Synthesis of New Optically Active 2-Pyrrolidinones

Panagiota Moutevelis-Minakakis *, Eleni Papavassilopoulou and Thomas Mavromoustakos

Laboratory of Organic Chemistry, Department of Chemistry, University of Athens, Panepistimiopolis, Athens 15771, Greece

* Author to whom correspondence should be addressed; E-Mail: pminakak@chem.uoa.gr, Tel.: +302-10-727-4484; Fax: +302-10-727-4761.

Received: 6 November 2012; in revised form: 5 December 2012 / Accepted: 12 December 2012 / Published: 21 December 2012

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-5S-carboxylic acid), which is considered as a unique chiral synthon. The asymmetric use of S-pyroglutamic acid is based on its two differentiated carbons, 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 methoxyalkyloxy 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) NaBH₄, dry EtOH; 94%; (ii) TES-Cl, Et₃N, DMAP in CH₂Cl₂; 83%; (iii) NaH, Z-Cl in dry THF; 50%; (iv) TFA in CH₂Cl₂; 86%; (v) Moffatt oxidation: EDC.HCl, Pyr, TFA drops in dry Tol and dry DMSO, under Ar; (vi) Ph₃P=CHCOOMe in dry THF, 1h reflux under Ar; 60%; (vii) H₂, 10% Pd/C in MeOH, overnight; 97%; (viii) 30, NaH in dry DMF; 40%; (ix) LiBH₄, dry THF; 87%; (x) TosCl, Et₃N in CH₂Cl₂; 72%; (xi) N₂, Na₂CO₃ in dry DMF; 58%; (xii) N₂, Na₂CO₃ in dry DMF; 55% for 12; 30% for 13; (xiii) H₂, 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 benzyloxy carbonyl chloride 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 1H-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 \(^1\)H-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) BuO-\(\text{Br}\), NaH in dry THF; 47%; (ii) \(\text{H}_2\), 10% Pd/C in MeOH; 99%; (iii) \(\text{PPh}_3\), DEAD in dry Tol; 60%; (iv) 2N NaOH in MeOH; 94%; (v) \(\text{Et}_3\text{N}, \text{HOBr}, \text{EDC.HCl in CH}_2\text{Cl}_2\); 48%; (vi) \(\text{H}_2\), 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–O–CH₃, 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) Br$_2$, K$_2$CO$_3$ in acetone; 40%; (ii) 1N MeONa/MeOH; 38%; (iii) NaBH$_4$ in dry THF; 80%; (iv) PBr$_3$ in Et$_2$O; 70%.

Scheme 6. Synthesis of bromide 39.

Reagents and Conditions: (i) PBr$_3$ in Et$_2$O; 60%; (ii) HO$_2$K$_2$CO$_3$, 18-Crown-6 in acetone; 67%; (iii) TMS-Cl, NaBr in CH$_3$CN; 42%.

Scheme 7. Synthesis of compound 42.

Reagents and Conditions: (i) Bn-Br, Cs$_2$CO$_3$ in DMF; 87%; (ii) Et$_2$NH in abs. EtOH, 82%.

As depicted in Scheme 3, a different approach was followed for the synthesis of product 26. Methyl S-pyroglutamate was benzylation 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 (4R)-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 C4H9BrO: 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; Rf 0.50 in
EtOAc–petroleum ether (bp. 40–60 °C), 3:7. 1H-NMR (CDCl3): δ 7.30 (d, J = 8.7 Hz, 2H, Ph), 6.87 (d, J = 8.7 Hz, 2H, Ph), 5.83 (m, 2H, CH2Br), 4.09 (t, J = 4.5 Hz, 2H, PhOCH2), 3.73 (t, J = 4.8 Hz, 2H, CH2OCH3), 3.43 (s, 3H, CH3). 13C-NMR: δ 158.7, 130.3, 114.7, 70.8 (CH2OCH3), 67.2 (PhOCH2), 59.1 (CH3), 33.9 (CH2Br). Anal. calcd for C10H13BrO2: 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. 1H-NMR (CDCl3): δ 7.31 (d, J = 8.7 Hz, 2H, Ph), 6.86 (d, J = 8.7 Hz, 2H, Ph), 4.50 (s, 2H, CH2Br), 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 159.1, 130.4, 129.8, 114.7, 69.1 (CH2OCH3), 64.8 (PhOCH2), 58.7 (CH3), 34.1 (CH2Br), 29.5 (CH2CH2CH2). Anal. calcd for C11H15BrO2: 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). 1H-NMR (CDCl3): δ 3.47–3.37 (m, 4H, OCH2, CH2Br), 3.33 (s, 3H, CH3), 2.02–1.88 (m, 2H, CH2CH2Br), 1.78–1.64 (m, 2H, CH2CH2O). 13C-NMR: δ 71.7 (OCH2), 58.6 (CH3), 33.7 (CH2Br), 29.6 (CH2CH2Br), 28.2 (CH2CH2O). Anal. calcd for C5H11BrO: 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 CH3CN (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 Et2O was washed with brine and H2O. The organic layer was dried over Na2SO4 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. 1H-NMR (CDCl3): 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, CH2Br), 3.95 (t, J = 5.9 Hz, 2H, PhOCH2), 3.42 (t, J = 6.2 Hz, 2H, CH2OCH3), 3.33 (s, 3H, CH3), 1.87–1.68 (m, 4H, CH2CH2CH2CH2). 13C-NMR: δ 159.0, 130.3, 114.5, 72.2 (CH2OCH3), 67.5 (PhOCH2), 58.5 (CH3), 34.0 (CH2Br), 26.1, 25.9. Anal. calcd for C12H17BrO2: 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), K2CO3 (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 H2O. The organic layer was dried over Na2SO4, 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 CHCl3–MeOH, 9.5:0.5; Yield: 76% (colorless oil); Rf 0.48 in CHCl3–MeOH, 9.5:0.5. 1H-NMR (CDCl3): δ 7.27 (d, J = 8.7 Hz, 2H, Ph), 6.90 (d, J = 8.7 Hz, 2H, Ph), 4.61 (s, 2H, CH2OH), 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); RF 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, CH₂OCH₃), 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. RF 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 μL) 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. RF 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. \(^1\)H-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). \(^13\)C-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.

