Synthesis of Conformationally Restricted Proline Chimeras

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Abstract

Conformational constraint is a usual way to modify the properties of bioactive peptides. In some cases, such modification improves their activity as well as their affinity for their biological target. Proline analogues play a pivotal role in such studies, thus encouraging the development of new methodologies, allowing access to so-called 'proline chimeras', in which the conformational constraint of proline is combined with the side chain of another amino acids. In this contribution, we would like to describe a straightforward approach to the enantiomerically pure polysubstituted lactams derived from pyroglutamic acid. Such oxoproline analogues provide a useful scaffold for synthesis of conformationally restricted analogues of proline-homophenylalanine or proline-homoglutamic acid derivatives.

Keywords

chimeras; proline; crystallisation-induced asymmetric transformation; Michael addition; stereoselective transformations

Introduction

Conformationally restricted α-amino acids are valuable tools for studying spatial requirements for receptor affinity and biological activity of natural amino acids. In this context, proline analogues possessing the characteristics of other amino acids (so-called *chimeras*) are of current interest. In addition, the conformationally rigid pyrrolidine fragment in their molecules stabilises the substituents attached, moreover, in a certain spatial orientation with respect to each other. As a result, the conformational mobility of the entire molecule is restricted, thus enhancing the interaction between the pyrrolidine ligand and the active site of a protein target, as compared to an acyclic analogue.[1] In the past decades, several analogues of proline chimeras with different stereochemistry and functionality have been synthesised[1-2] (Fig. 1). While these analogues have proved useful for inducing specific constraints in amino acids and peptides, their structures do not permit additional derivatisation; a trait that is often required in drug discovery and lead optimisation. Polyfunctional proline-amino acid chimera may overcome these drawbacks.

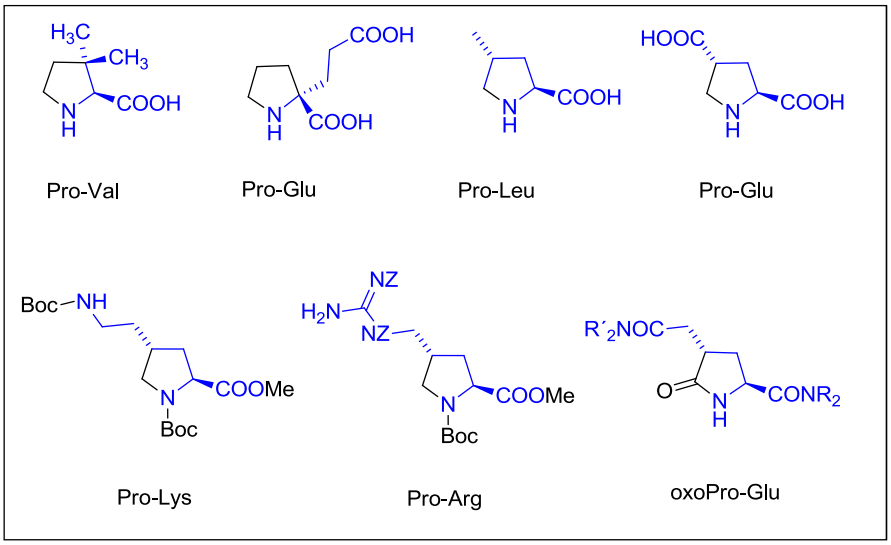


Figure 1: Various types of known proline chimeras

In past decades, a number of syntheses of various types of proline and 5-oxoproline chimeras were reported[1-2] (Figure 1). In conjunction with our ongoing research program, we have been involved in the development of a novel route to asymmetric synthesis of polysubstituted proline chimeras. In this paper, we describe a short and efficient synthesis of compounds like 5-oxoproline-homophenylalanine and 5-oxoproline-homoglutamic acid chimeras (Figure 2) in their enantiomerically pure form. Oxoproline-homoglutamic acid chimeras have been recognized recently as potent and selective inhibitors of fibroblast activation protein (FAP)[3] and several conformationally multi-functionalised homophenylalanines have also attracted considerable attention. Also pyroglutamic acid and its derivatives are structural units of widespread chemical significance, having been heavily utilised as building blocks for the synthesis of numerous biologically active compounds.[4]

Our concept for developing such polyfunctional 5-oxoproline-amino acid chimeras employs the highly stereoselective intramolecular Michael reaction as a key step.

