Parallel Solution-phase Synthesis of
(2S,4E)-4-(Arylaminomethylidene)pyroglutamic Acids

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A library of twelve N(4′)-substituted di-tert-butyl (2S,4E)-4-arylaminomethylidene-5-oxopyrrolidine-1,2-dicarboxylates 6a–l were prepared in 47 – 90 % yield by parallel acid-catalysed treatment of di-tert-butyl (2S,4E)-4-[(dimethylamino)methylidene]-5-oxopyrrolidine-1,2-dicarboxylate (4) with anilines 5a–j, ethyl glycinate (5k), and ethyl β-alaninate (3l). Acidolytic deprotection of compounds 6a–e, e–j afforded the corresponding (2S,4E)-4-arylaminomethylidene-5-oxopyrrolidine-2-carboxylic acids 7a–c, e–j in 39 – 99 % yield. The configuration around the C=C double bond in the enamiones 6 and 7 was determined by NMR spectroscopy.

Key words: Pyroglutamic Acid, Enaminones, Amines, Combinatorial Synthesis, Pyrrolidinone

Introduction

(S)-Pyroglutamic acid (1) is a naturally occurring heterocyclic α-amino acid which is abundant in peptides and proteins, and its structure can also be found in a variety of other biologically important compounds. On the other hand, 1 is also a useful chiral building block, which is frequently used as a commercially available starting material in chiral-pool syntheses of peptidomimetics, natural products, and their analogues. Therefore it is not surprising, that several reviews on the chemistry of (S)-pyroglutamic acid (1) have recently been published [1].

2-Substituted alkyl 3-(dimethylamino)prop-2-enates and related enamines are a group of enamino-masked alkyl α-formylacetates, which are easily available and versatile reagents in heterocyclic synthesis [2]. In addition to their extensive use in the synthesis of various heterocyclic systems, recent applications of enamines have mostly focused on the synthesis of functionalised heterocyclic compounds including natural product analogues [2 – 4], and on combinatorial syntheses of functionalised heterocycles [5]. Within this context, various functionalised enamines have been prepared as key intermediates in the synthesis of 3-heteroarylalanine derivatives [6], histamine analogues [5b, 7], and heterocyclic analogues of dipeptides containing the (S)-pyroglutamic acid structural motif [5c, 8]. Previously, we reported the synthesis of a series of N(4′)-substituted methyl (2S,4E)-1-acyl-4-(aminomethylidene)-5-oxopyrrolidine-2-carboxylates as stable intermediates in the ‘ring switching’ synthesis of 3-heteroarylalanines [9]. Recently, this type of compounds attracted our attention again, since such α-enamino pyroglutamic acids are conformationally constrained heterocyclic dipeptides comprising α,β-dehydro-β-alanine (Δ-β-Ala) and (S)-alanine (L-Ala) structural units (Fig. 1).

Therefore, we were intrigued to study the synthesis of γ-enamino pyroglutamic acids 7, which might be interesting and useful building blocks for further derivatisation. Herein, we report the result of this study – a simple parallel solution-phase
synthesis of di-tert-butyl (S)-4-arylamidomethylidene-5-oxopyrrolidine-1,2-dicarboxylytes \(6/6'a-1\) and (S)-4-arylamidomethylidene-5-oxopyrrolidine-1,2-dicarboxylytes \(7a-c\), \(e-j\).

**Results and Discussion**

The key intermediate, di-tert-butyl \((2S,4E)-4-[(dime-thylamino)methylidene]-5-oxopyrrolidine-1,2-dicarboxylate \(4\), was prepared in three steps from \((S)-

\[
\begin{align*}
\text{HOOC} & \quad \text{Ref. \[10\] AcOBU, HClO} & \quad \text{r. t.} \\
\text{N} & \quad \text{Boc} & \quad \text{BocO, MeCN, DMAP (cat.), r. t.} \\
\text{N} & \quad \text{Boc} & \quad \text{t-BuOCH\(N\text{Me}_2\)l-toluene, 100 °C} \\
\text{N} & \quad \text{Boc} & \quad \text{ArNH}_2 \quad \text{EtOH-H}_2\text{O, HCl, r. t.} \\
\text{Boc} & \quad \text{HCl-EtOAc} & \quad \text{HOOC} \\
\end{align*}
\]

\(6/6'a-1\) (E)-isomers \(6a-1\)

\(7a-c, e-j\)

Scheme 1.

Table 1. Selected experimental data of the di-tert-butyl \((2S,4E)-4-arylamidomethylidene-5-oxopyrrolidine-1,2-dicarboxylytes \(6a-1\) and \(7a-c, e-j\)