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

5-[(Triethylsilyloxy)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 benzyloxycarbonyl chloride 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-[(triethylsilyloxy)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). \(^1\)H-NMR (CDCl₃): δ 7.46–7.32 (m, 5H, Ph), 5.28 (dd, J₁ = 12.4 Hz, J₂ = 18.4 Hz, 2H, COOCH₂), 4.28–4.20 (m, 1H, NCH), 3.88 (dd, J₁ = 4.0 Hz, J₂ = 10.6 Hz, 1H, CHHOSi), 3.67 (dd, J₁ = 2.5 Hz, J₂ = 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)), \(^13\)C-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-{[(2S)-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). \(^1\)H-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, NCH₂Ph), 4.09–4.04 (m, 2H, PhOCH₂), 3.85 (d, J = 14.8 Hz, 1H, NCH₂Ph), 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). \(^13\)C-NMR: δ 174.8 (NCO), 173.0 (COO), 158.1, 129.2,
Molecules 2013, 18

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): ²/² = 358 (100) (M+Na⁺). Anal. calcld 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-proline (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, CH₂Ph), 4.07–4.02 (m, 2H, PhOCH₂), 3.93–3.86 (m, 2H, CH₂Ph, NCH₂COO), 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): ²/² = 308 (100) (M+H⁺). Anal. calcld 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-proline (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, NCH₂Ph), 3.99 (t, J = 6.3 Hz, 2H, PhOCH₂), 3.95–3.90 (m, 1H, NCH₂COO), 3.89 (d, J = 4.6 Hz, 1H, NCH₂Ph), 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): ²/² = 322 (100) (M+H⁺). Anal. calcld 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-proline (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, NCH₂Ph), 3.97–3.89 (m, 1H, NCH₂COO), 3.92 (t, J = 6.30 Hz, 2H, PhOCH₂), 3.90 (d, J = 14.7 Hz, 1H, NCH₂Ph), 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): ²/² = 336 (100) (M+H⁺). Anal. calcld for C₁₈H₂₅NO₅: C, 64.46; H, 7.51; N, 4.18 Found: C, 64.38; H, 7.48; N, 4.27.

Methyl 1-[4-(Benzylxoy)benzyl]-5-oxo-L-proline (20). Prepared from methyl-S-pyroglutamate (1) and 1-(benzylxy)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 1.0, 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, NCH₂Ph), 4.00–3.92 (m, 2H, NCH₂Ph, NCH₂), 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
(OCH₃Ph), 58.5 (NCH), 52.2 (CH₃), 44.8 (NCHPh), 29.4, 22.6. MS (ESI): m/z = 340 (100) (M+H⁺).