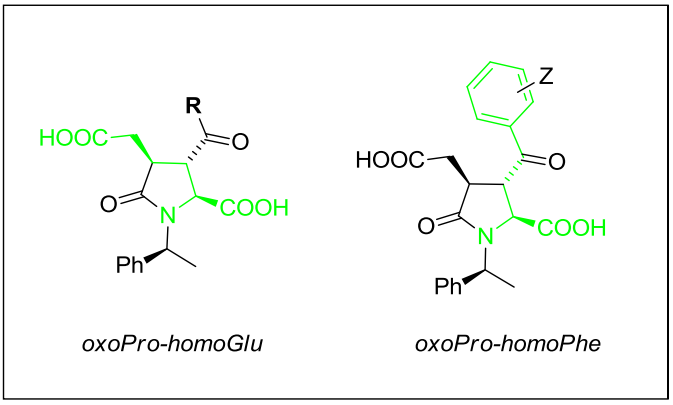
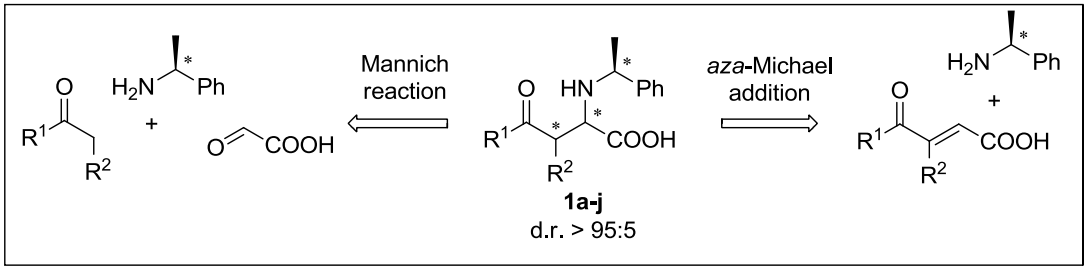


Figure 2: New 5-oxoproline chimeras

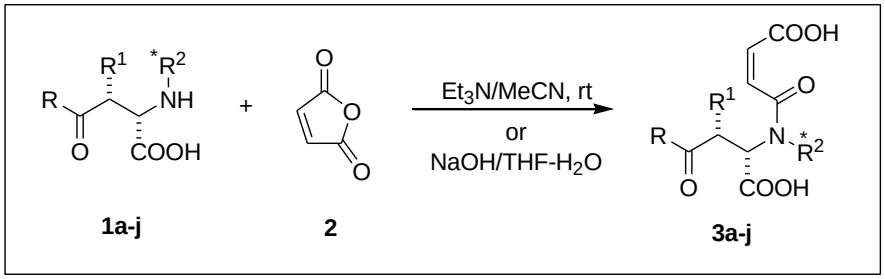
Results and Discussion

Recently, our research group has developed the synthetic strategy based on the tandem reaction sequence (Scheme 1) featuring *aza*-Michael addition of chiral *N*-nucleophiles to aroyl acrylic acids (or Mannich reaction) followed by crystallisation-induced asymmetric transformation (CIAT) targeted to the highly diastereoselective synthesis of γ-oxo-α-amino acids **1a-j**. The success of such asymmetric transformation is critically dependent on two principal conditions: (a) the formation of solid amino acids that are only slightly soluble in the reaction mixture at their isoelectric point, and, (b) the existence of fast equilibrium between the diastereoisomers in the solution. The different examples of CIAT processes coupled to reversible *aza*-Michael reaction or *retro*-Mannich reaction were published previously.[5]



Scheme 1: Preparation of γ-oxo-α-amino acids using tandem Michael or Mannich-CIAT

Having prepared a series of starting compounds in high diastereomeric purity (d.r. > 97:3), we have focused on *N*-acylation of *N*-substituted γ-oxo-α-aminocarboxylic acids **1a-j** (Scheme 2). Initially, the molar ratio of reaction partners, type of base (triethylamine, Bu_4NOH) and solvent (diethylether, THF, dioxane, ethyl acetate, dichloromethane, acetonitrile) as well as the reaction temperature (room temperature, reflux) were scrutinised. The reactions conducted in ethyl acetate, dichloromethane and/or ethers did not furnish the desired products. In such cases, either the starting material was recovered or complex reaction mixture was formed at reflux. However, using the Et_3N/MeCN mixture as a solvent resulted in a complete conversion of substrates and formation of desired products. Thus, 4-aryl-, heteroaryl- or (cyclo)alkyl derivatives of γ-oxo-α-amino acids **1a-j** were successfully acylated with maleic anhydride under the optimised reaction conditions (Scheme 2, Table 1). The excess of triethylamine provided the solubility of starting amino acids in the form of triethylammonium salts, which were subsequently smoothly acylated to furnish *N*-acylated derivatives **3a-j** in high yields. It is important to note that no epimerisation at the stereogenic centre at C-2 was observed during this transformation.



