Diastereoselective Synthesis of α-Methylpyroglutamates from α,β-Didehydro α-Amino Acids

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A new method for the diastereoselective synthesis of α-methylpyroglutamates from α,β-didehydro-*N*-(diphenylmethylene)glutamates has been developed. Deprotection of the (diphenylmethylene)amino moiety of the starting materials affords pyridazinone derivatives which can be transformed into α-methyl-6-oxoperhydropyridazine-3-carboxylates in a highly diastereoselective fashion. Ring contraction of the latter induced by LiHMDS affords α-methylpyroglutamates.

Introduction

The implication of glutamate receptors in Alzheimer's disease[1] and the therapeutic potential of substituted glutamic acid derivatives in the treatment of epilepsy[2] and stroke[3] has paved the way for the asymmetric synthesis of these unnatural α-amino acids. Pyroglutamates (5-oxoprolines) can be considered glutamic acid derivatives having the carboxylate group γ to the nitrogen atom internally protected (Figure 1, R^1 = H).[4]

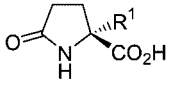
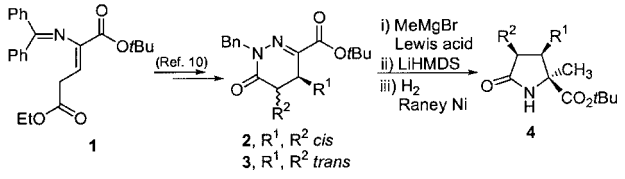


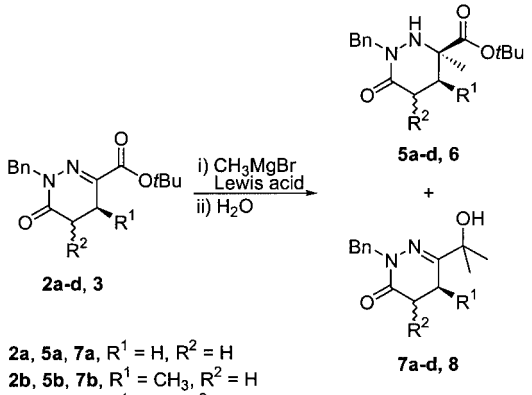
Figure 1. Pyroglutamates (5-oxoprolines)

The conformational constraints induced by these subunits in peptides can lead to their enhanced bioactivity and stability, which has found pharmacological use.[5] Amino acids constrained by the introduction of an alkyl chain at the α position, and in particular α-methyl α-amino acids (AMAAs), have assumed an important role in bioorganic chemistry as subunits for the definition of the secondary structure in de novo designs of peptides and proteins.[6] However, comparatively to other AMAAs, few efforts have been directed towards the preparation of cyclic α-substituted glutamic acid derivatives.[7,8]

α,β-Didehydro α-amino acids (DDAAs) constitute valuable synthetic intermediates for the preparation of more elaborated targets by means of hydrogenation of the C=C double bond, cyclopropanation or Diels–Alder reaction.[9] We have recently reported a new procedure which allows for the diastereoselective transformation of α,β-didehydroglutamates into the 6-oxoperhydropyridazine-3-carboxylic acid derivatives **2** and **3** (OPCAs) (Scheme 1).[10] We report herein our results on the diastereoselective synthesis of α-methylpyroglutamates using OPCAs **2** and **3** as starting materials[11] (Scheme 1).



Scheme 1



Scheme 2

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Results and Discussion

The addition of MeMgBr to **2a** (R^1, R^2 = H) was considered first (Scheme 2) in order to optimize the chemoselectivity of the addition of the organomagnesium reagent to the C=N or the ester groups. The results are given in Table 1.

