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Synthesis of (2*S*,3*S*)-3-Aroyl Pyroglutamic Acid Amides †

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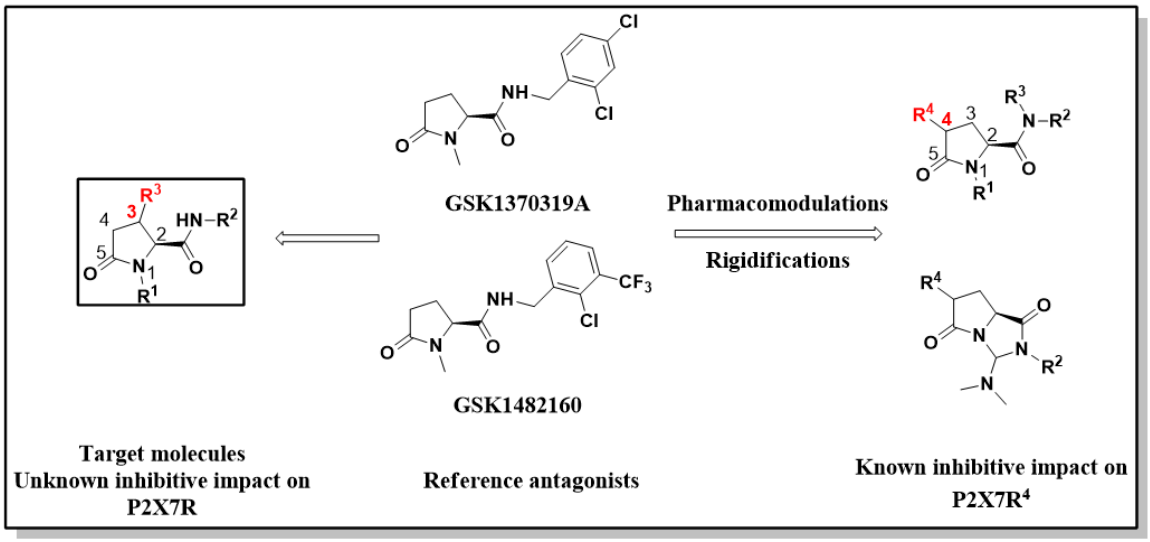
Abstract: A new methodology for the asymmetric synthesis of enantiomerically enriched 3-aroyl pyroglutamic acid derivatives has been developed through an effective 5-*exo*-tet cyclization of *N*-chloroacetyl aroylalanines. The three-step sequence starts with the *N*-substituted (*S*,*S*)-2-amino-4-aryl-4-oxobutanoic acids synthesis via the highly diastereoselective tandem of *aza*-Michael addition and crystallization-induced diastereomer transformation (CIDT). Their *N*-chloroacetylation followed by base-catalyzed cyclization and ultimate acid-catalyzed removal of chiral auxiliary without a loss of stereochemical integrity furnishes the target substituted pyroglutamic acids. Finally, several series of their benzyl amides were prepared as 3-aroyl analogues of known P2 × 7 antagonists.

Keywords: pyroglutamic acid; P2X7 receptors; *aza*-Michael addition; CIDT; *N*-debenzylation