Anal. calc’d 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-oxypyrrolidine-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%); Rf 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, J₁ = 3.2 Hz, J₂ = 11.8 Hz, 1H, CHHOH), 3.66 (dd, J₁ = 3.2 Hz, J₂ = 11.8 Hz, 1H, CHHOH), 3.09 (bs, 1H, OH), 3.86–1.95 (m, 4H, 2 × CH₂). ¹³C-NMR: δ 173.5 (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. calc’d for C₁₂H₁₃NO₄: 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-oxypyrrolidine-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. Rf 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, J₁ = 6.3 Hz, J₂ = 6.2 Hz, 1H, CHCHOOCOCH₃), 5.25 (dd, J₁ = 12.3 Hz, J₂ = 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 (COOC₂H), 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. calc’d 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 (0.110 g, 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 Na$_2$SO$_4$ 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). Rf 0.34 in EtOAc–MeOH 9:1; [α]$_D$ +7.6 (c 0.95, CHCl$_3$). $^1$H-NMR (CDCl$_3$): 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, NCH$_2$Ph), 4.10–4.05 (m, 2H, PhOCH$_2$H), 3.88 (d, J = 14.8 Hz, 1H, NCH$_2$Ph), 3.74–3.70 (m, 2H, CH$_2$OCH$_3$), 3.64–3.54 (m, 2H, CH$_2$OH), 3.42 (s, 4H, NCH$_2$CH$_3$), 2.47–1.36 (m, 8H, 4 × CH$_2$). $^{13}$C-NMR: δ 175.1 (NCO), 158.1, 129.2, 128.8, 114.6, 70.9 (CH$_2$OCH$_3$), 67.1 (PhOCH$_2$H), 62.2 (CH$_2$OH), 59.2 (CH$_3$), 56.6 (NCH), 43.4 (NCH$_2$Ph), 30.2, 28.9, 27.3, 23.7. MS (ESI): m/z = 308 (90) (M+H$^+$). Anal. calcd for C$_{17}$H$_{23}$NO$_4$: C, 66.43; H, 6.77; N, 3.03. Found: C, 66.38; H, 6.82; N, 3.18.