<table>
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<th>Compound (Ar)</th>
<th>Yield (%) (E: Z)</th>
<th>Purity (%) (d)</th>
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<tr>
<td>(6a/6'a) phenyl</td>
<td>90 (56:44^{d})</td>
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</tr>
<tr>
<td>(6b/6'b) 3-methylphenyl</td>
<td>65 (21:79)</td>
<td>(&gt;95)</td>
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<td>(6c/6'c) 4-methylphenyl</td>
<td>83 (17:83)</td>
<td>(&gt;95)</td>
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<tr>
<td>(6d/6'd) 3-hydroxyphenyl</td>
<td>62 (100:0)</td>
<td>(&gt;95)</td>
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<tr>
<td>(6e/6'e) 4-hydroxyphenyl</td>
<td>69 (100:0)</td>
<td>(&gt;95)</td>
</tr>
<tr>
<td>(6f/6'f) 3-methoxynaphthyl</td>
<td>73 (16:84)</td>
<td>(&gt;95)</td>
</tr>
<tr>
<td>(6g/6'g) 3-bromophenyl</td>
<td>73 (15:85)</td>
<td>(&gt;95)</td>
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<tr>
<td>(6h/6'h) 4-bromophenyl</td>
<td>79 (15:85)</td>
<td>(&gt;95)</td>
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<tr>
<td>(6i/6'i) 3-nitrophenyl</td>
<td>65 (100:0)</td>
<td>(&gt;95)</td>
</tr>
<tr>
<td>(6j/6'j) 4-nitrophenyl</td>
<td>81 (100:0)</td>
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<tr>
<td>(6k/6'k) (\text{CH}_2\text{COOEt} )</td>
<td>47 (85:15)</td>
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<tr>
<td>(6'l/6'1) (\text{CH}_2\text{CH}_2\text{COOEt} )</td>
<td>68 (88:12)</td>
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<td>(7a) phenyl</td>
<td>39 (100:0)</td>
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<tr>
<td>(7b) 3-methylphenyl</td>
<td>96 (100:0)</td>
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<tr>
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<td>99 (100:0)</td>
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<td>(7f) 3-methoxynaphthyl</td>
<td>99 (100:0)</td>
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<td>(7g) 3-bromophenyl</td>
<td>87 (100:0)</td>
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<td>(7h) 4-bromophenyl</td>
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<tr>
<td>(7j) 4-nitrophenyl</td>
<td>88 (100:0)</td>
<td>(&gt;95)</td>
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</table>

\(a\) Determined by \(^1\text{H}-\text{NMR spectroscopy}; \(b\) determined by CHN-analyses and \(^1\text{H}-\text{NMR spectroscopy}. \)The values found for C, H, and N were within ±0.4% with respect to the calculated values; \(c\) the configuration around the C=C double bond was determined by HMBC NMR spectroscopy; \(d\) the configuration around the C=C double bond was determined by NOESY spectroscopy.

pyroglutamic acid \((1)\) following the literature procedures \([5c, 10, 11]\). Thus, acid-catalysed esterification of \((S)\)-pyroglutamic acid \((1)\) with tert-butyl acetyl gave tert-butyl pyroglutamate \((2) [10]\), which was \(N\)-acylated with \(\text{Boc}_2\text{O}\) in acetonitrile in the presence of catalytic amounts of 4-dimethylaminopyridine (DMAP) to afford di-tert-butyl \((2S,4E)-5,5\)-oxopyrrolidine-1,2-dicarboxylate \((3) [11]\). Finally, heating of \(3\) with one equivalent of tert-butoxy-bis(dimethylamino)methane (Bredereck’s reagent, TBDMAM) furnished di-tert-butyl \((2S,4E)-4-[\text{[(dimethylamino)-methylidene]}-5\)-oxopyrrolidine-1,2-dicarboxylate \((4)\) in 70% yield over three steps \([5c]\) (Scheme 1).

Further parallel treatment of the enamino lactam \(4\) with 1.2 equivalents of amine hydrochlorides \(5a-1\) in 50% aqueous ethanol at r.t. resulted in the formation of the dimethylamine substitution products, \(N(4')\)-substituted di-tert-butyl \((2S,4E)-4\)-amino-phenylidene-5-oxopyrrolidine-1,2-dicarboxylates \(6/6'a-1\), which precipitated from the reaction mixtures and were isolated by filtration. Upon washing with water and thorough drying in vacuo over \(\text{P}_4\text{O}_{10}\), a library of twelve analytically pure esters \(6/6'a-1\) was
obtained in 47–90 % yield. In the final step, parallel acidolytic deprotection of compounds 6/6′a – l was carried out. Stirring of esters 6/6′ with 2 M HCl/EtOAc at r.t. for 12 h resulted in the initial formation of clear colourless or yellow solutions followed by formation of precipitates, which were then collected by filtration, washed with EtOAc, and dried in vacuo over P4O10. In this manner, analytically pure carboxylic acids 7a–c, e–j were prepared in 37–99 % yield. Acidolysis of compounds 6d, k, l did not produce precipitates. Attempts to isolate the final products 7d, k, l by evaporation of the reaction mixtures followed by crystallisation and/or chromatographic workup failed. Since we were particularly interested in a simple and practical procedure using just a filtration work-up, no further attempts to isolate compounds 7d, k, l were made (Scheme 1, Table 1).

The structures of the novel compounds 6/6′a – l and 7a–c, e–j were determined by spectroscopic (NMR, IR, MS) methods and by elemental analyses. The configuration around the exocyclic C=C bond in compounds 6a, 6′a, and 7i was determined by HMBC NMR spectroscopy on the basis of the long-range coupling constant (∆JC−H) between the methylidene proton (H−C(4′)) and the carbonyl carbon atom (O=O(5)), measured from the antiphase splitting of cross peaks. Generally, the magnitude of this coupling constant, ∆JC−H, for nuclei with cis-configuration around the C=C double bond is smaller (2–6 Hz) than that for trans-oriented nuclei (8–12 Hz) [2,12]. In compounds 6a and 7i, the magnitude of the coupling constants, ∆JC(1)−H(4′) = 4 Hz (cis) and 5 Hz (cis), respectively, confirmed the (E)-configuration around the exocyclic C=C double bond. In the minor isomer 6′a, on the other hand, a large coupling constant, ∆JC(1)−H(4′) = 10 Hz (trans), confirmed the (Z)-configuration around the C=C double bond (Fig. 2). Additionally, the configuration around the exocyclic C=C double bond in compounds 6a, 6′a, and 7h–j was confirmed by NOESY spectroscopy. A NOE between the NH and the CH2 group in compounds 6a and 7h–j was in agreement with the (E)-configuration around the exocyclic C=C double bond, whilst a NOE between the 4′-H and the CH2 group in the minor isomer 6′a supported the (Z)-configuration (Fig. 2).