Scheme 2: The *N*-acylation of Mannich or Michael aducts.

Table 1: The *N*-acylation of *N*-substituted 4-oxo-2-aminocarboxylic acids (**1a-j**) with maleic anhydride.

Compound	R	R^1	R^2	Et_3N (eq.)	Reaction time [a]	Yield (%)[b]	d.r. [a]
3a	*p*-MeO-C_6H_4	H	(*S*)-PEA	7	1 h	77	> 99:1
3b	*p*-MeO-C_6H_4	H	Bn	5	2 h	88	-
3c	Tol	H	(*S*)-PEA	11	3 h	88	98:2
3d	Ph	H	(*S*)-PEA	5	3 h	68	98:2
3e	Ph	H	Bn	3	30 min	72	-
3f	Ph	Me	(*S*)-PEA	1.2	12 h	77	98:0:1:1
3g	Cy	H	(*S*)-PEA	1.2	4 h	86	97:3
3h	*t*-Bu	H	(*S*)-PEA	1.2	3 h	88	95:5
3i	*p*-Br-C_6H_4	H	(*S*)-PEA	5	2 h	80	98:2
3j	5-Br-tio [c]	H	(*S*)-PEA	5	1 h	75	98:2

[a] Data obtained from HPLC analysis; [b] Yields after extraction; [c] 5-Br-tio = 5-bromotiophen-2-yl.

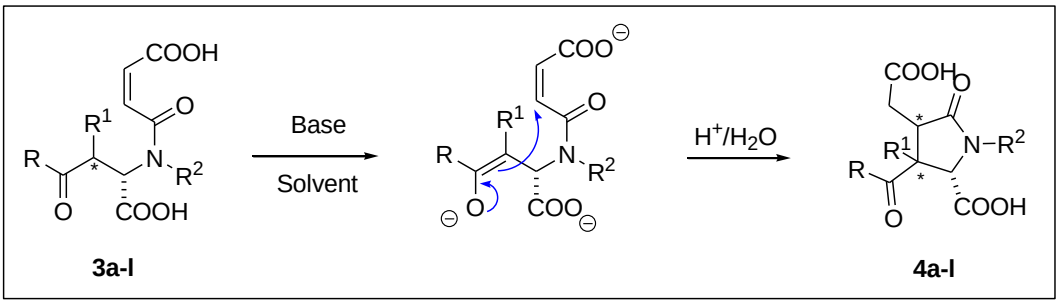
In the case of *N*-unsubstituted racemic oxoamino acids **3k,l** the procedure was slightly modified (Scheme 2). Thus, the *N*-acylation was accomplished by using NaOH/H_2O/THF system (Table 2).

Table 2: The *N*-acylation of 4-oxo-2-aminocarboxylic acids (**1k,l**) with maleic anhydride.

Compound	R	R^1	R^2	NaOH (eq)	Reaction time [a]	Solvent	Yield (%)[b]
3k	Tol	H	H	1	0.5 h	THF-H_2O	83
3l	Ph	H	H	1	1 h	THF-H_2O	62

[a] Data obtained from HPLC analysis; [b] Yields after extraction.

With the compounds **3a-l** in hand, the formation of pyrrolidine ring *via* the cyclisation of the corresponding enolate was attempted. Therefore, we have investigated the base-promoted enolisation of the corresponding *N*-acylated derivatives of γ-oxo-α-amino acids. As the formation of pyrrolidine takes place *via* nucleophilic attack of enolate onto the activated Michael acceptor (Scheme 3), the optimal type of base was briefly scrutinised (Table 3).



Scheme 3: The base-promoted intramolecular Michael reaction

Table 3: The base screening for the intramolecular Michael reaction

Entry	Comp.	Base	Eq.	Solvent	[°C]	Time[a]	Conversion[a]
1	**3a**	Et_3N	4	MeCN	25	7,5 h	5%
2	**3a**	*i*-Pr_2Net	3	MeCN	25	8 h	0%
3	**3a**	MeONa/MeOH	4	MeOH	25	6.5 h	100%
4	**3a**	K_2CO_3	4	MeOH	25	7 h	100%
5	**3a**	NaOH	4	MeOH	40	15 min	100%

[a] Data obtained from HPLC analysis.