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 Et$_3$N (17.5 μL). The reaction mixture was stirred at 0 ºC 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 NaHCO$_3$ and brine. After drying over Na$_2$SO$_4$ 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). Rf 0.35 in EtOAc; [α]$_D$ +5.6 (c 1, CHCl$_3$). $^1$H-NMR (CDCl$_3$): 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, NCH$_2$Ph), 4.11–4.06 (m, 2H, PhOCH$_2$H), 3.95 (t, J = 5.9 Hz, 2H, CH$_2$OSO$_2$), 3.83 (d, J = 14.9Hz, 1H, NCH$_2$Ph), 3.75–3.71 (m, 2H, CH$_2$OCH$_3$), 3.43 (s, 3H, OCH$_3$), 3.39–3.31 (m, 1H, NCH), 2.44 (s, 3H, CH$_3$), 2.41–1.50 (m, 8H, 4 × CH$_2$). $^{13}$C-NMR: δ 174.9 (NCO), 158.1, 144.9, 132.8, 129.9, 129.2, 128.7, 127.8, 114.7, 70.9 (CH$_2$OCH$_3$), 69.9 (CH$_2$OSO$_2$), 67.2 (PhOCH$_2$H), 59.2 (CH$_3$), 56.1 (NCH), 43.5 (NCH$_2$Ph), 30.1, 28.7, 23.9, 23.5, 21.6 (PhCH$_3$). MS (ESI): m/z = 462 (100) (M+H$^+$). Anal. calcd for C$_{25}$H$_{31}$NO$_6$: 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 1H-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 ºC, a solution of tosyl ester 10 (1 mmol) dissolved in dry DMF (3 mL) was added and the stirring was continued overnight at 50 ºC 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 Na$_2$SO$_4$ 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%. Rf 0.29 in EtOAc–MeOH, 7:3. [α]$_D$ +4.1 (c 0.8, MeOH). $^1$H-NMR (CD$_3$OD): δ 7.61 (s, 1H, NC(NH)), 7.11 (d, J = 8.6 Hz, 2H, Ph), 7.07 (s, 1H, CH$_2$NCH(=CH)N), 6.98 (s, 1H, CH = NCH = CHN), 6.89 (d, J = 8.6 Hz, 2H, Ph), 4.69 (d, J = 14.9 Hz, 1H, NCH$_2$Ph), 4.12–4.07 (m, 2H, PhOCH$_2$H), 4.03–3.93 (m,
3H, NCH/Ph, 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-ylpropyl}-IH-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). Rf 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, NCH/Ph), 4.20 (t, J = 6.7 Hz, 2H, CH₂N), 4.10–4.06 (m, 2H, PhOCH₂), 3.87 (d, J = 14.9 Hz, 1H, NCH/Ph), 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 (CH₂NCOO), 43.6 (NCH₂Ph), 30.1, 29.6, 26.0, 23.6. MS (ESI): m/z = 492 (100) (M+H⁺). Anal. calcd for C₂₈H₃₃N₅O₅: 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-ylpropyl}-IH-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). Rf 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, NCH/Ph), 4.09–4.05 (m, 2H, PhOCH₂), 3.97–3.82 (m, 3H, NCH/Ph, 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 C₂₈H₃₃N₅O₅: 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- benzoyloxycarbonyl 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 CHCl₃ 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. Rf 0.14 in EtOAc; mp. 72–75 °C; [α]₀ +14.3 (c 0.95, CHCl₃). ¹H-NMR (CDCl₃): δ 7.01 (bs, 1H, NH), 3.73–3.64 (m, 1H, NCH), 3.66 (s, 3H, CH₃), 2.41–1.60 (m, 8H, 4 × CH₂). ¹³C-NMR: δ 178.6 (NCO), 173.1 (COOCH₃), 53.7 (NCH), 51.4 (CH₃), 31.3, 30.1, 26.5. MS (ESI): m/z = 172 (100) (M+H⁺). Anal. calcd for C₁₃H₁₃NO₃: 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. Rf 0.18 in EtOAc–MeOH, 3:2. [α]₀ +2.1 (c 1, MeOH). ¹H-NMR (CD₃OD): δ 7.83 (s, 1H, NCH₃), 7.68 (s, 1H, NCHCOO), 7.10 (d, J = 8.2 Hz, 2H, Ph), 6.88 (d, J = 8.5 Hz, 2H, Ph), 4.60 (d, J = 14.9 Hz, 1H, NCHHPh), 4.11–3.99 (m, 5H, PhOCH₂, CH₂NCHCOO), 3.75–3.71 (m, 2H, CH₂OCH₃), 3.51–3.47 (m, 1H, NCH), 3.41 (s, 3H, OCH₃), 2.47–1.21 (m, 8H, 4 × CH₂). ¹³C-NMR: δ 177.7 (NCO), 162.8 (COOCH₃), 159.8, 142.0, 134.2, 130.4, 126.5, 115.8, 72.2 (CH₂OCH₃), 68.4 (PhOCH₂), 59.3 (CH₃), 58.6 (NCH), 48.1 (CH₂NCCOOH), 44.5 (NCH₂Ph), 31.2, 30.5, 27.0, 24.5. MS (ESI): m/z = 402 (100) (M+H⁺). Anal. calcd for C₂₁H₂₇N₃O₅: 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 benzyl-5-oxo-L-prolyl-L-histidine (19a). Prepared from compound 18a as a colorless oil in 97% yield. Rf 0.1 in EtOAc–MeOH, 1:1. [α]₀ +3.0 (c 1, MeOH). ¹H-NMR (CD₃OD): δ 8.85 (s, 1H, NCH₃), 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, PhOCH₂), 4.01–3.95 (m, 1H, NCHCON), 3.75–3.62 (m, 3H, CH₂OCH₃, NCHHPh), 3.42 (s, 3H, CH₃), 3.15–3.02 (m, 2H, CH₂CHN), 2.57–1.96 (m, 4H, 2 × CH₂). ¹³C-NMR: δ 178.3 (NCO), 173.9, 173.2, 160.0, 153.5, 131.7, 130.8, 129.1, 118.3, 115.9, 72.2 (CH₂OCH₃), 68.5 (OCH₂), 61.1 (NCHCON), 59.3 (OCH₃), 52.7 (HNCHCO), 45.8 (CH₂Ph), 30.8 (CH₂CHN), 28.0, 24.2. MS (ESI): m/z = 431 (100) (M+H⁺). Anal. calcd for C₂₁H₂₆N₄O₆: 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. Rf 0.11 in EtOAc–MeOH, 1:1. [α]D +11.5 (c 1, MeOH). 1H-NMR (CD3OD): δ 8.75 (s, 1H, NCH), 7.32 (s, 1H, NCHN), 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, NCH/Ph), 4.75–4.65 (m, 1H, NHCHO), 4.04–3.98 (m, 1H, NCHCO), 4.01 (t, J = 6.3 Hz, 2H, PhOCH2), 3.63 (d, J = 14.8 Hz, 1H, NCH/Ph), 3.54 (t, J = 6.2 Hz, 2H, CH2OCH3), 3.33 (s, 3H, OCH3), 3.28–3.03 (m, 2H, CH2CN), 2.53–1.93 (m, 6H, 3 × CH2). 13C-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 (CH2OCH3), 65.9 (PhOCH2), 61.2 (NCH), 58.9 (OCH3), 53.4 (CHCOOH), 45.8 (NCH2Ph), 30.9, 30.6, 28.4, 24.2. MS (ESI): m/z = 445 (100) (M+H+). Anal. calcd for C22H26N4O6: 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. Rf 0.16 in EtOAc–MeOH, 1:1. [α]D +6.9 (c 1, MeOH). 1H-NMR (CD3OD): δ 8.84 (s, 1H, HNCHN), 7.36 (s, 1H, NCHN), 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, NCH/Ph), 4.80–4.73 (m, 1H, NHCHO), 4.02–3.96 (m, 1H, NCH), 3.95 (t, J = 5.4 Hz, 2H, PhOCH2), 3.63 (d, J = 14.7 Hz, 1H, NCH/Ph), 3.45 (t, J = 6.1 Hz, 2H, CH2OCH3), 3.33 (s, 3H, CH3), 3.17–3.05 (m, 2H, CH2CN), 2.49–1.96 (m, 4H, 2 × CH2), 1.84–1.65 (m, 4H, (OCH2CH2)2). 13C-NMR: δ 178.2 (NCO), 173.9, 160.3, 135.2, 131.8, 131.1, 130.7, 128.9, 118.8, 115.8, 73.5 (CH2OCH3), 68.9 (PhOCH2), 61.1 (NCH), 58.8 (OCH3), 52.9 (CHCOOH), 45.8 (NCH2Ph), 30.8, 28.0, 27.3, 27.2, 24.1. MS (ESI): m/z = 459 (100) (M+H+). Anal. calcd for C23H30N4O6: 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-proline (21). Prepared from compound 20 as a colorless oil in 99% yield. Rf 0.69 in EtOAc. [α]D +35.5 (c 1.1, CHCl3). 1H-NMR (CDCl3): 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, NCH/Ph), 4.02–3.91 (m, 2H, NCH/Ph, NCH), 3.67 (s, 3H, CH3), 2.55–2.04 (m, 4H, 2 × CH2). 13C-NMR: δ 175.7 (NCO), 172.2 (COOCH3), 156.3, 130.0, 126.5, 115.7, 58.9 (NCH), 52.5 (COOCH3), 45.3 (NCHPh), 29.8, 22.7. MS (ESI): m/z = 250 (97) (M+H+). Anal. calcd for C13H15NO4: C, 62.64; H, 6.07; N, 5.62 Found: C, 62.59; H, 6.17; N, 5.54.