Finally, the configurations around the C=C double bond in compounds 6 and 7 were confirmed by correlation of chemical shifts for 4′-H and NH and vicinal coupling constants, ∆JH−H. The major and most characteristic difference was observed in chemical shifts δ
for the aminomethylidene –NH–CH= protons. In the 
H-NMR spectra of the E/Z-mixtures 6/6 a–c, f–h, 
k, l taken in CDCl₃, the NH protons of the (E)-isomers 
6a–c, f–h, k, l had lower δ values (~ 6.2 ppm) 
that the 4′-H protons (~ 7.1 ppm), while in the (Z)- 
isomers 6′a–c, f–h, k, l the NH protons exhibited 
higher δ values (~ 9.9 ppm) than the 4′-H protons 
(~ 7.2 ppm). Such a difference in chemical shifts of 
the NH protons in CDCl₃ solution could be explained 
by intramolecular N–H···O=C hydrogen bonding, which 
is possible only in the (Z)-isomers 6′a–c, f–h, k, l 
and not in the (E)-isomers 6a–c, f–h, k, l. Accordingly, 
in [D₆]DMSO as a hydrogen bond acceptor, the 
NH protons of the (E)-isomers 6d, e, j and 
7a–c, e–j appear at ~ 8.5 ppm. Similarly, small 
yet characteristic differences between typical coupling 
constant values, 2J_H3H3b, 3J_NHCHe, and 4J_H3H4′, were 
also observed; typical values were larger in case of the 
(E)-isomers: 2J_H3H3b ~ 16 Hz (E) > 2J_H3H3b ~ 15 
Hz (Z), 3J_NHCHe ~ 13.5 Hz (E) > 3J_NHCHe ~ 12.5 
Hz (Z), and 4J_H3H4′ ~ 2 Hz (E) > 4J_H3H4′ ~ 1.3 Hz (Z). 
These characteristic values are also in agreement with 
the literature data for related aminomethylidene com-
ounds [2–4, 13] (Table 2, Fig. 2).

**Conclusion**

Di-tert-butyl(2S,4E)-4-{[(dimethylamino)methylid- 
e]-5-oxopyrrolidine-1,2-dicarboxylate (4) is an easily 
available reagent, which is suitable for two-step 
parallel solution-phase synthesis of 4-aryliminomethy-
lidene-substituted (S)-pyroglutamic acids 7 as 
conformationally constrained analogues of N-{[N-(aryl)- 
α,β-didehydro-β-alanyl]-(S)-alanine (c.f. Fig. 1). The 
synthesis comprises acid-catalysed substitution of the 
dimethylamino group in the enamine lactam 4 with 
unreactive and aliphatic primary amines 5 to give the 
substitution products 6/6′; followed by acidolytic de-
protection to furnish the title compounds 7 in good 
yields over two steps. Furthermore, all intermediates

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<th>Compound</th>
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<th>δ (ppm)</th>
<th>4′-H</th>
<th>4′-NH</th>
<th>3 – 4′</th>
<th>2J_H3H3b (Hz)</th>
<th>3J_NHCHe</th>
<th>4J_H3H4′</th>
<th>CHNH</th>
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<td>6b</td>
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<td>CDCl₃</td>
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Table 2. Correlation between the chemical shifts for 4′-H and (4′)N-H and coupling constants, 2J_H3H3b, 3J_NHCHe, and 4J_H3H4′, in compounds 6a–l, 6′a–c, f–h, k, l, and 7a–c, e–j.
6a–l and final products 7a–c, e–j were obtained in analytical purity following a simple parallel filtration work-up protocol in both synthetic steps. In conclusion, this synthetic method offers an easy access to diversity-oriented libraries of (S)-4-[(substituted amino)methylidene]pyrrolglutamic acid derivatives in search for novel bioactive compounds.

Experimental Section

Melting points were determined on a Stanford Research Systems MPA100 OptiMelt automated melting point system. The NMR spectra were obtained on a Bruker Avance DPX 300 spectrometer at 300 MHz for $^1$H and 75.5 MHz for $^{13}$C, using CDC13 and [D$_6$]DMSO (with TMS as the internal standard) as solvents. Mass spectra were recorded on a Q-TOF Premier spectrometer. IR spectra on a Perkin-Elmer Spectrum BX FTIR spectrophotometer. Micronalyses were performed on a Perkin-Elmer CHN analyser 2400 II.

(S)-Pyrrolglutamic acid (I), di-tert-butoxy-bis(dimethylamino)methane (Bredereck’s reagent), and amines 5a–l are commercially available (Sigma Aldrich). Di-tert-butyl (2S,4E)-4-[(dimethylamino)methylidene]-5-oxopyrrolidin-1,2-dicarboxylate (4) was prepared from I following the literature procedures [5c, 10, 11].

Parallel stirring and filtrations were carried out on a Mettler-Toledo Bohdan MiniBlock™ Compact Shaking and Washing Station and Vacuum Collection Base (12 positions, Vortex stirring, 400 r.p.m. in all cases).