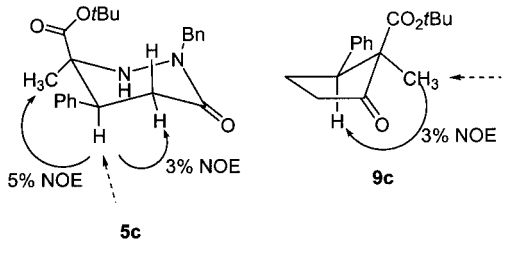
Table 1. Reactions of **2** and **3** with MeMgBr

Entry	**6**, **7**	Solvent	*T* [°C]	Lewis acid[a]	**5**,**6**/**7**,**8**[b]	**5**, **6** (%)[c]
1	**2a**	THF	−78	BF_3	−	−
2	**2a**	THF	−50	BF_3	**5a/7a** = 5:3	**5a** (40)
3	**2a**	Et_2O	−50	BF_3	−	−
4	**2a**	Et_2O	0	BF_3	**5a/7a** = 6:2	**5a** (50)
5	**2a**	toluene	−50	BF_3	**5a/7a** = 1:0	**5a** (10)
6	**2a**	toluene	−50	$Yb(OTf)_3$	**5a/7a** = 5:1	**5a** (70)
7	**2a**	toluene	0	$Yb(OTf)_3$	**5a/7a** = 7:3	**5a** (60)
8	**2b**	toluene	−50	$Yb(OTf)_3$	**5b/7b** = 7:1	**5b** (70)
9	**2c**	toluene	−50	$Yb(OTf)_3$	**5c/7c** = 7:1	**5c** (70)
10	**2d**	toluene	−50	$Yb(OTf)_3$	**5d/7d** = 1:0	**5d** (75)
11	**3**	toluene	−50	$Yb(OTf)_3$	**6/8** = 5:1	**6** (65)

[a] 1 equiv. [b] Determined by integration of the ^1H NMR (200 MHz) spectrum of the crude reaction products. [c] Isolated yield after chromatography.

No reaction was observed when the addition of MeMgBr was carried out in a THF solution at −78 °C using BF_3 as catalyst (Entry 1), and the reaction at −50 °C was unselective (Entry 2). Similar results were observed with Et_2O as solvent (Entries 3, 4). On the other hand, the reaction in toluene took place with low yield but good chemoselectivity (Entry 5). Best results were observed when $Yb(OTf)_3$ was used as catalyst in a toluene solution (Entries 6−7). The reaction conditions given in Entry 6 were used for the synthesis of the rest of compounds **5** and **6** (Entries 8−11).

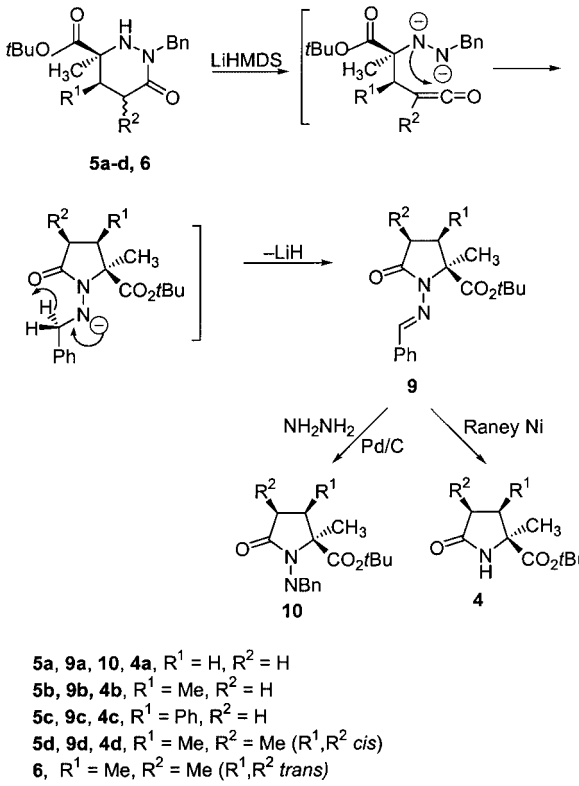
Compounds **5** and **6** were isolated as single diastereomers. The stereochemical outcome of the addition was controlled by the substituent at C-4, giving rise to a *trans* relative disposition between the CH_3 group at C-3 and the R^1 group at C-4. This relative stereochemistry was determined by the NOE effects observed in the ^1H NMR spectrum of compound **5c** (Scheme 3). Thus, saturation of the 4-H signal of compound **5c** (δ = 3.07 ppm, dd, ^3J = 9.0, ^3J = 5.5 Hz, 1 H) gave rise to a 5% enhancement of the signal of the CH_3 group at C-3 (δ = 1.26 ppm, s, 3 H) and a 3% enhancement of the pseudo-equatorial hydrogen signal at C-5 (δ = 2.63 ppm, dd, ^2J = 16.0, ^3J = 5.5 Hz). No NOE was observed with the pseudo-axial hydrogen atom at C-5 (δ = 2.83 ppm, dd, ^2J = 16.0, ^3J = 9.0 Hz) upon saturation of the 4-H signal of compound **5c**. The stereochemistry of the rest of compounds **5** and **6** was supposed to be similar to that of **5c**.[12]