1. Introduction

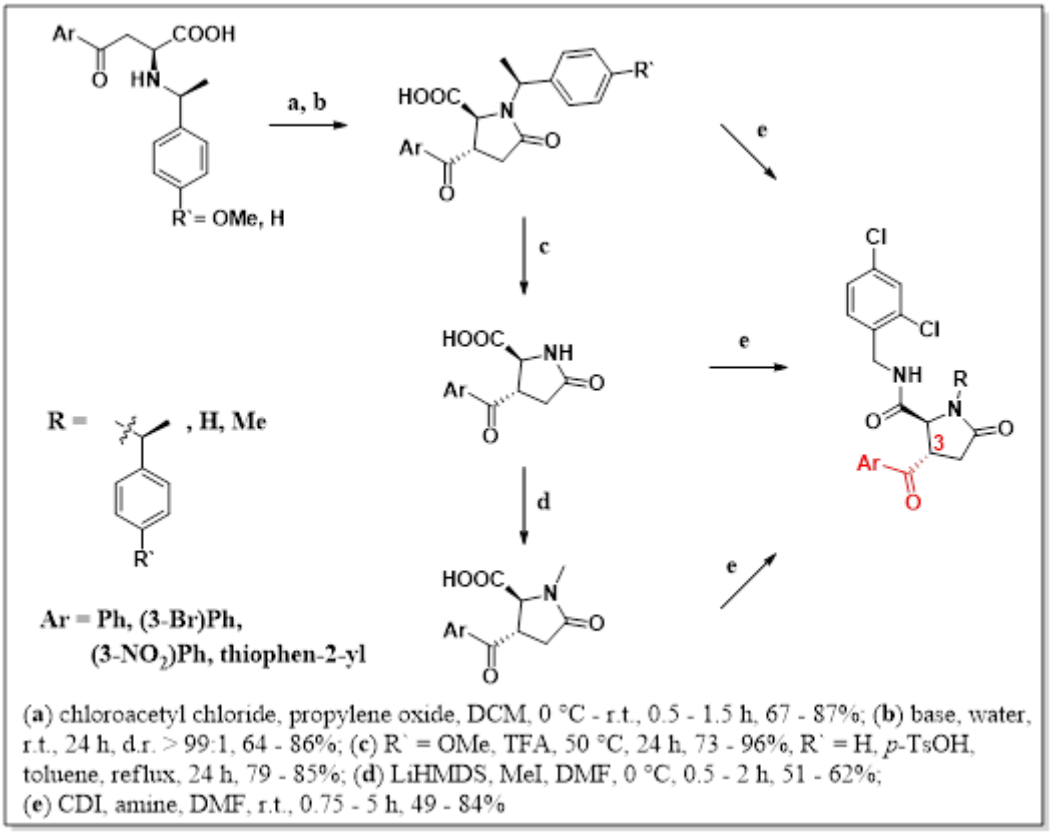
Pyroglutamic acid and its derivatives are a valuable class of compounds, being found in various natural products and pharmaceuticals. It represents either an important chiral auxiliary or building block for the asymmetric synthesis of many biologically and pharmaceutically valuable compounds.[1] Moreover, pyroglutamic acid derivatives have recently appeared to be efficient antagonists of specific types of purinergic receptors. Their inhibition has a promising impact on treating neurodegenerative diseases such as Alzheimer, Huntington, and Parkinson's disease [2]. This knowledge led to various researches towards the mentioned receptors based on the pyroglutamic derivatives inhibitive activity.

Among two pyroglutamic compounds, GSK1370319A and GSK1482160, the inhibitive activity was confirmed by clinical tests [3]. Accordingly, various potential antagonists were designed. The affinity with receptors has been modulated by changing substituents in the first, second, and fourth position of the lactam ring (**Scheme 1**) [4]. Stereoselective preparation of 3-substituted analogues has not attracted significant attention. The preparation of enantiomerically pure 3-substituted pyroglutamic acid derivatives enables to explore the importance of substitution in the first and the third positions of lactam ring and their impact on biological activity.



Scheme 1.

To our surprise, despite the numerous synthetic approaches towards substituted pyroglutamic acid derivatives and the widely recognized importance and utility of these compounds, synthesis of 3-acyl substituted analogues is still relatively unexplored [5]. This led us to develop the novel synthetic approach towards 3-aroyl pyroglutamic acid amides in few steps.

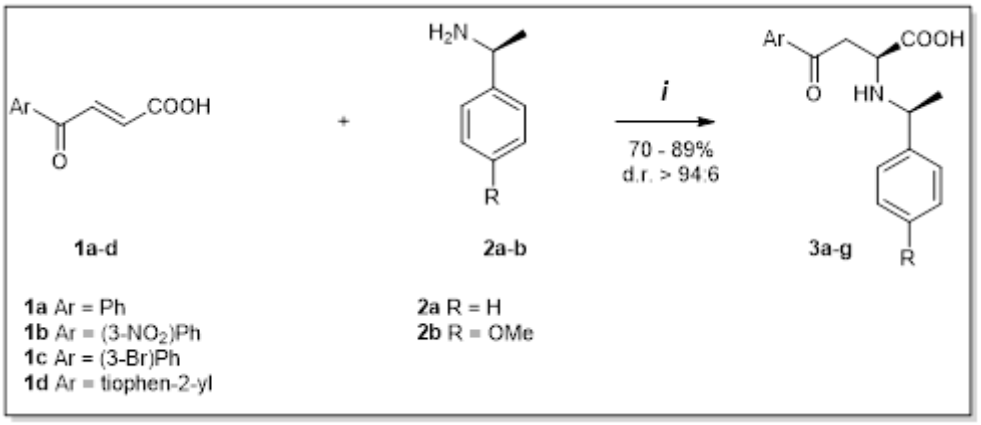


Scheme 2.

2. Results and discussion

The initial step represents the *aza*-Michael addition of chiral mediators (**2a,b**) to appropriate aroyl acrylic acids (**1a–d**) in tandem with CIDT (crystallization-induced diastereomer transformation). This efficient methodology spread among our research group allows us to prepare

aroyl alanines with high diastereoselectivity. The methodology is based on equilibration of stereoisomers in a solution, and continuous crystallization of a single isomer acts as a driving force for its gradual accumulation in the reaction suspension [6–9]. This enables isolation of products (**3a–g**) by simple filtration.