Parallel solution-phase synthesis of N(4′)-substituted di-tert-butyl (2S)-4-aminomethylidene-5-oxopyrrolidin-1,2-dicarboxylate 6/6′a–l

The MiniBlock™ was assembled with 12 fritted vessels, and the frits were wetted with ethanol (0.5 mL each). A stock solution of enammine 4 (0.25 mM in ethanol, 12 × 4 mL, 12 × 1 mmol) was added followed by addition of aqueous solutions of amines 5a–l hydrochlorides* (0.25 mM in water, 12 × 5 mL, 12 × 1.2 mmol). The MiniBlock™ was closed and the reaction mixtures were stirred at 20°C for 24 h. The precipitates were collected by filtration, washed with water (12 × 3 mL), and dried in vacuo at r.t. over P$_2$O$_5$ for 24 h to give 6/6′a–l. The following compounds were prepared in this manner:

Di-tert-butyl (2S,4E)-4-aminomethylidene-5-oxopyrrolidin-1,2-dicarboxylate (6a) and its minor (4Z)-isomer 6a′

Compound 6a was prepared from 4 and aniline hydrochloride (5a). Yield: 365 mg (90%) of a pale-biege solid. – M. p. 177–180°C; 6a: 6′a = 56:44. – $\alpha$$_{589}^{\text{D}}$ = 19.5 (c = 0.33, CH$_2$Cl$_2$). – IR (KBr): ν = 3237, 3120, 3040, 2978, 1757, 1710, 1686, 1639, 1594, 1495, 1445, 1369, 1313, 1231, 1151, 1000, 959, 866, 806, 775, 753, 692 cm$^{-1}$. – $^1$H-NMR (CDCl$_3$), major (E)-isomer 6a: δ = 1.48 and 1.53 (18H, 2s, 1 : 1, 2, 4′-Bu), 2.54 (1H, ddd, J = 2.2, 3.6, 15.8 Hz, 3-Ha), 2.98 (1H, ddd, J = 2.2, 10.7, 15.8 Hz, 3-Hb), 4.56 (1H, ddd, J = 3.6, 10.7, 2-H), 6.09 (1H, d, J = 13.7 Hz, NH), 6.90–7.05 (3H, m, o-C$_6$H$_5$), 7.24–7.35 (2H, m, m-C$_6$H$_5$), 7.79 (1H, dt, J = 1.9, 13.7 Hz, 4′-H); minor (Z)-isomer 6a′: δ = 1.48 and 1.54 (18H, 2s, 1 : 1, 2, 4′-Bu) 2.61 (1H, ddd, J = 1.3, 3.5, 15.2 Hz, 3-Ha), 3.06 (1H, ddd, J = 1.3, 10.6, 15.2 Hz, 3-Hb), 4.51 (1H, ddd, J = 3.7, 10.6 Hz, 2-H), 6.90–7.05 (3H, m, o-p-C$_6$H$_5$), 7.17 (1H, br d, J = 12.3 Hz, 4′-H), 7.24–7.35 (2H, m, m-p-C$_6$H$_5$), 9.95 (1H, d, J = 12.3 Hz, NH) – C$_{32}$H$_{26}$N$_2$O$_5$ (388.5): calcld. C 64.93, H 7.27, N 7.21; found C 65.11, H 7.48, N 7.44.

Di-tert-butyl (2S,4Z)-4-[(3-methylanilino)methylidene]-5-oxopyrrolidin-1,2-dicarboxylate (6b) and its minor (4E)-isomer 6b′

Compound 6b′ was prepared from 4 and 3-methylaniline hydrochloride (5b). Yield: 260 mg (65%) of a pale-beige solid. – M. p. 155–157°C; 6b: 6′b = 21:79. – $\alpha$$_{589}^{\text{D}}$ = 17.4 (c = 0.48, CH$_2$Cl$_2$). – IR (KBr): ν = 3464, 3318, 2979, 2933, 1756, 1686, 1632, 1599, 1368, 1246, 1231, 1155, 1001, 1155, 781 cm$^{-1}$. – $^1$H-NMR (CDCl$_3$), major (Z)-isomer 6b: δ = 1.48 and 1.54 (18H, 2s, 1 : 1, 2, 4′-Bu). 2.31 (3H, s, Me), 2.60 (1H, ddd, J = 1.2, 3.6, 15.2 Hz, 3-Ha), 3.06 (1H, ddd, J = 1.2, 10.6, 15.2 Hz, 3-Hb), 4.50 (1H, ddd, J = 1.2, 3.6, 10.6 Hz, 2-H), 6.69–6.85 (3H, m, o-p-C$_6$H$_4$), 7.12–7.20 (1H, m, m-C$_6$H$_5$), 7.17 (1H, br d, J = 12.2 Hz, 4′-H), 9.89 (1H, d, J = 12.2 Hz, NH); minor (E)-isomer 6b′: δ = 2.32 (3H, s, Me), 4.55 (1H, d, J = 3.4, 10.7 Hz, 2-H), 6.14 (1H, broad signal, NH), 7.79 (1H, br d, J = 13.5 Hz, 4′-H), – C$_{27}$H$_{23}$N$_2$O$_4$ (402.5): calcld. C 65.65, H 7.51, N 7.26; found C 65.81, H 7.48, N 7.42.