The employment of either Et_3N or DIPEA did not provide the desired products in any useful yield (Table 3, entries 1 and 2). However, treatment of *N*-acylated compound **3a** with anhydrous pulverised potassium carbonate in MeOH led to the formation of desired cyclic derivatives **4a** (Table 3, entry 4). The use of MeONa/MeOH gave an analogous result (Table 3, entry 3). The best results were obtained with sodium hydroxide as a base in MeOH/H_2O solution as the reaction was completed in 15 minutes at 40 °C (Table 3, entry 5). Under such optimised reaction conditions, a series of adducts **4a-l** was prepared (Table 4).

Table 4: The products of stereoselective intramolecular Michael reaction

Compound	R	R^1	R^2NH_2	Time[a] (h)	Yield[b] (%)	mp (°C)
4a	*p*-MeO-C_6H_4	H	(*S*)-PEA	0.5	98	72-73
4b	*p*-MeO-C_6H_4	H	Bn	1	72	62-66
4c	Tol	H	(*S*)-PEA	1	77	54-56
4d	Ph	H	(*S*)-PEA	2	80	78-80
4e	Ph	H	Bn	1.5	89	62-64
4f	Ph	Me	(*S*)-PEA	2	92	102-103
4g	Cy	H	(*S*)-PEA	1.5	95	45-46
4h	*t*-Bu	H	(*S*)-PEA	2	80	40-41
4i	*p*-Br-C_6H_4	H	(*S*)-PEA	2	75	82-83
4j	5-Br-tio[c]	H	(*S*)-PEA	2	93	66-68
4k	*p*-MeO-C_6H_4	H	H	2.5	76	52-54
4l	Ph	H	H	2	71	50-52

[a] Data obtained from HPLC analysis; [b] Yields after extraction; [c] 5-Br-tio = 5-bromotiophen-2-yl

All oxoproline chimeras were obtained in high yields and diastereomeric purity. The observed level of diastereoselectivity may be explained by assuming the thermodynamically more stable conformation (having *Z*-geometry of unsaturated carboxylic acid and Z-geometry of enolate), in which the enolate should approach the reaction site preferentially from the less hindered side with the formation of *„all-trans“* diastereomer (Figure 3). For the interpretation of a stereochemical outcome of this reaction, calculations of energies for *„all-cis“* and *„all-trans“* isomers were carried out. Quantum-chemical calculations were realised using two methods:

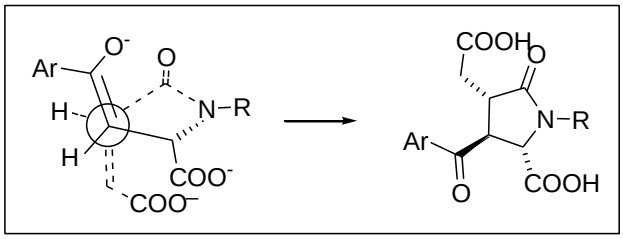


Figure 3: Proposed cyclisation mode.

Method 1: Conformational analysis CONFLEX + MM3, followed by single point computation of energies DFT B88LYP in both cases, basis set DZVP[6] ; The obtained energy difference **ΔE = 7,559 kcal/mol.**

Method 2: Structures of "*all-cis*" and "*all-trans*" isomers were optimized by DFT method using Gaussian (B3LYP/6-31+g(d,p)). The estimated energy difference **ΔE = 9,051 kcal/mol** was in favour of *„all-trans*" isomer.

The difference in the energy (ΔE = 7,559 kcal/mol) of these isomers supported the formation of thermodynamically more stable *„all-trans"* derivative.

The oxoproline chimeras were fully characterised by ^{1}H NMR, ^{13}C NMR, COSY and HMBC experiments. The relative configurations at C-2, C-3 and C-4 were deduced from NOE experiments (Figure 4). A significant NOE was observed between H-2 and H-4, between H-3 and H-4´ and weak NOE between H-2 and H-4; all were in accordance with the "*all - trans*" stereochemistry. Also 1D NOESY experiments of compound **4f**, with quaternary stereocenter confirmed the same stereochemistry. Positive NOE between H-4´and methyl group at C-3 position was proofed. This result is in accordance with the stereochemistry shown in Figure 4.