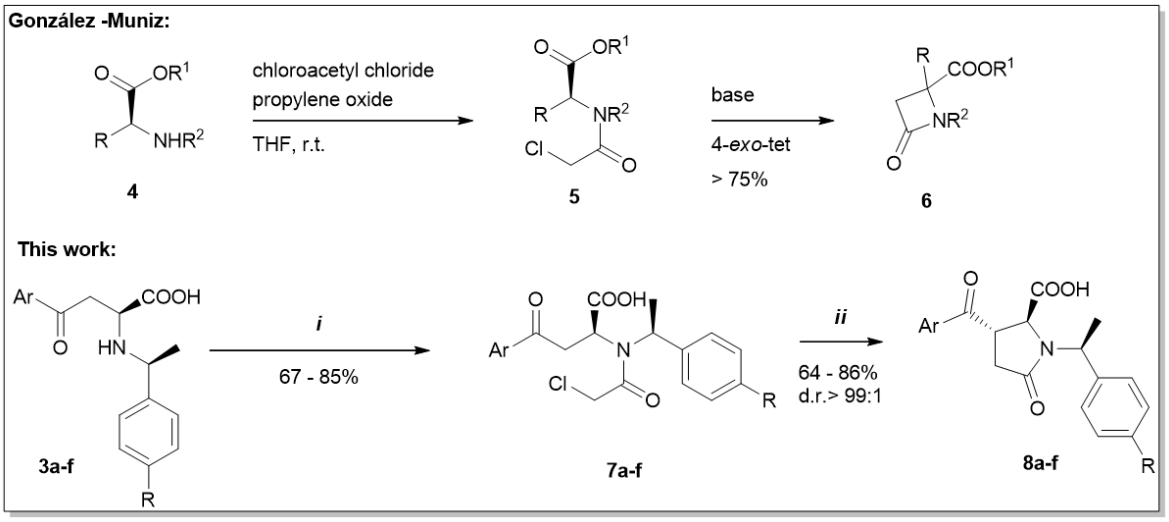


Scheme 3. *aza*-Michael addition of (*S*)-1-phenylethanamine (2a) and (*S*)-1-(4-methoxyphenyl)ethanamine (2b) to aroyl acrylic acids (1a-d) in tandem with CIDT.(i) 1.2 equiv, amine, solvent, r.t.—40 °C, 6–48 h.

Table 1. Results of *aza*-Michael addition of (*S*)-1-phenylethanamine (**2a**) and (*S*)-1-(4-methoxyphenyl)ethanamine (**2b**) to aroyl acrylic acids (**1a–d**) in tandem with CIDT.

Product 3a–g	Ar	R	Yield 3 (%)	d.r.	m.p. (°C)
3a	Ph	OMe	84	98:2	174–177
3b	(3-NO_2)Ph	H	89	99:1	172–173
3c		OMe	86	99:1	179–181
3d	(3-Br)Ph	H	70	98:2	172–175
3e		OMe	73	97:3	173–178
3f	tiophen-2-yl	H	80	94:6	196–198
3g		OMe	-	-	-

Recently, we published a strategy of *N*-acylation of amino acids in the presence of chloroacetyl chloride, which yielded the acetylated derivatives [10]. These intermediates represent suitable starting materials for cyclization in the presence of a base. It has been reported previously that *N*-chloroacetylated amino acids undergo 4-*exo*-tet cyclization to form β-lactams (**6**) (**Scheme 4**).[11] Due to the occurrence of the enolizable ketone, we expected that the in situ formed enolate undergoes fast 5-*exo*-tet cyclization instead of the 4-*exo*-cyclization observed by González-Muniz [11] (**Table 2**).

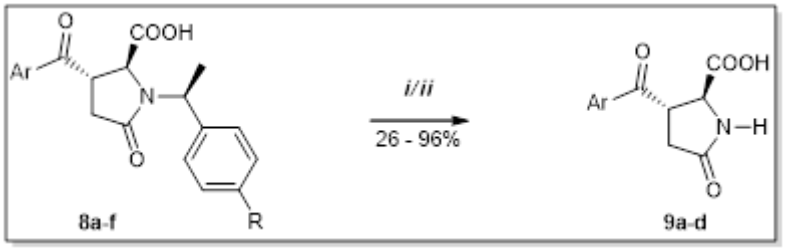


Scheme 4. *N*-chloroacetylation followed by base-catalyzed cyclization of (*S*,*S*)-aroylalanines (3a-f). (*i*) chloroacetyl chloride, propylene oxide, DCM, 0 °C—r.t., (*ii*) NaOH, H_2O, r.t.

Table 2. Results of *N*-chloroacetylation followed by base-catalyzed cyclization of (*S*,*S*)-aroylalanines (**3a–f**).

