4 (CPh), 69.2 (CH₂OCH₃), 67.0 (OCH₂Ph), 64.7 (PhOCH₂), 60.0 (NCH), 58.7 (OCH₃), 52.5 (HNCHCO), 44.5 (CH₂Ph), 29.8, 29.5 (CH₂CH₂CH₂), 28.9 (NHCHCH₂C), 23.2. MS (ESI): m/z = 777 (100) (M+H⁺). Anal. calcd for C₄₈H₄₈N₄O₆: C, 74.21; H, 6.23; N, 7.21 Found: C, 74.11; H, 6.32; N, 7.28.

Benzyl 1-[4-(4-Methoxybutoxy)benzyl]-5-oxo-L-prolyl-3-trityl-L-histidinate (18c). Prepared from compound **17c**. Eluent EtOAc–MeOH 9:1. Yield: 63% (colorless oil); R_f 0.56 in EtOAc–MeOH 9:1; [α]_D +3.8 (c 1, CHCl₃). ¹H-NMR (CDCl₃): δ 8.21 (d, *J* = 7.9 Hz, 1H, NH), 7.40 (d, *J* = 1.3 Hz, 1H, NCHN), 7.35–7.04 (m, 22H, Ph), 6.76 (d, *J* = 8.6 Hz, 2H, Ph), 6.48 (d, *J* = 1.1 Hz, 1H, NCHCN), 5.02 (d, *J* = 14.5 Hz, 1H, NCHHPh), 5.01 (s, 2H, COOCH₂Ph), 4.87–4.79 (m, 1H, NCHCOO), 3.92 (t, *J* = 5.9 Hz, 2H, PhOCH₂), 3.88–3.83 (m, 1H, NCH), 3.76 (d, *J* = 14.5 Hz, 1H, NCHHPh), 3.43 (t, *J* = 6.1 Hz, 2H, CH₂OCH₃), 3.34 (s, 3H, OCH₃), 3.13–2.92 (m, 2H, CHCH₂CN), 2.65–1.98 (m, 4H, 2 × CH₂), 1.86–1.65 (m, 4H, (OCH₂CH₂)₂). ¹³C-NMR: δ 175.4 (NCO), 171.6, 170.5, 158.4, 142.0, 138.7, 135.9, 135.2, 129.9, 129.6, 128.4, 128.3, 128.1, 128.0, 127.9, 119.4, 114.5, 75.3 (CPh), 72.2 (CH₂OCH₃), 67.5 (OCH₂Ph), 66.9 (PhOCH₂), 59.9 (NCH), 58.5 (OCH₃), 52.5 (HNCHCO), 44.5 (CH₂Ph), 29.7, 28.8, 26.1, 25.9, 23.2. MS (ESI): *m/z* = 791 (100) (M+H⁺). Anal. calcd for C₄₉H₅₀N₄O₆: C, 74.41; H, 6.37; N, 7.08 Found: C, 74.35; H, 6.42; N, 7.18.

Benzyl 1-(4-{[(4R)-3-(tert-Butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidin-4-yl]methoxy}benzyl)-5-oxo-L-prolyl-3-trityl-L-histidinate (24). Prepared from compound **23**. Eluent EtOAc–petroleum ether (bp. 40–60 °C) 9:1, followed by EtOAc. Yield: 60% (colorless oil); R_f 0.64 in EtOAc; [α]_D −16.4 (c 1, CHCl₃). ¹H-NMR (CDCl₃): δ 8.23 (t, *J* = 8.3 Hz, 1H, NH), 7.40–6.80 (m, 25H, Ph), 6.47 (s, 1H, Ph), 5.05–4.98 (m, 3H, COOCH₂, NCHHPh), 4.86–4.77 (m, 1H, HNCHCOO), 4.26–3.69 (m, 7H, NCHHPh, NCHCONH, PhOCH₂CHCH₂O), 3.13–2.92 (m, 2H, HNCHCH₂C), 2.68–2.03 (m, 4H, 2 × CH₂), 1.61–1.48 (m, 15H, 5 × CH₃). ¹³C-NMR: δ 175.5 (NCO), 171.6, 170.5, 158.0, 152.2 (NCOO), 142.0, 138.6, 135.8, 135.2, 130.0, 129.9, 129.6, 128.6, 128.5, 128.3, 128.1, 119.6, 114.7, 93.5 (OC(CH₃)₂N), 80.2 (C(CH₃)₃), 75.4 (CPh₃), 67.0 (COOCH₂Ph), 66.1, 65.3, 60.0 (NCHCO), 55.7 (PhOCH₂), 52.5 (NHCHCOO), 44.5 (NCH₂Ph), 29.7, 28.5 (CH₃), 27.5, 24.2, 23.3, 23.0. MS (ESI): *m/z* = 919 (100) (M+H⁺). Anal. calcd for C₅₅H₅₉N₅O₈: C, 71.95; H, 6.48; N, 7.63 Found: C, 72.07; H, 6.24; N, 7.58.