Di-tert-butyl (2S,4Z)-4-[(4-methylanilino)methylidene]-5-oxopyrrolidin-1,2-dicarboxylate (6c) and its minor (4E)-isomer 6c′

Compound 6c′ was prepared from 4 and 4-methylaniline hydrochloride (5c). Yield: 334 mg (83%) of a pale-beige solid. – M. p. 163–170°C; 6c: 6′c = 17:83. – $\alpha$$_{589}^{\text{D}}$ = 21.5 (c = 0.40, CH$_2$Cl$_2$). – IR (KBr): ν = 3454, 3285, 2980, 2930, 1761, 1710, 1684, 1641, 1524, 1454, 1366, 1307, 1233, 1153, 999, 962, 870, 810, 774 cm$^{-1}$. – $^1$H-NMR (CDCl$_3$), major (Z)-isomer 6c: δ = 1.48 and 1.54 (18H, 2s, 1 : 1, 2, 4′-Bu), 2.28 (3H, s, Me), 2.60 (1H, ddd, J = 1.2, 3.7, 15.1 Hz, 3-Ha), 3.05 (1H, ddd, J = 1.2, 10.6, 15.1 Hz, 3-Hb), 4.50 (1H, d, J = 3.7, 10.6 Hz, 2-H), 6.83 (2H, br d, J = 8.3 Hz, m-C$_6$H$_4$), 7.08 (2H, br d, J = 8.3 Hz, o-C$_6$H$_4$), 7.13 (1H, br
d, J = 12.3 Hz, 4'C-H), 9.90 (1H, d, J = 12.3 Hz, NH); minor (E)-isomer 6c: δ = 2.29 (3H, s, Me), 4.55 (1H, dd, J = 3.6, 10.6 Hz, 2'H), 6.09 (1H, broad signal, NH), 6.83 (2H, br d, J = 8.3 Hz, m-C6H4), 7.76 (1H, br d, J = 13.6 Hz, 4'H) – C23H30N2O3 (402.5); calcd. C 65.65, H 7.51, N 6.96; found C 65.73, H 7.72, N 7.28.

Di-tert-butyl (2S,4E)-4-((3-hydroxyanilino)methylidene)-5-oxopyrrolidine-1,2-dicarbonylate (6d)

Compound 6d was prepared from 4 and 3-hydroxyaniline hydrochloride (5d). Yield: 251 mg (62%) of a pale-grey solid. – M. p. 180 – 181 °C; 6d: υ = 100 – 0. – [α]20D +2.0 (c = 0.49, EtOH). – IR (KBr): ν = 3383, 3307, 2978, 1757, 1709, 1688, 1634, 1612, 1500, 1469, 1372, 1369, 1346, 1305, 1240, 1156, 979, 959, 779 cm−1. – 1H-NMR ([D6]DMSO): δ = 1.42 and 1.44 (18H, 2 × 1 – Bu), 2.53 (1H, ddd, J = 1.9, 3.4, 14.4 Hz, 3,Ha), 2.99 (1H, ddd, J = 1.9, 10.7, 16.4 Hz, 3-Hb), 4.52 (1H, ddd, J = 3.4, 10.7 Hz, 2-H), 6.36 (1H, ddd, J = 1.6, 7.9 Hz, o-C6H4), 6.49 – 6.57 (2H, m, o, o-C6H4). – 13C-NMR (CDCl3): δ = 13.1 Hz, NH) exchanged. – C23H30N2O3 (404.5); calcd. C 62.36, H 6.98, N 6.93; found C 62.62, H 7.22, N 6.92.

Di-tert-butyl (2S,4E)-4-((4-hydroxyanilino)methylideneth)-5-oxopyrrolidine-1,2-dicarbonylate (6e)

Compound 6e was prepared from 4 and 4-hydroxyaniline hydrochloride (5e). Yield: 279 mg (69%) of a pale-grey solid. – M. p. 167 – 168 °C; 6e: υ = 100 – 0. – [α]20D +2.1 (c = 0.34, EtOH). – IR (KBr): ν = 3383, 3321, 2978, 2924, 1659, 1634, 1579, 1439, 1391, 1369, 1321, 1225, 1150, 1005, 962, 822, 791, 745, 673 cm−1. – 1H-NMR ([D6]DMSO): δ = 1.42 and 1.44 (18H, 2 × 1 – Bu), 2.48 (1H, ddd, J = 1.8, 3.5, 16.1 Hz, 3-Ha), 2.96 (1H, ddd, J = 1.8, 10.7, 16.1 Hz, 3-Hb), 4.51 (1H, ddd, J = 3.5, 10.8 Hz, 2-H), 6.70 (2H, d, J = 8.8 Hz, o-C6H4), 6.95 (2H, d, J = 8.8 Hz, m-C6H4), 7.47 (1H, br d, J = 13.4 Hz, 4'H), 8.77 (1H, d, J = 13.4 Hz, NH) exchanged. – C21H23N2O3 (404.5); calcd. C 62.36, H 6.98, N 6.93; found C 62.66, H 7.21, N 7.09.

Di-tert-butyl (2S,4E)-4-((3-bromoanilino)methylideneth)-5-oxopyrrolidine-1,2-dicarbonylate (6f) and its minor (4E)-isomer 6g

Compound 6f was prepared from 4 and 3-bromoaniline hydrochloride (5f). Yield: 341 mg (73%) of a pale-grey solid. – M. p. 163 – 164 °C; 6f: υ = 15.85 – 15.57 (c = 1.00, CH2Cl2). – IR (KBr): ν = 3447, 3295, 3260, 2979, 2923, 1763, 1734, 1716, 1686, 1638, 1594, 1475, 1368, 1312, 1236, 1223, 1154, 964, 899, 964, 773, 680 cm−1. – 1H-NMR (CDCl3), major (Z)-isomer 6f: δ = 1.48 and 1.54 (18H, 2 × 1 – Bu), 2.61 (1H, ddd, J = 1.4, 15.4 Hz, 3-Ha), 3.06 (1H, ddd, J = 1.4, 10.5, 15.4 Hz, 3-Hb), 4.51 (1H, ddd, J = 3.5, 10.5 Hz, 2-H), 6.82 (1H, br dt, J = 1.8, 7.4 Hz, o-C6H4), 7.05 – 7.16 (4H, m, 3H of C6H4 and 4'H). – 1H-NMR (CDCl3), minor (E)-isomer 6g: δ = 1.24 (1H, br d, J = 13.3 Hz, 3-Ha), 7.70 (1H, br d, J = 13.3 Hz, 4'-H). – C21H22Br2N2O2 (467.4); calcd. C 53.97, H 5.82, N 5.99; found C 54.01, H 5.95, N 6.01.