Substrate 3a–f	Ar	R	Yield 7 (%)	m.p. (°C)	Yield 8 (%)	m.p. (°C)
3a	Ph	OMe	75	164–165	74	220–222
3b	(3-NO_2)Ph	H	85	144–146	64	232–234
3c		OMe	67	173–175	86	182–183
3d	(3-Br)Ph	H	85	129–132	73	216–217
3e		OMe	78	158–160	73	162–167
3f	tiophen-2-yl	H	79	204–205	72	227–229

According to Abdi et al. [3], the occurrence of bulky benzylic group on the nitrogen of lactam ring causes inhibitive activity decline towards target receptors. Because of that, we decided to find the suitable conditions for debenzylation of the functional groups descended from the former chiral mediator used in the initial step. In the case of removing 1-ethyl-4-methoxybenzylic group the reaction was successful under conditions ***i***. In the contrary, removing 1-ethylbenzylic group in the same conditions didn't proceed, and according to HPLC analysis, there wasn`t observed any conversion to product. However, reactions took place in the presence of *p*-TsOH in refluxing toluene yielded deprotected derivatives **9b,d,f** without loss of stereochemical integrity.



Scheme 5. Acid-catalyzed debenzylation of lactam nitrogen. (***i***) TFA, 50 °C, 24 h; (***ii***) *p*-TsOH, toluene, reflux, 2–8 h [12].

Table 3. Result of acid-catalyzed debenzylation of lactam nitrogen.

Substrate 8a–g	Ar	R	Conditions	Yield 9 (%)	m.p. (°C)
8a	Ph	OMe	*i*	96	166–167
8b	(3-NO_2)Ph	H	*ii*	85	221–223
8c		OMe	*i*	94	221–222
8d	(3-Br)Ph	H	*ii*	79	212–215
8e		OMe	*i*	73	215–216
8f	tiophen-2-yl	H	*ii*	26	-

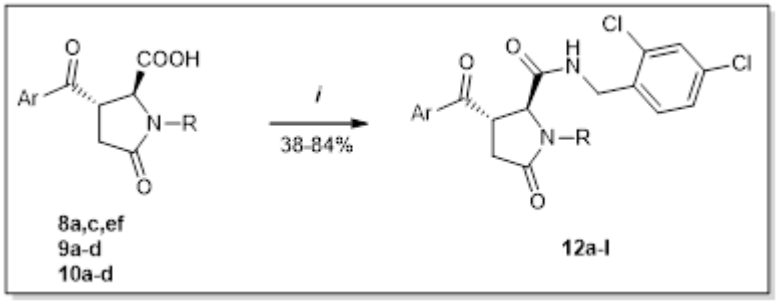
The second part of the synthetic approach represents the preparation of 3-aroyl-*N*-methyl pyroglutamic acids (**10a–d**), which covered up a sequence of three reactions. The first step demands the preparation of methyl esters (***Ma–d***) due to the low solubility of starting deprotected derivatives (**9a–d**). The establishment of the methyl group on lactam nitrogen requires a basic environment. Due to the enolizable functional group occurrence, the importance of a sufficient amount of base and low temperature was essential. The 3-aroyl-*N*-methylated pyroglutamic acids (**10a–d**) were obtained after three steps in gratifying overall yields.

Scheme 6. ***N*-alkylation of lactam nitrogen.**(***i***) MeI, $NaHCO_3$, DMF, 50 °C, 24 h; (***ii***) MeI, LiHMDS, DMF, 0 °C—r.t., 0.5–2 h; (***iii***) LiOH, THF/H_2O, r.t., 0.5–3 h.

Table 4. Results of *N*-alkylation of lactam nitrogen.

Substrate 9a–d	Ar	Overall Yield 10 (3 Steps) (%)
9a	Ph	44
9b	(3-NO_2)Ph	36
9c	(3-Br)Ph	42
9d	tiophen-2-yl	-

Another valuable source about antagonism of P2X7 receptors delivered knowledge that disubstituted benzylamides of corresponding pyroglutamic acids are the most effective. We prepared four series of pyroglutamic acid amides that vary in substituents in the first and the third position of the lactam ring. These compounds were obtained as products of well-known acid amine coupling with corresponding activation agent—CDI (**Scheme 7**) [13]. The desired final products (**12**) were isolated in yields within the range of 34–84% (**Table 5**).



Scheme 7. Amide formation (*i*) CDI, amine 11, solvent, r.t., 3–24 h.

Table 5. Results of amide formation by CDI.