1-[(4R)-3-(tert-Butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidin-4-yl]methoxybenzyl]-5-oxo-L-prolyl-L-histidine (25). Prepared from compound 24 as a colorless oil in 97% yield. Rf 0.18 in EtOAc–MeOH, 1:1. [α]D −24.9 (c 0.8, MeOH). 1H-NMR (CD3OD): 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, NCH/Ph), 4.17–3.81 (m, 6H, NCHCOO, PhOCH2CH2CH2O), 3.64 (d, J = 15.0 Hz, 1H, NCH/Ph), 3.41–3.06 (m, 2H,HOOCCCH2), 2.58–1.94 (m, 4H, 2 × CH2), 1.58–1.45 (m, 15H, 5 × CH3). 13C-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 (NC(CH3)2O), 82.2 (C(CH3)3), 67.3, 66.2, 61.1 (NCHCOO), 57.5 (PhOCH2), 52.5 (NHCHCOOH), 45.8 (NCH2Ph), 30.8, 28.8 (CH3), 27.9, 27.7, 24.5, 24.2. MS (ESI): m/z = 586 (100) (M+H+). Anal. calcd for C29H39N5O8: 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. Rf 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, CH2Ph), 4.11–4.06 (m, 2H, PhOC2H5), 3.99–3.93 (m, 1H, NCHCOO), 3.91 (d, J = 4.7 Hz, 1H, CH2Ph), 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. Rf 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, CH2Ph), 4.04–3.94 (m, 3H, NCHCOO, PhOC2H5), 3.91 (d, J = 14.7 Hz, 1H, CH2Ph), 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 (PhOC2H5), 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. Rf 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, NCH2Ph), 4.00–3.88 (m, 4H, NCH2Ph, NCH2, 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. Rf 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, J1 = 14.6 Hz, J2 = 3.1 Hz, 1H, NCH2Ph), 4.28–3.80 (m, 7H, NCH2Ph, NCHCOOH, OCH2CH2O), 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); Rf 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, NCHNCH), 5.01 (d, \( J = 14.3 \) Hz, 1H, CHHPh), 5.00 (s, 2H, OCH₂Ph), 4.86–4.77 (m, 1H, NCHCOO), 4.12–4.04 (m, 2H, PhOCH₂), 3.89–3.83 (m, 1H, NCHCON), 3.75 (d, \( J = 14.3 \) Hz, 1H, CHH/Ph), 3.74–3.69 (m, 2H, CH₂OCH₃), 3.43 (s, 3H, OCH₃), 3.13–2.91 (m, 2H, COCH₂CHN), 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 (NPh), 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 (NHCH₂CH₃), 23.2. MS (ESI): \( m/z = 763 \) (100) (M+H⁺). Anal. calcd for C₄₇H₄₅N₄O₇: 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); Rf 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 (NHCH₂CH₃), 23.2. MS (ESI): \( m/z = 777 \) (100) (M+H⁺). Anal. calcd for C₄₈H₄₈N₄O₈: 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); Rf 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, CH2CN), 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, 128.6, 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 (HNCHCOO), 44.5 (CH3Ph), 29.7, 28.8, 26.1, 25.9, 23.2. MS (ESI): m/z = 791 (100) (M+H+). Anal. calcd for C49H59N5O6: 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-Butyloxycarbonyl)-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); Rf 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, NCHCOO), 4.26–3.69 (m, 7H, NCHHPH, NCHCONH, PhOCH2CH2CH2O), 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, 128.3, 128.1, 119.6, 114.7, 93.5 (O(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 (HNCHCOO), 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 C55H59N5O4: 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-Butyloxycarbonyl)-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], (0.231g, 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). Rf 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, PhOCH2CH2CH2O), 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 (N(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 C28H34N2O7: 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). [α]D +3.4 (c 0.7, H₂O). ¹H-NMR (D₂O): δ 8.87 (s, 1H, HNCHCH₂), 7.32 (s, 1H, HNCHCH₂), 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, NCH₃Ph), 4.33–4.19 (m, 2H, PhOCH₂), 4.16–4.12 (m, 1H, NCH), 3.98–3.80 (m, 4H, NCH₂Ph, CHNH₂, CH₂OH), 3.33 (dd, J₁ = 5.4 Hz, J₂ = 15.6 Hz, 1H, HNCHCH₃HC), 3.15 (dd, J₁ = 9.0 Hz, J₂ = 15.5 Hz, 1H, HNCHCH₃HC), 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⁺).