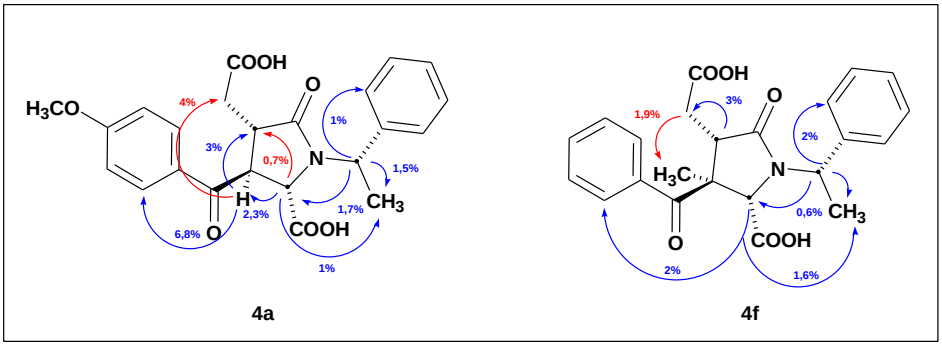


Figure 4: NOE experiment of oxoproline chimeras

Experimental Section

All reagents were used as received without further purification unless otherwise specified. (*S*)-Phenylethylamine (99+%, 99% ee) was obtained from Alfa Aesar. Melting points were obtained using Kofler hot plate and are uncorrected. Optical rotations were measured with a POLAR L-µP polarimeter (IBZ Messtechnik) with a water-jacket 10.000 cm cell at a wavelength of sodium line D (λ = 589 nm). Specific rotations are given in units of 10^{-1} deg cm^2 g^{-1} and concentrations are given in mol/dm^3. ^{1}H NMR spectra were recorded on a Varian VXR-300 (299.94 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million and are referenced to tetramethylsilane (TMS) as an internal standard (δ_{Me} = 0.00 for 299.94 MHz). Coupling constant (J) are recorded in Hertz. The following abbreviations were used to characterize signal multiplicities: s (singlet), d (doublet), t (triplet), m(multiplet) and br (broad). Abbreviations with quotation marks mean that the appearance of the signal is different from what is theoretically predicted. ^{13}C NMR spectra were recorded on a Varian VRX-300 (75.43 MHz) spectrometer. The multiplicities of the carbons were assigned from a

broadband decoupled analysis used in a conjunction with either APT or DEPT. Chemical shifts (δ) are quoted in parts per million and are referenced to tetramethylsilane (TMS) as an internal standard (δ = 0.00 for 75.43 MHz). HPLC experiments were performed on a PYE UNICAM chromatographic system (PU 4015 pump working in isocratic mode). Multichannel detector PU 4021 was performed in SUM ABS mode at wavelengths ranging from 210 to 310 nm. The following columns and eluents were used for HPLC experiments:
Conditions 1: Column Phenomenex Luna, Phenyl-Hexyl 250 x 4.6 mm; mobile phase: $MeCN/H_2O/Et_3N$ = 500 : 500 : 10 (ml), and the pH of the solution was adjusted to 3.6 using H_3PO_4.
Conditions 2: Column Phenomenex Luna, Phenyl-Hexyl 250 x 4.6 mm; mobile phase: $MeCN/H_2O/Et_3N$ = 600 : 400 : 10 (ml), and the pH of the solution was adjusted to 3.6 using H_3PO_4.