Substrate	Ar	R	Yield 12 (%)	m.p. (°C)
8a	Ph	(*S*)-1-((4-OMe)Ph)Et	70	136–137
9a		H	65	134–136
10a		Me	84	-
8c	(3-NO_2)Ph	(*S*)-1-((4-OMe)Ph)Et	49	191–192
9b		H	36	223–225
10b		Me	56	-
8e	(3-Br)Ph	(*S*)-1-((4-OMe)Ph)Et	69	-
9c		H	49	116–118
10c		Me	57	-
8f	tiophen-2-yl	(*S*)-1-(Ph)Et –	77	154–156
9d		H	82	157–159
10d		Me	-	-

3. General Methods

Unless otherwise noted all the chemicals were purchased from commercial sources and used without further purifications. Bulk solutions were evaporated under reduced pressure using a Büchi rotary evaporator. HPLC analyses were performed on Varian system using Phenomenex Phenyl-Hexyl 5 μm column. The used mobile phase is specified for each experiment. Due to the long-term use of columns, retention time values are only approximate.

mobile phase A: MeCN/H_2O = 1:1 (500/500 mL) + Et_3N/H_3PO_4 = 1:1 (10/10 mL)

mobile phase B: MeCN/H_2O = 1:2 (333/666 mL) + Et_3N/H_3PO_4 = 1:1 (10/10 mL)

mobile phase C: MeCN/H_2O = 1:3 (250/75 + Et_3N/H_3PO_4 = 2:1 (10/5 mL)

mobile phase D: MeCN/H_2O = 2:3 (400/600 mL) + Et_3N/H_3PO_4 = 1:1 (10/10 mL)

Column chromatography was carried out using Silica 60A, particle size 20–45 micron, Davisil, purchased from Fischer Chemical. All reactions were followed by thin-layer chromatography (TLC) where practical, using Macherey-Nagel's pre-coated TLC sheets POLYGRAM SIL G/UV254 visualized under UV light (254 nm) or by staining with aqueous basic potassium permanganate or cerium molybdate solutions as appropriate.

All ^1H and ^{13}C NMR spectra were recorded using a Varian INOVA 300 MHz and Varian VNMRS 600 MHz spectrometers. Chemical shifts (δ) are given in parts per million (ppm). ^1H NMR chemical shift scale is referenced to TMS internal standard or solvent residual peak. ^{13}C NMR chemical shift scale is referenced to the solvent peak. Coupling constants (*J*) are given in Hertz (Hz). The multiplicity of ^1H NMR signals is reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet. Optical rotations were recorded using a JASCO P-2000 polarimeter; $[\alpha]_D$ values are reported in deg $cm^3g^{-1}dm^{-1}$; concentration (c) is given in g/100 mL at 589 nm. HRMS were

measured using Thermo Scientific mass spectrometer with Orbitrap analyzer and HESI and APPI ionization.

4. Experimental

4.1. Procedure A

Michael addition: Starting aroyl acrylic acids **1a–d** were prepared according to general procedures described in literatures [14–16]. Synthetic strategy and the general procedures are shown on phenyl derivatives (Ar = Ph).

(*S*)-2-(((*S*)-1-(4-methoxyphenyl)ethyl)amino)-4-oxo-4-phenylbutanoic acid—**3a**

((*E*)-4-oxo-4-phenylbut-2-enoic acid (**1a**, 25.0 g, 0.142 mol) was dissolved in methanol (570 mL) followed by the addition of (*S*)-1-(4-methoxyphenyl)ethanamine (**2b**, 1.2 equiv, 0.170 mol, 25 mL). Mixture was stirred for 48 h at 40 °C and monitored by HPLC. The suspension was filtered, washed with Et_2O, yielding **3a** as a colourless solid (40.0 g, 84 %, d.r. 98:2); **m.p.** = 174–177 °C, **[α]$_D^{25}$** = +58.5 (c 1.0, MeOH: (5 % aq. HCl) 9:1);

HPLC: (mobile phase B): **t_R** = 7.0 min, flow rate 0.7 mL/min;

^{1}H NMR (300 MHz, acetone-d_6 + DCl): δ = 8.03–7.91 (m, 2H), 7.69 (d, *J* = 8.8 Hz, 2H), 7.66–7.59 (m, 1H), 7.55–7.47 (m, 2H), 7.01 (d, *J* = 8.9 Hz, 2H), 4.87 (q, *J* = 6.8 Hz, 1H), 4.17 (t, *J* = 5.2 Hz, 1H), 4.02 (m, 2H), 3.82 (s, 3H), 1.87 (d, *J* = 6.9 Hz, 3H);

^{13}C NMR (75 MHz, acetone-d_6 + DCl): δ = 196.4, 169.7, 161.3, 136.7, 134.4, 131.0, 129.5, 129.1, 128.5, 115.3, 59.3, 55.6, 53.6, 39.7, 21.0.

Accordingly, derivatives **3b–f** were prepared.