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 μL, 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). Rf 0.50 in EtOAc–petroleum ether (bp. 40–60 °C) 1:1; [α]D −2.7 (c 1, CHCl₃). ¹H-NMR (CDCl₃): δ 7.77–7.06 (m, 29H, Ph, NCH₃), 6.61 (d, J = 8.2 Hz, 1H, NH), 6.54 (s, 1H, NCH₃HC), 5.07 (dd, J₁ = 12.5 Hz, J₂ = 14.9 Hz, 2H, OCH₂Ph), 4.73–4.64 (m, 1H, HNCHCO), 4.40–4.19 (m, 3H, CH₂CH₂OCO), 3.12 (d, J = 5.0Hz, 2H, CH₂CH₃). ¹³C-NMR: δ 171.2 (HNCHCO), 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 (CH₂COO), 29.7 (CH₂CH₃). MS (ESI): m/z = 710 (100) (M+H⁺). Anal. calcd for C₄₇H₃₉N₅O₄: 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 μL, 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 × 5mL) 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). Rf 0.37 in EtOAc–MeOH 9:1; [α]D −11.7 (c 1, CHCl₃). ¹H-NMR (CDCl₃): δ 7.32–7.08 (m, 21H, 4 × Ph, NCH₃), 6.54 (s, 1H, NCH₃HC), 5.04 (dd, J₁ = 12.3 Hz, J₂ = 20.8 Hz, 2H, OCH₂Ph), 3.90–3.85 (m, 1H, H₂NCH), 3.08–2.82 (m, 2H, CH₂CH₃). 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 (CH₂CH₃). MS (ESI): m/z = 488 (100) (M+H⁺). Anal. calcd for C₃₂H₃₀N₅O₂: 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.

Acknowledgments

Financial support from the EPEAEK Program “Organic Synthesis and Applications in Chemical Industry” as well as from the Special Research Account of the University of Athens is highly appreciated.