Scheme 3

The stereochemistry of the nucleophilic addition to the C=N bond was not dependent on the substituent R^2 at C-5, either *cis* or *trans*. This was evidenced in the reactions of compounds **2d** (R^1, R^2 *cis*) and **3** (R^1, R^2 *trans*), which took place with the same diastereoselectivity as that of compounds **2b**, unsubstituted at C-5 (R^2 = H).

Treatment of compounds **5** and **6** with an excess of LiHMDS (4 equiv., THF) gave rise to compounds **9** (Scheme 4). The results are given in Table 2.



Scheme 4

Table 2. Synthesis of compounds **9** and **4**

Entry	**5**, **6**	**9** (%)[a]	**4** (%)[a]
1	**5a**	**9a** (85)	**4a** (90)
2	**5b**	**9b** (80)	**4b** (85)
3	**5c**	**9c** (75)	**4c** (85)
4	**5d**	**9d** (75)	**4d** (85)
5	**6**	**9d** (80)	**4d** (85)

[a] Isolated yield after chromatography

The ring contraction of compounds **5** and **6** into **9** may be understood on the basis of proton abstraction by LiHMDS from the α carbon atom of the carbonyl group and N-1, followed by formation of a ketene, thus planariz-

ing the stereogenic center. Intramolecular cyclization would then explain the formation of compounds **9**. It is worth mentioning that ring contraction did not take place by using LDA as the base.

The *trans* relative stereochemistry between R^1 and the CH_3 group α to the carboxyl group of the starting materials **5** and **6** was conserved in the reaction, as evidenced by the NOE effects observed in the ^1H NMR spectrum of compound **9c** (Scheme 3). Thus, saturation of the signal of the CH_3 group at C-2 (δ = 1.72 ppm, s, 3 H) gave rise to a 3% enhancement of the signal of 3-H (δ = 3.49 ppm, dd, ^3J = 11.5, ^3J = 8.5 Hz, 1 H). On the other hand, either **5d** (R^1, R^2 *cis*) or **6** (R^1, R^2 *trans*) gave rise to the same ring contraction product **9c**, which showed a *cis* relative disposition between R^1 and R^2. Therefore, the ring contraction process took place with epimerization at C-5 of compounds **5** or **6**.[13,14]

Treatment of compound **9a** with hydrazine afforded **10**. However, the N−N linkage in compounds **9** could be reduced with Raney Ni to afford the corresponding pyroglutamates **4** (Scheme 4). The results are given in Table 2.