Methyl 1-(4-{[(4R)-3-(tert-Butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidin-4-yl]methoxy}benzyl)-5-oxo-L-prolinate (22). To a stirred solution of alcohol (*tert*-butyl (4R)-4-(hydroxymethyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate) [33], (0.231 g, 1 mmol) in dry toluene (5 mL), compound **21** (0.249 g, 1 mmol), DEAD (0.19 mL, 1.2 mmol), and PPh₃ (0.314 g, 1.2 mmol) were added consecutively and the reaction mixture was refluxed for 15 h under argon. After evaporation of the solvent under reduced pressure the product was purified using column chromatography and EtOAc–petroleum ether (bp. 40–60 °C) 7:3 as eluent and isolated as a colorless oil in 60% yield (0.278 g). R_f 0.45 in EtOAc–petroleum ether (bp. 40–60 °C) 7:3; [α]_D −17.7 (c 1, CHCl₃). ¹H-NMR (CDCl₃): δ 7.10 (d, *J* = 7.9 Hz, 2H, Ph), 6.70 (bs, 2H, Ph), 4.94 (d, *J* = 14.6 Hz, 1H, NCHHPh), 4.21–3.81 (m, 7H, NCHHPh, NCHCOOCH₃, PhOCH₂CHCH₂O), 3.67 (s, 3H, OCH₃), 2.64–2.02 (m, 4H, 2 × CH₂), 1.60–1.48 (m, 15H, 5 × CH₃). ¹³C-NMR: δ 174.8 (NCO), 172.2 (COOCH₃), 158.1, 152.2 (NCOO), 129.8, 127.9, 114.7, 93.4 (NC(CH₃)₂O), 80.4 (C(CH₃)₃), 66.0, 65.1, 58.5 (NCHCOO), 55.6 (PhOCH₂), 52.3 (COOCH₃), 44.8 (NCHPh), 29.5, 28.3 (C(CH₃)₃), 27.4, 24.2, 22.6. MS (ESI): *m/z* = 480 (100) (M+NH₄⁺). Anal. calcd for C₂₄H₃₄N₂O₇: C, 62.32; H, 7.41; N, 6.06 Found: C, 62.28; H, 7.39; N, 6.15.

1-(4-{[(2S)-2-Ammonio-3-Hydroxypropyl]oxy}benzyl)-5-oxo-L-prolyl-L-histidine hydrochloride (26). To a stirred solution of compound **25** (21 mg, 0.036 mmol) in dioxane (1 mL) at 0 °C, a 4 M solution

of HCl in dioxane (0.108 mL, 0.432 mmol) was added and the reaction mixture was left stirring at room temperature for 1 h. After evaporation of the solvent under reduced pressure, the product was precipitated by the addition of Et₂O and recrystallized from dioxane/Et₂O twice. It was obtained as a white gummy solid in 90% yield (16 mg). $[\alpha]_D^{+3.4}$ (c 0.7, H₂O). ¹H-NMR (D₂O): δ 8.87 (s, 1H, HNCHN), 7.32 (s, 1H, HNCHNCH), 7.14 (d, J = 8.4 Hz, 2H, Ph), 6.99 (d, J = 8.4 Hz, 2H, Ph), 4.75–4.70 (m, 2H, CHCOOH, NCHHPh), 4.33–4.19 (m, 2H, PhOCH₂), 4.16–4.12 (m, 1H, NCH), 3.98–3.80 (m, 4H, NCHHPh, CHNH₂, CH₂OH), 3.33 (dd, J_1 = 5.4 Hz, J_2 = 15.6 Hz, 1H, HNCHCHHC), 3.15 (dd, J_1 = 9.0 Hz, J_2 = 15.5 Hz, 1H, HNCHCHHC), 2.61–1.87 (m, 4H, 2 × CH₂). ¹³C-NMR: δ 179.6 (NCO), 174.2, 173.6, 158.0, 134.2, 130.3, 129.5, 128.7, 117.7, 115.5, 65.6 (PhOCH₂), 61.3 (NCHCO), 59.3 (CH₂OH), 52.8, 52.3, 45.7 (NCH₂Ph), 30.4, 26.6, 23.2. MS (ESI): m/z = 446 (100) (M+H⁺). Anal. calcd for C₂₁H₂₈N₅O₆Cl: C, 52.34; H, 5.86; N, 14.53 Found: C, 52.28; H, 5.92; N, 14.47.