References

1. Winbal, B. Piracetam: A review of pharmacological properties and clinical uses. CNS Drug Rev. 2005, 11, 169–182.
2. Singh, P.; Dimitriou, V.; Malajan, R.P.; Crossley, A.W. Double-blind comparison between doxapram and pethidine in the treatment of postanaesthetic shivering. Br. J. Anaesth. 1993, 71, 685–688.
3. Siddiqui, N.; Ahsan, W.; Alam, M.S.; Ali, R.; Srivastava, K. Design, synthesis and evaluation of anticonvulsant activity of pyridinyl-pyrrolidones: A pharmacophore hybrid approach. Arch. Pharm. Chem. Life Sci. 2012, 345, 185–194.
4. Volkhard, A.; Eisert, W.; Himmelsbach, F.; Linz, G.; Mueller, T.; Pieper, H.; Weisenberger, J. 2-Pyrrolidinones, Pharmaceutical composition containing these compounds and processes for preparing them. U.S. Patent 5455348, 3 November 1995.
5. Zhongli, G.; Ryan, H.; David, S. Substituted tetrahydropyran spiro pyrrolidinone and piperidinone, preparation and therapeutic use thereof. U.S. Patent 20120238757, 20 September 2012.
6. Ohfune, Y.; Tomita, M. Total synthesis of (-) Domoic Acid. A revision of the original structure. J. Am. Chem. Soc. 1982, 104, 3511–3513.
7. Petersen, J.S.; Rapoport, H. Chirospecific syntheses of (+)- and (-) Anatoxin a. J. Am. Chem. Soc. 1984, 106, 4539–4547.
8. Fang, F.; Danishefsky, J.S. Total synthesis of the angiotensin-converting enzyme inhibitor A58365: On the use of pyroglutamate as a chiral educt. Tetrahedron Lett. 1989, 30, 3621–3624.
9. Davies, G.S.; Dixon, J.D.; Doisneau, J.-M.D.; Prodger, C.J.; Sanganee, J.H. Synthesis and utility of the 3,3-dimethyl-5-substituted-2-pyrrolidinone “Quat” chiral auxiliary. Tetrahedron: Asymmetry 2002, 13, 647–658.
10. Coppola, G.M.; Schuster, H.F. Asymmetric Synthesis. Construction of Chiral Molecules Using Amino Acids; John Wiley: New York, NY, USA, 1987.
11. Najera, C.; Yus, M. Pyroglutamic acid: A versatile block in asymmetric synthesis. Tetrahedron: Asymmetry 1999, 10, 2245–2303.
12. Panday, S.K.; Prasad, J.; Dikshit, K.D. Pyroglutamic acid: A unique chiral synthon. Tetrahedron: Asymmetry 2009, 20, 1581–1632.
13. Moutevelis-Minakakis, P.; Gianni, M.; Stoigiannou, H.; Zoumpoulakis, P.; Zoga, A.; Vlahakos, E.; Ilidromitis, E.; Mavromoustakos, T. Design and synthesis of novel antihypertensive drugs. Bioorg. Med. Chem. Lett. 2003, 13, 1737–1740.
14. Mavromoustakos, T.; Moutevelis-Minakakis, P.; Kokotos, C.G.; Kontogianni, P.; Politi, A.; Zoumpoulakis, P.; Findlay, A.; Cox, A.; Balmforth, A.; Zoga, A.; et al. Synthesis, binding studies and in vivo biological evaluation of novel non-peptide antihypertensive analogues. *Bioorg. Med. Chem.* **2006**, *14*, 4353–4360.

15. Mavromoustakos, T.; Fotakis, C.; Siapi, E.; Potamitis, C.; Viras, K.; Moutevelis-Minakakis, P.; Kokotos, G.; Durgasi, S.; Grdadolnik, S.; Sartori, B.; et al. Interactions at the bilayer interface and receptor site induced by the novel synthetic pyrrolidinone analog MMK3. *BBA-Biomembranes* **2010**, *1798*, 422–432.

16. Moutevelis-Minakakis, P.; Papavassilopoulou, E.; Michas, G.; Georgiopoulou, K.; Ragoussi, M.E.; Neophytou, N.; Zoumpoulakis, P.; Mavromoustakos, T.; Hadjipavlou-Litina, D. Synthesis, in silico docking experiments of new 2-pyrrolidinone derivatives and study of their anti-inflammatory activity. *Bioorg. Med. Chem.* **2011**, *19*, 2888–2902.

17. Otsuka, M.; Masuda, T.; Haupt, A.; Ohno, M.; Shiraki, T.; Sugiuira, Y.; Maeda, K. Synthetic studies on antitumor, antibiotic bleomycin. 27. Man-designed bleomycin with altered sequence specificity in DNA cleavage. *J. Am. Chem. Soc.* **1990**, *112*, 838–845.

18. Roush, W.R.; Russo-Rodriguez, S. Trichothecene Degradation Studies. 2. Synthesis of [13-14C] Anguidine. *J. Org. Chem.* **1987**, *52*, 598–603.

19. Lee, Y.S.; Cho, D.J.; Kim, S.N.; Choi, J.H.; Park, H. Chiral synthesis of trans-1-aminoidololo[2,3-a]quinolizidine and trans-1-aminobenzo[a]quinolizidine derivatives from L-pyrogulatamic acid. *J. Org. Chem.* **1999**, *64*, 9727–9730.

20. Bauer, J.; Brandenburg, K.; Zähringer, U.; Rademann, J. Chemical synthesis of a glycolipid library by a solid-phase strategy allows elucidation of the structural specificity of immunostimulation by rhamnolipids. *Chem. Eur. J.* **2006**, *12*, 7116–7124.