Di-tert-butyl (2S,4E)-4-((4-bromoanilino)methylideneth)-5-oxopyrrolidine-1,2-dicarbonylate (6h) and its minor (4Z)-isomer 6i

Compound 6h was prepared from 4 and 4-bromoaniline hydrochloride (5h). Yield: 369 mg (79%) of a pale-grey solid. – M. p. 175 – 177 °C; 6h: υ = 85.15 – 17.4 (c = 0.35, CH2Cl2). – IR (KBr): ν = 3264, 2980, 2934, 1759, 1725, 1687, 1638, 1588, 1485, 1454, 1368, 1312, 1231, 1152, 999, 960, 820, 775 cm−1. – 1H-NMR (CDCl3), major (E)-isomer 6h: δ = 1.47 and 1.52 (18H, 2 × 1 – Bu), 2.55 (1H, ddd, J = 2.1, 3.5, 16.1 Hz, 3-Ha), 2.99 (1H, ddd, J = 2.1, 10.6, 16.1 Hz, 3-Hb), 4.53 (1H, ddd, J = 3.5, 10.6 Hz, 2-H), 6.42 (1H, d, J = 13.4 Hz, NH), 6.87 (2H, d, J = 8.8 Hz, o-C6H4), 7.39 (2H, d, J = 8.8 Hz, m-C6H4), 7.68 (1H, dt, J = 2.1, 13.4 Hz, 4'H); minor (Z)-isomer 6i: δ = 1.53 (9H, s, – 1Bu), 2.60 (1H, ddd, J = 1.4, 3.5, 15.4 Hz, 3-Ha), 3.05 (1H, ddd, J = 1.4, 10.5, 15.4 Hz, 3-Hb), 4.51 (1H, ddd, J = 3.5, 10.5 Hz, 2-H), 6.80 (2H, br d, J = 8.8 Hz, o-C6H4), 7.09 (1H, br d, J = 12.2 Hz, 4'-H), 7.37 (2H, br d, J = 8.8 Hz, m-C6H4). – C21H22Br2N2O2 (467.4); calcd. C 53.97, H 5.82, N 5.99; found C 54.18, H 5.96, N 6.00.
Di-tert-butyl (2S,4E)-4-[(3-nitroamino)methylidene]-5-oxopyrrolidine-1,2-dicarbamate (6i)

Compound 6i was prepared from 4 and 3-nitroaniline (5i) in the presence of one equivalent of hydrochloric acid. Yield: 282 mg (65%) of a yellow solid. – M. p. 149 – 152°C; δi 6i: 100 : 0. – [α]20° 33.0 = 16.0 (c = 0.50, CH2Cl2). – IR (KBr): ν = 3435, 3285, 3090, 2981, 2937, 1771, 1710, 1688, 1648, 1516, 1535, 1749, 1369, 1532, 1317, 1238, 1224, 1155, 999, 968, 845, 814, 777, 737, 674 cm⁻¹. – 1H-NMR (CDCl3): δ = 1.48 and 1.51 (18H, 2s, 1 : 1, 2 × –Bu), 2.67 (1H, ddd, J = 2.3, 2.9, 16.4 Hz, 3-Ha), 3.09 (1H, dd, J = 2.3, 10.5, 16.4 Hz, 3-Hb), 3.43 (1H, dd, J = 3.3, 10.5 Hz, 2-H), 4.28 (1H, dd, J = 3.3, 10.5 Hz, 2-H), 7.07 (2H, d, J = 9.2 Hz, o-C6H4), 7.39 (1H, br d, J = 13.0 Hz, NH). – found C 58.19, H 6.28, N 9.69; found C 58.34, H 6.44, N 9.73.

Di-tert-butyl (2S,4E)-4-[(4-oxo-2-oxazolinyl)methylidene]-5-oxopyrrolidine-1,2-dicarbamate (6j)

Compound 6j was prepared from 4 and 4-nitroaniline (5j) in the presence of one equivalent of hydrochloric acid. Yield: 351 mg (81%) of a pale-grey solid. – M. p. 169 – 170°C; δj 6j: 130 : 0. – [α]20° 33.0 = 2.1 (c = 0.34, EtOH). – IR (KBr): ν = 3480, 3379, 3267, 3181, 1756, 1706, 1669, 1648, 1589, 1506, 1492, 1371, 1315, 1285, 1263, 1224, 1153, 1109, 995, 876, 844, 775, 753, 693 cm⁻¹. – 1H-NMR (CDCl3): δ = 1.48 and 1.52 (18H, 2s, 1 : 1, 2 × –Bu), 2.65 (1H, ddd, J = 2.2, 3.4, 16.5 Hz, 3-Ha), 3.08 (1H, ddd, J = 2.2, 10.5, 16.5 Hz, 3-Hb), 4.56 (1H, dd, J = 3.4, 10.5 Hz, 2-H), 7.08 (2H, dt, J = 2.6, 9.1 Hz, o-C6H4). –found C 57.54, H 7.78, N 7.33. – 1H-NMR (CDCl3), major (E)isomer 6l: δ = 1.27 (3H, t, J = 7.1 Hz, CH2CH2), 1.47 and 1.51 (18H, 2s, 1 : 1, 2 × –Bu), 2.33 (1H, ddd, J = 1.9, 3.7, 15.3 Hz, 3-Ha), 2.56 (2H, t, J = 5.9 Hz, CH2COOEt). – found C 59.00, H 7.45, N 6.84. – 1H-NMR (CDCl3), minor (Z)isomer 6l: δ = 2.51 (2H, t, J = 6.4 Hz, CH2COOEt). – found C 59.00, H 7.45, N 6.84. – 1H-NMR (CDCl3). – found C 58.12, H 6.45, N 9.62.