Conclusion

In conclusion, a new method for the diastereoselective synthesis of α-methylpyroglutamates has been developed making use of α,β-didehydroglutamates as starting materials.[15]

Experimental Section

General Remarks: Toluene, THF, and Et_2O were distilled after refluxing in the presence of Na/benzophenone. Silica gel 60 F_{254} was used for TLC, and the spots were detected with UV. Flash column chromatography was carried out on silica gel 60. IR spectra were recorded as $CHCl_3$ solutions. ^1H NMR spectra were recorded at 200 or 300 MHz in $CDCl_3$ solution with TMS as internal reference. ^{13}C NMR spectra were recorded at 75 or 50 MHz in $CDCl_3$ solution with $CHCl_3$ (δ = 77.0 ppm) as internal reference. Melting points are uncorrected. The starting materials **1** were prepared as described previously.[10]

Addition of Methylmagnesium Bromide. General Procedure: A solution of compounds **2** or **3** (0.32 mmol) in toluene (1.5 mL) was added to a solution of $Yb(OTf)_3$ (0.32 mmol, 200 mg) in toluene (1 mL) at −50 °C and the mixture was stirred for 15 min. Methylmagnesium bromide (3 M in Et_2O, 0.64 mmol, 0.21 mL) was added dropwise, and the reaction mixture was stirred for 24 h. The temperature of the mixture was raised to room temp. and a solution of saturated $NaHCO_3$ (15 mL) was added. The organic layer was decanted, the aqueous layer was extracted with EtOAc (3 × 15 mL), and the combined organic extracts were dried with $MgSO_4$. Evaporation of the solvent under reduced pressure afforded a residue, which was purified by column chromatography (hexane/EtOAc, 70:30).

***tert*-Butyl 1-Benzyl-3-methyl-6-oxoperhydropyridazine-3-carboxylate (5a):** White solid (70 mg, 70%); m.p. 82−84 °C (hexane). IR ($CHCl_3$): ν̃ = 3296, 1716, 1658 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36−7.28 (m, 5 H), 4.75 (AB, 1 H, ^2J = 14.0 Hz), 4.59 (d, 1 H, ^2J = 14.0 Hz), 4.57 (s, 1 H), 2.48−2.21 (m, 3 H), 1.87−1.76 (m, 1 H), 1.46 (s, 9 H), 1.19 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2, 171.6, 137.2, 128.6, 128.5, 127.5, 82.2, 60.2, 52.1, 33.9, 29.2, 27.9, 23.4 ppm. $C_{17}H_{24}N_2O_3$ (304.18): calcd. C 67.08, H 7.95, N 9.20; found C 67.21, H 7.79, N 9.23.

***tert*-Butyl (3*S**,4*R**)-1-Benzyl-3,4-dimethyl-6-oxoperhydropyridazine-3-carboxylate (5b):** White solid (70 mg, 70%); m.p. 95−97 °C (hexane). IR ($CHCl_3$): ν̃ = 3298, 1718, 1630 cm^{-1}. ^1H NMR (200 MHz): δ = 7.28−7.21 (m, 5 H), 4.75 (s, 1 H), 4.69 (AB, ^2J = 14.0 Hz, 1 H), 4.48 (AB, ^2J = 14.0 Hz, 1 H), 2.42 (dd, ^2J = 16.0, ^3J = 5.5 Hz, 1 H), 2.25 (dd, ^2J = 16.0, ^3J = 8.5 Hz, 1 H), 1.99−1.82 (m, 1 H), 1.38 (s, 9 H), 1.10 (s, 3 H), 0.91 (d, ^3J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (50.5 MHz): δ = 171.7, 170.9, 137.1, 128.8, 128.5, 127.5, 82.5, 63.1, 52.1, 38.6, 36.7, 28.0, 22.4, 16.8 ppm. $C_{18}H_{26}N_2O_3$ (318.19): calcd. C 67.90, H 8.23, N 8.80; found C 68.00, H 8.18, N 8.83.