21. Chida, N.; Takeoka, J.; Ando, K.; Tsutsumi, N.; Ogawa, S. Stereoselective total synthesis of (+)-lactacytin from 2-glucose. *Tetrahedron* **1997**, *53*, 16287–16298.

22. Elems, Y.; Foote, C.S. Stepwise mechanisms in the ene reaction of α, β-unsaturated esters with N-phenyl-1,2,4-triazoline-3,5-dione and singlet oxygen. Intermolecular primary and secondary hydrogen isotope effects. *J. Am. Chem. Soc.* **1992**, *114*, 6044–6050.

23. Brefa-Valle, L.J.; Sánchez, C.R.; Cruz-Almanza, R. Diastereoselective alkylation of 1-benzyl-(5S)-substituted 2-pyrrolidinones. *Tetrahedron: Asymmetry* **1996**, *7*, 1019–1026.

24. Salvatore, R.N.; Nagle, A.S.; Jung, K.W. Cesium effect: High chemoselectivity in direct N-alkylation of amines. *J. Org. Chem.* **2002**, *67*, 674–683.

25. Sheehan J.C.; Cruickshank, P.A.; Boshart, G.L. A convenient synthesis of water-soluble carbodiimides. *J. Org. Chem.* **1961**, *26*, 2525–2528.

26. Oeveren, V.A.; Jansen, J.F.G.; Feringa, B.L. Enantioselective synthesis of natural dibenzylbutyrolactone lignans (−)-enterolactone, (−)-hinokinin, (−)-pluviatolide, (−)-enterodiol, and furofuran lignan (−) eudesmin via tandem conjugate addition to γ-alkoxybutenolides. *J. Org. Chem.* **1994**, *59*, 5999–6007.

27. Mandoli, A.; Calamante, M.; Feringa, B.L.; Salvadori, P. An insoluble polymer-bound phosphoramidite for the copper-catalysed enantioselective 1,4-addition of ZnEt2 to 2-cyclohexenone. *Tetrahedron: Asymmetry* **2003**, *14*, 3647–3650.
28. Zinieris, N.; Kokinaki, S.; Leontiadis, L.; Ferderigos, N. Synthesis of 4-(Fmoc-aminoacyloxymethyl)phenoxyacetic acids for use in solid-phase peptide synthesis. *Synthesis* **2006**, *16*, 1789–2793.

29. Chong, J.M.; Sokoll, K.K. Enantiotopic group differentiation and kinetic resolution: Asymmetric reduction of meso-1,3-dihalides. *Tetrahedron Lett.* **1992**, *33*, 879–882.

30. Ziegler, E.F.; Klein, S.I.; Pati, U.K.; Wang, T.F. Acyclic diastereoselection as a synthetic route to quassinoids: A Claisen rearrangement based strategy for bruceantin. *J. Am. Chem. Soc.* **1985**, *107*, 2730–2737.

31. Güschke, R.; Stutz, S.; Heinzelmann, W.; Maibaum, J. The nonchiral bislactim diethoxy ether as a highly stereo-inducing synthon for sterically hindered, γ-branched α-amino acids: A practical, large-scale route to an intermediate of the novel rennin inhibitor Aliskiren. *Helv. Chim. Acta* **2003**, *86*, 2848–2870.

32. Thakkar, K.; Geahlen, R.L.; Cushman, M. Synthesis and protein-tyrosine kinase inhibitory activity of polyhydroxylated stilbene analogues of piceatannol. *J. Med. Chem.* **1993**, *36*, 2950–2955.

33. Williams, L.; Zhang, Z.; Shao, F.; Carroll, P.J.; Joullié, M.M. Grignard reactions to chiral oxazolidine aldehydes. *Tetrahedron* **1996**, *52*, 11673–11694.

34. Pavé, G.; Usse-Versluys, S.; Viaud-Massuard, M.C.; Guillaumet, G. Synthesis of 3-aminochroman derivatives by radical cyclization. *Org. Lett.* **2003**, *5*, 4253–4256.

35. Wang, S.; Gisin, B.F.; Winter, D.P.; Makofske, R.; Kulesha, I.D.; Tzougraki, C.; Meienhofer, J. Facile synthesis of amino acid and peptide esters under mild conditions via cesium salts. *J. Org. Chem.* **1977**, *42*, 1286–1290.

36. Zvilichovsky, G.; Gurvich, V. Products of ozonolysis of L-1,4-cyclohexadienylalanine. Intramolecular cyclization and cyclization with hydroxylamine. The synthesis of two isomers of L-isoaxazolylalanine. *Tetrahedron* **1997**, *53*, 4457–4468.

Sample Availability: Contact the authors.

© 2013 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/3.0/).