Di-tert-butyl (2S,4E)-4-[(2-ethoxy-2-oxoethylamino)methylidene]-5-oxopyrrolidine-1,2-dicarbamate (6k) and its minor (4Z)-isomer 6k’

Compound 6k’ was prepared from 4 and ethyl glycinate hydrochloride (5k). Yield: 188 mg (47%) of a colourless solid. – M. p. 128 – 132°C; δk 6k: 85 : 15. – [α]20° 33.0 = 20.2 (c = 1.00, CH2Cl2). – IR (KBr): ν = 3286, 2979, 2936, 1755, 1728, 1686, 1622, 1458, 1370, 1314, 1257, 1194, 1152, 1094, 1025, 989, 945, 861, 846, 778, 764, 739, 716 cm⁻¹. – 1H-NMR (CDCl3), major (E)isomer 6k: δ = 1.29 (3H, t, J = 7.1 Hz, CH2CH2), 1.47 and 1.51 (18H, 2s, 1 : 1, 2 × –Bu), 2.42 (1H, ddd, J = 2.0, 3.6, 15.4 Hz, 3-Ha), 2.87 (1H, ddd, J = 2.0, 10.6, 15.4 Hz, 3-Hb), 3.96 (2H, d, J = 5.5 Hz, NHCH2), 4.23 (2H, q, J = 7.1 Hz, CH2CH2), 4.40 – 4.52 (1H, broad signal, NH), 4.49 (1H, dd, J = 3.6, 10.6 Hz, 2-H). – found C 58.34, H 6.44, N 9.73.

Di-tert-butyl (2S,4E)-4-[(3-ethoxy-3-oxopropylamino)methylidene]-5-oxopyrrolidine-1,2-dicarbamate (6l) and its minor (4Z)-isomer 6l’

Compound 6l’ was prepared from 4 and ethyl β-alanine hydrochloride (5l). Yield: 279 mg (68%) of a pale-yellow solid. – M. p. 85 – 87.1°C; δl 6l: 88 : 12. – [α]20° 33.0 = 20.2 (c = 0.50, CH2Cl2). – IR (KBr): ν = 3447, 3291, 3259, 2981, 2935, 1750, 1678, 1626, 1458, 1369, 1317, 1253, 1155, 1081, 1024, 1001, 952, 848, 773 cm⁻¹. – 1H-NMR (CDCl3), major (E)isomer 6l: δ = 1.27 (3H, t, J = 7.1 Hz, CH2CH2), 1.47 and 1.51 (18H, 2s, 1 : 1, 2 × –Bu), 2.33 (1H, ddd, J = 1.9, 3.7, 15.3 Hz, 3-Ha), 2.56 (2H, t, J = 5.9 Hz, CH2COOEt). – found C 59.00, H 7.45, N 6.84. – 1H-NMR (CDCl3), minor (Z)isomer 6l: δ = 2.51 (2H, t, J = 6.4 Hz, CH2COOEt). – found C 59.00, H 7.45, N 6.84. – 1H-NMR (CDCl3). – found C 58.12, H 6.45, N 9.62.

Parallel solution-phase synthesis of (2S,4E)-4-(aminomethylidene)pyroglutamic acids 7a – c, e – j

The MiniBlock™ was assembled with 12 flotted vessels and charged with compounds 6j/6j’/(12 × 0.5 mmol) and 2M HCl-EtOAc (12 × 5 mL). The MiniBlock™ was closed and the reaction mixtures were stirred at 20°C for 12 h. The precipitates were collected by filtration, washed with EtOAc (4 × 3 mL), and dried in vacuo at r. t. with P2O5 for 24 h to give 7a – c, e – j. Compounds 7d, k, l, which did not precipitate from the reaction mixtures, were not isolated.

The following compounds were prepared in this manner:

(2S,4E)-4-(Aminomethylidene)pyroglutamic acid hydrochloride (7a)
(2S,4E)-4-(3-Methoxylanilinomethylidene)pyroglutamic acid hydrochloride (7f)

Compound 7f was prepared from 6f/6′. Yield: 153 mg (99%) of a yellowish solid. – M. p. 153 – 155 °C (partial decomposition above 130 °C). – [α]20

Compound 7g was prepared from 6g. Yield: 152 mg (87%) of a colourless solid. – M. p. 188 – 190 °C (partial decomposition above 140 °C). – [α]20

Compound 7h was prepared from 6h. Yield: 149 mg (86%) of a light-yellow solid. – M. p. 170 – 174 °C (partial decomposition above 114 °C). – [α]20