4.2. Procedure B

N-chloroacetylation:

(*S*)-2-(2-chloro-*N*-((*S*)-1-(4-methoxyphenyl)ethyl)acetamido)-4-oxo-4-phenylbutanoic acid—**7a**

(*S*)-4-oxo-4-phenyl-2-(((*S*)-1-phenylethyl)amino)butanoic acid (**3a,** 18.00 g, 55.0 mmol) was suspended in dichloromethane (275 mL) and cooled to 0 °C. Racemic propylene oxide (10.0 equiv, 0.672 mol, 38.5 mL) was added to the reaction mixture, followed by the solution of chloroacetyl chloride (1.1 equiv, 60.5 mmol, 4.8 mL) in dichloromethane (30 mL). The resulting mixture was stirred for 30 min at r.t. and concentrated under reduced pressure. The obtained crude product was triturated with ethyl acetate/hexane mixture to yield **7a** as a pale-yellow solid (16.8 g, 75%); **m.p.** = 164–165 °C; **TLC:** ***Rf*** = 0.37 (EtOAc:MeOH);

HPLC: (mobile phase A): **t_R** = 17.2 min, flow rate: 0.7 mL/min;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02–7.98 (m, 2H), 7.62–7.53 (m, 1H), 7.49–7.38 (m, 4H), 6.91 (d, *J* = 8.8 Hz, 2H), 5.19 (q, *J* = 6.9 Hz, 1H), 4.66 (dd, *J* = 7.7, 2.5 Hz, 1H), 4.46 (dd, *J* = 18.3, 7.7 Hz, 1H), 4.28 (d, *J* = 12.4 Hz, 1H), 4.19 (d, *J* = 12.4 Hz, 1H), 3.82 (s, 3H), 2.88 (dd, *J* = 18.3, 2.6 Hz, 1H), 1.60 (d, *J* = 7.0 Hz, 3H).

Accordingly, derivatives **7b–f** were prepared.

4.3. Procedure C

Cyclization

(2*S*,3*S*)-3-benzoyl-1-((*S*)-1-(4-methoxyphenyl)ethyl)-5-oxopyrrolidine-2-carboxylic acid—**8a**

(*S*)-2-(2-chloro-*N*-((*S*)-1-(4-methoxyphenyl)ethyl)acetamido)-4-oxo-4-phenylbutanoic acid (**7a**, 16.8 g, 41.6 mmol) was dissolved in the solution of sodium hydroxide (2.5 equiv, 140 mmol, 4.14 g) and water (260 mL). The reaction mixture was stirred at r.t. for 24 h. Subsequently, pH value of reaction mixture was adjusted to 2–3 with 1M aqueous HCl. The precipitated product was filtered off and washed with water. Crude product was crystallized from MeOH to yield **8a** as a colourless solid (11.3 g, 74% yield, d.r. > 99:1); **m.p.** = 220–222 °C; **TLC:** ***Rf*** = 0.48 (EtOAc:MeOH = 3:2);

HPLC: (mobile phase A): **t_R** = 9.3 min, flow rate: 0.7 mL/min;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.08–7.90 (m, 2H), 7.75–7.64 (m, 1H), 7.60–7.51 (m, 2H), 7.22 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 5.01 (q, *J* = 7.0 Hz, 1H), 4.32 (d, *J* = 1.6 Hz, 1H), 4.24 (dd, *J* =

9.3, 1.6 Hz, 1H), 3.72 (s, 3H), 2.81 (dd, *J* = 16.7, 9.4 Hz, 1H), 2.34 (dd, *J* = 16.7, 2.0 Hz, 1H), 1.45 (d, *J* = 7.1 Hz, 3H).

Accordingly, derivatives **8b–f** were prepared.

4.4. Procedure D

N-debenzylation—conditions *i*

(2*S*,3*S*)-3-benzoyl-5-oxopyrrolidine-2-carboxylic acid—**9a**

Carboxylic acid (**8a**, 4 g, 10.9 mmol) was dissolved in TFA (24.0 equiv, 0.261 mol, 20.0 mL) and the resulting colourless reaction mixture was stirred at 50 °C for 24 h. Reaction was accompanied with colour change from colourless to dark purple. Upon completion, TFA was evaporated under reduced pressure and the dark-purple crude product was triturated with Et_2O yielding pale-brown solid (2.4 g, 96%); **m.p.** = 166–168 °C; **TLC:** R_f = 0.30 (EtOAc:MeOH = 3:2);

HPLC: (mobile phase B): t_R = 8.0 min, flow rate: 0.7 mL/min;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.12 (bs, 1H), 8.11–8.05 (m, 2H), 7.76–7.55 (m, 3H), 4.48–4.36 (m, 2H), 2.70 (dd, *J* = 16.8, 10.0 Hz, 1H), 2.27 (dd, *J* = 16.8, 4.9 Hz, 1H).

Accordingly, derivatives **9c, e** were prepared.