Benzyl N-[(9H-Fluoren-9-ylmethoxy)carbonyl]-L-trityl-L-histidinate (41). To a solution of Fmoc-S-His(Trt)-OH (0.20 g, 0.33 mmol) in DMF (1 mL) Cs₂CO₃ (53 mg, 0.162 mmol) was added with some drops of H₂O to dissolve the inorganic salt. The solvent was evaporated under reduced pressure to dryness and the residue, dissolved in DMF (3 mL) was stirred for 5 min at rt, followed by the addition of benzyl bromide (44 μ L, 0.371 mmol). After stirring overnight at rt and evaporation of DMF under reduced pressure, the residue was dissolved in EtOAc and the organic phase was washed with H₂O, 5% aq. solution of NaHCO₃ and H₂O. The organic layer was dried over Na₂SO₄, evaporated in vacuo and the residue was purified by column chromatography on silica gel, eluting with EtOAc-petroleum ether (bp. 40–60 °C) 1:1. The product was isolated as colorless oil in 87% yield (0.20 g). R_f 0.50 in EtOAc-petroleum ether (bp. 40–60 °C) 1:1; $[\alpha]_D$ −2.7 (c 1, CHCl₃). ¹H-NMR (CDCl₃): δ 7.77–7.06 (m, 29H, Ph, NCHN), 6.61 (d, J = 8.2 Hz, 1H, NH), 6.54 (s, 1H, NCHNCHC), 5.07 (dd, J_1 = 12.5 Hz, J_2 = 14.9 Hz, 2H, OCH₂Ph), 4.73–4.64 (m, 1H, HNCHCO), 4.40–4.19 (m, 3H, CHCH₂OCO), 3.12 (d, J = 5.0 Hz, 2H, CH₂CHN). ¹³C-NMR: δ 171.2 (HNCHCOO), 156.2 (COONH), 144.1, 143.9, 142.0, 141.2, 138.4, 135.8, 135.4, 129.7, 128.5, 128.2, 128.1, 127.6, 127.0, 125.4, 125.3, 119.8, 75.6 (CPh), 67.2 (CH₂COONH), 66.9 (OCH₂Ph), 54.3 (HNCHCOO), 47.1 (CHCH₂COO), 29.7 (CH₂CHN). MS (ESI): m/z = 710 (100) (M+H⁺). Anal. calcd for C₄₇H₃₉N₃O₄: C, 79.53; H, 5.54; N, 5.92 Found: C, 79.60; H, 5.58; N, 5.85.

Benzyl-3-trityl-L-histidinate (42). Compound 41 (0.15 g, 0.21 mmol) was dissolved in EtOH (1.5 mL) and Et₂NH (153 μ L, 1.48 mmol) was added. After leaving overnight at rt the solvent was evaporated under reduced pressure. The crude product was redissolved in water, washed by EtOAc (3 × 5 mL) and the combined organic layers were dried over Na₂SO₄ and evaporated in vacuo. After purification by column chromatography and using EtOAc–MeOH (9:1) as eluent the product was isolated as colorless oil in 82% yield (84 mg). R_f 0.37 in EtOAc–MeOH 9:1; $[\alpha]_D$ −11.7 (c 1, CHCl₃). ¹H-NMR (CDCl₃): δ 7.32–7.08 (m, 21H, 4 × Ph, NCHN), 6.54 (s, 1H, NCHNCHC), 5.04 (dd, J_1 = 12.3 Hz, J_2 = 20.8 Hz, 2H, OCH₂Ph), 3.90–3.85 (m, 1H, H₂NCH), 3.08–2.82 (m, 2H, CH₂CHN). ¹³C-NMR: δ 174.4 (COO), 142.3, 138.6, 137.0, 135.6, 129.7, 128.5, 128.3, 128.2, 128.1, 128.0, 119.5, 75.2 (CPh), 66.6 (CH₂Ph), 54.6 (H₂NCH), 32.9 (CH₂CHN). MS (ESI): m/z = 488 (100) (M+H⁺). Anal. calcd for C₃₂H₂₉N₃O₂: C, 78.82; H, 5.99; N, 8.62 Found: C, 78.68; H, 5.79; N, 8.74.

4. Conclusions

In this paper the synthesis of new, optically active 2-pyrrolidinones starting from the natural chiral synthon of *S*-pyroglutamic acid is described.

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