General procedure for the preparation of *N*-acylated 4-oxo-2-aminocarboxylic acids:
*A typical procedure for the preparation of **3a** is as follows:* Triethylamine (35 mmol, 1.045 g, 7 eq) was added to a suspension of γ-oxo-α-amino acid **1a** (5 mmol, 1.660 g) in acetonitrile (50 ml) . After being stirred for 10 min, maleic anhydride **2** (6.1 mmol, 0.579 g, 1.2 eq) was added and the resulting heterogenous mixture was stirred at room temperature until HPLC analysis had shown complete consumption of starting materials (1 h). The solution was evaporated *in vacuo*. Water (100 ml) was added to a colourless residue and the pH of the mixture was adjusted to 2.0 - 2.5 using 4N HCl. The resulting emulsion was extracted by ethylacetate (2 x 30 ml), washed with water (3 x 30ml) and dried with Na_2SO_4. The product was obtained after evaporation of solvent. **3a** (1.660 g, 77% as a white solid), Mp = 103–107°C (acetone/hexane); $[\alpha]_D^{20}$= -63.6 (c 0.5, MeOH), TLC: R_f = 0.63 (EtOAc : MeOH = 1 : 2); HPLC (conditions 1): t_R = 14 min, flow: 0.4 ml/min; IR: ν 3062, 2979, 2578, 1721, 1674, 1600, 1576, 1512, 1453, 1262, 1171, 1028 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.45 (d, 3H, H-2´´, J = 6.8 Hz); 3.03 (d, 1H, H-3´B, J = 6.8 Hz); 3.85 (s, 3H, OCH_3); 4.22 (dd, 1H; H- 3´A; J = 8.2 Hz, 18.3 Hz); 4.34 (d, 1H, H-2´, J = 7.3 Hz); 5.11 (q, 1H, H-1´´, J = 6.8 Hz); 6.08 (d, 1H, H-2, J = 11.9 Hz); 7.08 (d, 2H, H-Ph, J = 8.8 Hz); 7.10 (d, 1H, H-3, J = 11.8 Hz); 7.32-7.42 (m, 3H, H-Ph); 7.51 (d, 2H, H-Ph, J = 7.4 Hz); 7.93 (d, 2H, H-Ph, J = 8.8 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 16.8 (C-2´´); 40.3 (C-3´); 49.8 (C-1´´); 55.2 (OCH_3); 56.5 (C-2´); 113.9 124.5, 127.6, 127.9, 128.1, 130.0, 136.7, (C-2, C-3, CH-Ph); 129.1, 138.9, 137.5 (C-Ph), 163.2, 166.2 , 171.1 (C-1, C-4, C-1´); 195.5 (C-4´).

General procedure for the preparation of polysubstituted 5-oxoprolines:
*A typical procedure for the preparation of **4a** is as follows:* NaOH (7.2 mmol, 0.288 g, 3 eq) was added to the *N*-acylated derivatives of γ-oxo-α-amino acid **3a** (2.4 mmol, 1 g) in $MeOH/H_2O$ solution. The resulting solution was stirred at 40°C until HPLC analysis had shown complete consumption of starting materials (30 min). Methanol was evaporated in vacuo and the pH of the mixture was adjusted to 2.0 - 2.5 using 4N HCl. The resulting solution was extracted with ethylacetate (2 x 30 ml), washed with water (3 x 30 ml) and dried with Na_2SO_4. The product was obtained after the evaporation of the solvent. **4a** (0.98 g, 98% as a white solid), Mp = 72–73°C (CH_3CN/H_2O); $[\alpha]_D^{20}$ = +16.45 (c 0.5, MeOH); TLC: R_f = 0.525 (EtOAc : MeOH = 1 : 2); HPLC (conditions 2): t_R = 10.72 min, flow: 1 ml/min; IR: ν 2937, 1731, 1666, 1651, 1596, 1214, 1169 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.57 (d, 3H, H-1´´, J = 7.0 Hz); 2.55-2.71 (m, 2H, H-4´); 2.97 (m, 1H, H-4, J = 4.6 Hz, J = 9.1 Hz); 3.85 (s, 3H, OCH_3); 4.94 (t, 1H, H-3, J = 3.8 Hz); 4.20 (d, 1H, H-2, J = 3.4 Hz); 4.90 (q, 1H, H-1´, J = 6.9 Hz); 7.06 (d, 2H, H-Ph, J = 8.7 Hz); 7.23-7.34 (m, 5H, H-Ph); 7.99 (d, 2H, H-Ph, J = 8.7 Hz); ^{13}C NMR (300 MHz, DMSO-d_6): δ 17.5 (C-1´´); 35.0 (C-4´); 42.1, 46.8, 52.5, 60.8 (C-1´,C-2, C-3, C-4); 55.6 (OCH_3);

114.1, 127.2, 127.4, 128.0, 131.3 (CH-Ph); 127.9, 140.1, 163.7 (C-Ph); 172.5, 172.6 (2 x COOH); 173.9 (C-5) 196.3 (C=O).

Conclusion

Polysubstituted oxoprolines **4a,c,d,f-j** were prepared in two steps in high diastereomeric purity as *all-trans* stereoisomers. The required optically pure γ-oxo-α-amino acids **1a,c,d,f-j** were prepared by reversible *aza*-Michael addition and/or multicomponent Mannich reaction using the crystallisation-induced asymmetric transformation (CIAT). The following acylation with maleic anhydride and highly diastereoselective intramolecular Michael reaction provided desired polysubstituted oxoprolines **4a,c,d,f-j** as single diastereomers.

Acknowledgements

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