N-debenzylation—conditions *ii*

(2*S*,3*S*)-3-(3-nitrobenzoyl)-5-oxopyrrolidine-2-carboxylic acid—**9b**

Carboxylic acid (**8d**, 200 mg, 0.582 mmol) was dissolved in toluene (5.8 mL) and *p*-TsOH (4.0 equiv, 2.33 mmol, 443 mg) was added. The resulting colourless solution was stirred under reflux for 6 h. Reaction was accompanied with colour change from colourless to dark brown, indicated styrene polymer formation. Upon completion, the reaction mixture was cooled down to room temperature and poured into water (10 mL). Resulting mixture was extracted with EtOAc (3 × 10 mL). Collected organic layers were washed with 10% solution of K_2CO_3 (3 × 15 mL). pH value of water phase was adjusted to 2–3 and extracted with EtOAc (3 × 20 mL). Extract was dried over $MgSO_4$ and concentrated under reduced pressure. Crude product was triturated with small amount of Et_2O (ca. 15 mL) yielding white powder (**9b**, 118 mg, 85%); **m.p.** = 221–223 °C; **TLC:** R_f = 0.33 (EtOAc:MeOH = 3:2);

HPLC: (mobile phase A): t_R = 4.5 min, flow rate: 0.7 mL/min;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.78–8.76 (m, 1H), 8.53–8.44 (m, 2H), 8.17 (bs, 1H), 7.91–7.83 (m, 1H), 4.60–4.51 (m, 1H), 4.40 (dd, *J* = 3.5, 0.8 Hz, 1H), 2.68 (dd, *J* = 16.8, 10.0 Hz, 1H), 2.33 (dd, *J* = 16.8, 4.7 Hz, 1H).

Accordingly, derivatives **9d, f** were prepared.

4.5. Procedure E

N-metylation

(2*S*,3*S*)-3-benzoyl-1-methyl-5-oxopyrrolidine-2-carboxylic acid—**10a**

To a solution of carboxylic acid (**9a**, 1.5 g, 6.43 mmol) in dry DMF (21 mL) $NaHCO_3$ (3.0 equiv, 19.3 mmol, 1.61 g) and MeI (5 equiv, 32.2 mmol, 2.0 mL) was added. Reaction mixture was stirred 24 h at 50 °C. Upon completion, concetrated solution of NH_4Cl (60 mL)

was added to a reaction mixture which was consequently extracted with DCM (3 × 40 mL). Collected organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purrified by flash column chrotography (100% EtOAc). Obtained colourless solid—methylesther ***Ma*** (1.35 g, 85%) was used in subsequent step.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.22 (bs, 1H), 8.10–7.97 (m, 2H), 7.75–7.65 (m, 1H), 7.62–7.52 (m, 2H), 4.55–4.44 (m, 2H), 3.69 (s, 3H), 2.72 (dd, *J* = 16.9, 10.0 Hz, 1H), 2.25 (dd, *J* = 16.9, 4.7 Hz, 1H).

(265 mg, 1.07 mmol) of ***Ma*** was dissolved in dried DMF (10 mL), cooled down to 0 °C and LiHMDS (1.3 equiv, 1.39 mmol, 1.4 mL) was added. After 10 min of stirring, MeI (1.3 equiv, 1.39 mmol, 87 μL) was added and reaction mixture was stirred under argone atmospehere at 0 °C. After 50 min, concentrated solution of NH_4Cl (50 mL) was added and resulting solution was extracted with DCM (3 × 60 mL). Collected organic layers were dried over $MgSO_4$ and concentrated under reduced

pressure. Crude product was purrified by flash column chromatography (60% EtOAc) resulting pale-yellow solid substance—*N*-methylated intermediate (***Na***,174 mg, 62%); **TLC:** ***Rf*** = 0.4 (EtOAc);

HPLC: (mobile phase B): t_R: 22.0 min, flow rate 0.7 mL/min;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98–7.93 (m, 2H), 7.67–7.59 (m, 1H), 7.55–7.48 (m, 2H), 4.70 (d, *J* = 3.2 Hz, 1H), 4.16 (ddd, *J* = 10.4, 4.2, 3.3 Hz, 1H), 3.80 (s, 3H), 2.93 (s, 3H), 2.90 (dd, *J* = 17.0, 11.0 Hz, 1H), 2.57 (dd, *J* = 17.2, 3.7 Hz, 1H);

^{13}C NMR (151 MHz, $CDCl_3$): δ = 196.22, 172.19, 171.61, 134.36, 134.13, 129.10, 128.87, 62.53, 52.87, 42.55, 33.77, 29.33.

N-methylated derivative (***Na,*** 300 mg, 1.15 mmol) was dissolved in mixture of THF/H_2O (1:1, 12 mL) and LiOH (2.0 equiv, 2.3 mmol, 55 mg) was added. Reaction mixture was stirred at r.t. for 30 min. Upon completion, water (10 mL) was added to a reaction mixture and pH was adjusted to 2–3 with 1 M HCl. The resulting solution was extracted wit EtOAc (3 × 15 mL). Collected organic layers were dried over $MgSO_4$ and concentrated under reduced pressure resulting desired colourless solid substance **10a** (237 mg, 84%).