MeOH). – IR (KBr): ν = 3269, 3236, 3086, 2543,2473, 1732, 1666, 1595, 1575, 1500, 1323, 1247, 1203, 1086, 924, 804, 754, 719, 687 cm⁻¹. – 1H-NMR (CDCl₃): δ = 2.77 (1H, ddd, J = 2.0, 11.7, 16.5 Hz, 3-Ha), 3.03 (1H, ddd, J = 2.0, 10.0, 16.5 Hz, 3-Ha), 4.16 (1H, dd, J = 3.9, 10.0 Hz, 2-H), 6.66 (2H, br d, J = 8.8 Hz, o-C₆H₄), 6.86 (2H, br d, J = 8.8 Hz, m-C₆H₄), 7.29 (1H, br s, 4′-H), 8.34 (1H, br s, NH), 1-NH₂⁺, OH, and COOH exchanged. – C₁₂H₁₂N₂O₃·HCl (268.7): calc. C 50.63, H 4.60, N 9.84; found C 50.24, H 4.67, N 9.54.

(2S,4E)-4-(3-Methoxylanilinomethylidene)pyroglutamic acid hydrochloride (7f)

(2S,4E)-4-(3-Methoxylanilinomethylidene)pyroglutamic acid hydrochloride (7f)

(2S,4E)-4-(3-Methoxylanilinomethylidene)pyroglutamic acid hydrochloride (7f)

(2S,4E)-4-(3-Methoxylanilinomethylidene)pyroglutamic acid hydrochloride (7f)

MeOH). – IR (KBr): ν = 3269, 3236, 3086, 2543,2473, 1732, 1666, 1595, 1575, 1500, 1323, 1247, 1203, 1086, 924, 804, 754, 719, 687 cm⁻¹. – 1H-NMR (CDCl₃): δ = 2.77 (1H, ddd, J = 2.1, 3.7, 16.8 Hz, 3-Ha), 3.06 (1H, ddd, J = 2.1, 9.9, 16.7 Hz, 3-Hb), 4.19 (1H, dd, J = 3.8, 9.9 Hz, 2-H), 6.85 (1H, br t, J = 7.3 Hz, p-C₆H₄), 7.05 (2H, br d, J = 7.8 Hz, o-C₆H₄), 7.05 (2H, br d, J = 7.3, 7.8 Hz, m-C₆H₄), 7.37 (1H, br d, J = 11.5 Hz, 4′-H), 8.59 (1H, d, J = 11.7 Hz, NH), 1-NH₂⁺ and COOH exchanged. – C₁₂H₁₂N₂O₃·HCl (268.7): calc. C 53.64, H 4.88, N 10.43; found C 53.52, H 4.83, N 10.15.

(2S,4E)-4-(3-Methoxylanilinomethylidene)pyroglutamic acid hydrochloride (7f)

(2S,4E)-4-(3-Methoxylanilinomethylidene)pyroglutamic acid hydrochloride (7f)

(2S,4E)-4-(3-Methoxylanilinomethylidene)pyroglutamic acid hydrochloride (7f)

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(2S,4E)-4-(3-Methoxylanilinomethylidene)pyroglutamic acid hydrochloride (7f)

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(2S,4E)-4-(3-Methoxylanilinomethylidene)pyroglutamic acid hydrochloride (7f)

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1730, 1665, 1587, 1498, 1244, 1024, 1086, 1075, 984, 819, 718, 652 cm⁻¹. – ¹H-NMR (D₂O): δ = 2.75 (1H, d, J = 2.2, 3.8, 16.9 Hz, 3-Ha), 2.34 (1H, d, J = 2.2, 9.9, 16.9 Hz, -CH₂Br), 4.17 (1H, dd, J = 3.8, 9.9 Hz, 2-H). 7.02 (2H, d, J = 8.9 Hz, o-C₆H₄), 7.28 (1H, br d, J = 12.7 Hz, 4'-H), 7.38 (2H, br d, J = 8.9 Hz, m-C₆H₄), 8.65 (1H, d, J = 12.7 Hz, NH), 1-NH₂⁺ and COOH exchanged. – C₁₂H₁₁BrN₂O₃·HCl (347.6): calcld. C 41.46, H 3.48, N 8.06; found C 41.50, H 3.32, N 7.95.

(2S,4E)-4-(3-Nitroanilinomethylidene)pyroglutamic acid (7i)

Compound 7i was prepared from 6i. Yield: 141 mg (90 %) of a yellow solid. – M. p. 190 – 194 °C (partial decomposition above 150 °C). – [α]₀²⁰° = +52.3 (c = 0.78, MeOH). – IR (KBr): ν = 3233, 3072, 2615, 2524, 2445, 1728, 1669, 1621, 1602, 1532, 1483, 1447, 1347, 1328, 1244, 1206, 1087, 986, 930, 814, 796, 739, 720, 663 cm⁻¹. – ¹H-NMR (D₂O): δ = 2.79 (1H, d, J = 2.2, 3.7, 17.0 Hz, 3-Ha), 3.09 (1H, d, J = 2.2, 9.8, 17.0 Hz, 3-Hb), 4.20 (1H, dd, J = 3.7, 9.8 Hz, 2-H), 7.37 (1H, br d, J = 12.3 Hz, 4'-H), 7.44 – 7.55 (2H, m, 2H of C₆H₄), 7.62 – 7.69 (1H, m, 1H of C₆H₄), 7.84 – 7.87 (1H, m, 1H of C₆H₄), 9.04 (1H, d, J = 12.3 Hz, NH), 1-NH₂⁺ and COOH exchanged. – C₁₂H₁₁N₂O₅·HCl (313.7): calcld. C 45.95, H 3.86, N 13.40; found C 46.26, H 3.86, N 13.40.

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