^{1}H NMR (300 MHz, DMSO-d_6) δ = 13.30 (s, 1H), 8.12–8.00 (m, 2H), 7.74–7.65 (m, 1H), 7.62–7.51 (m, 3H), 4.44 (d, *J* = 3.0 Hz, 1H), 4.40–4.33 (m, 1H), 2.87–2.69 (m, 5H), 2.34 (dd, *J* = 16.9, 3.3 Hz, 1H).

Accordingly, derivatives **10b–d** were prepared.

4.6. Procedure F

Amide formation

(2*S*,3*S*)-3-benzoyl-*N*-(2,4-dichlorobenzyl)-1-((*S*)-1-(4-methoxyphenyl)ethyl)-5-oxopyrrolidine-2-carboxamide—**12a**

Carboxylic acid (**8a**, 300 mg, 0.817 mol) was dissolved in dry DMF (5.4 mL) and CDI (1.2 equiv, 0.980 mol, 159 mg) was added. After 10 min, amine (**11**, 1.2 equiv, 0.980 mol, 0.132 mL) was added and the reaction mixture was stirred at r.t. for 45 min. Upon completion the reaction was quenched with 1M solution of $KHSO_4$ (10 mL) and extracted with EtOAc (3 × 30 mL). The collected organic layers were washed with water (30 mL) and with Brine (30 mL) and concentrated under reduced pressure. Crude product was purified on flash column chromatography (80% EtOAc, 20% Hex). Product **12a** was isolated as colourless solid substance (298 mg, 70%); **m.p.** = 136–137 °C; **TLC**: R_f = 0.49 (EtOAc);

HPLC: (mobile phase A): t_r = 39.6 min, flow rate: 0.7 mL/min;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16–7.87 (m, 2H), 7.65–7.56 (m, 1H), 7.54–7.46 (m, 2H, H), 7.33 (d, *J* = 2.1 Hz, 1H), 7.26 (d, *J* = 8.6 Hz, 2H), 7.16 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.77 (d, *J* = 8.8 Hz, 2H), 5.60 (t, *J* = 6.1 Hz, 1H), 5.43 (q, *J* = 7.0 Hz, 1H), 4.51 (d, *J* = 1.6 Hz, 1H), 4.14 (dd, *J* = 14.7, 6.3 Hz, 1H), 4.09–4.04 (m, 1H), 3.85 (dd, *J* = 14.7, 5.6 Hz, 1H), 3.77 (s, 3H), 2.87 (dd, *J* = 16.9, 9.3 Hz, 1H), 2.61 (dd, *J* = 16.9, 2.2 Hz, 1H), 1.50 (d, *J* = 7.1 Hz, 3H).

(2S,3S)-3-benzoyl-N-(2,4-dichlorobenzyl)-5-oxopyrrolidine-2-carboxamide—**12b**

Amide **12b** was prepared according to procedure B from corresponding acid **9a**. Reaction time—30 min. Colourless solid substance, (325 mg, 65%); **m.p.** = 134–136 °C; **TLC**: R_f = 0.33 (EtOAc);

HPLC: (mobile phase A): t_r = 11.1 min, flow rate: 0.7 mL/min;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02–7.97 (m, 2H), 7.67–7.59 (m, 1H), 7.54–7.46 (m, 2H), 7.32 (d, *J* = 2.1 Hz, 1H), 7.27 (d, *J* = 8.3 Hz, 1H), 7.17 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.13 (bs, 1H), 4.64 (dd, *J* = 4.6, 1.1 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 4.32 (ddd, *J* = 9.7, 6.0, 4.6 Hz, 1H), 2.70 (dd, *J* = 17.0, 9.6 Hz, 1H), 2.50 (dd, *J* = 17.0, 6.0 Hz, 1H).

(2*S*,3*S*)-3-benzoyl-*N*-(2,4-dichlorobenzyl)-1-methyl-5-oxopyrrolidine-2-carboxamide—**12c**

Amide **12c** was prepared according to procedure B from corresponding acid **10a**. Reaction time–30 min. Pale-yellow foam, (327 mg, 84%); **TLC**: R_f = 0.32 (EtOAc);

HPLC: (mobile phase A): t_r = 13.4 min, flow rate: 0.7 mL/min;

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99–7.83 (m, 2H), 7.68–7.59 (m, 1H), 7.54–7.45 (m, 2H), 7.34 (d, *J* = 2.0 Hz, 1H), 7.28 (d, *J* = 8.8 Hz, 1H), 7.19 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.67 (t, *J* = 5.8 Hz, 2H), 4.64 (d, *J* = 5.9 Hz, 1H), 4.51 (d, *J* = 5.0 Hz, 1H), 4.50 (d, *J* = 5.9 Hz, 1H), 4.08 (ddd, *J* = 10.3, 6.4, 5.0 Hz, 1H), 2.91 (dd, *J* = 16.9, 10.3 Hz, 1H), 2.84 (s, 3H), 2.51 (dd, *J* = 16.7, 6.2 Hz, 1H).

Accordingly, derivatives **12d–l** were prepared.

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