***tert*-Butyl (3*S**,4*S**)-1-Benzyl-3-methyl-4-phenyl-6-oxoperhydropyridazine-3-carboxylate (5c):** Colorless oil (70%). IR ($CHCl_3$): ν̃ = 3352, 1708, 1630 cm^{-1}. ^1H NMR (300 MHz): δ = 7.24−6.96 (m, 10 H), 4.98 (s, 1 H), 4.89 (AB, ^2J = 14.0 Hz, 1 H), 4.41 (AB, ^2J = 14.0 Hz, 1 H), 3.07 (dd, ^3J = 9.0, ^3J = 5.5 Hz, 1 H), 2.83 (dd, ^2J = 16.0, ^3J = 9.0 Hz, 1 H), 2.63 (dd, ^2J = 16.0, ^3J = 5.5 Hz, 1 H), 1.26 (s, 3 H), 1.17 (s, 9 H) ppm. ^{13}C NMR (75 MHz): δ = 171.3, 170.7, 139.0, 137.0, 129.1, 128.6, 128.5, 128.0, 127.6, 127.5, 82.3, 64.2, 52.3, 49.8, 34.9, 27.5, 23.2 ppm. $C_{23}H_{28}N_2O_3$ (380.21): calcd. C 72.60, H 7.42, N 7.36; found C 72.57, H 7.53, N 7.24.

***tert*-Butyl (3*S**,4*R**,5*S**)-1-Benzyl-3,4,5-trimethyl-6-oxoperhydropyridazine-3-carboxylate (5d):** Colorless oil (85 mg, 70%). IR ($CHCl_3$): ν̃ = 3313, 1714, 1627 cm^{-1}. ^1H NMR (300 MHz): δ = 7.38−7.29 (m, 5 H), 4.80 (AB, ^2J = 13.5 Hz, 1 H), 4.73 (AB, ^2J = 13.5 Hz, 1 H), 2.72−65 (m, 1 H), 2.15−2.03 (m, 1 H), 1.48 (s, 9 H), 1.26 (d, ^3J = 7.0 Hz, 3 H), 1.23 (s, 3 H), 0.86 (d, ^3J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz): δ = 172.3, 172.3, 128.6, 128.5, 127.4, 82.1, 62.7, 52.0, 41.1, 41.1, 28.0, 22.2, 12.6, 11.7 ppm. $C_{19}H_{28}N_2O_3$ (332.21): C 68.65, H 8.49, N 8.43; found C 68.70, H 8.48, N 8.53.

***tert*-Butyl (3*S**,4*R**,5*R**)-1-Benzyl-3,4,5-trimethyl-6-oxoperhydropyridazine-3-carboxylate (6):** Colorless oil (70 mg, 65%). IR ($CHCl_3$): ν̃ = 3303, 1713, 1624 cm^{-1}. ^1H NMR (200 MHz): δ = 7.28−7.19 (m, 5 H), 4.96 (AB, ^2J = 10.0 Hz, 1 H), 4.75 (AB, ^2J = 10.0 Hz, 1 H), 2.46−2.35 (m, 2 H), 1.32 (s, 9 H), 1.19 (s, 3 H), 1.11 (d, ^3J = 7.0 Hz, 3 H), 1.05 (d, ^3J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (50.5 MHz): δ = 170.2, 169.8, 128.7, 128.3, 128.0, 127.3, 82.4, 60.8, 52.2, 39.4, 40.2, 27.8, 22.1, 16.4, 15.8 ppm. $C_{19}H_{28}N_2O_3$ (332.21): calcd. C 68.65, H 8.49, N 8.43; found C 68.75, H 8.37, N 8.49.

2-Benzyl-6-(1-hydroxy-1-methylethyl)-4,5-dihydropyridazin-3(2*H*)-one (7a): Colorless oil (8 mg, 10%). IR ($CHCl_3$): ν̃ = 3470, 1665 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.31−7.26 (m, 5 H), 4.98 (s, 2 H), 3.62 (s, 1 H), 2.52−2.48 (m, 4 H), 1.38 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.2, 159.4, 137.2, 128.4, 128.3, 127.4, 72.2, 51.9, 27.7, 27.2, 21.3 ppm. $C_{14}H_{18}N_2O_2$ (246.14): C 68.27, H 7.37, N 11.37; found C 68.42, H 7.56, N 11.10

2-Benzyl-6-(1-hydroxy-1-methylethyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-one (7b): Colorless oil (8 mg, 10%). IR ($CHCl_3$): ν̃ = 3465, 1660 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.24−7.19 (m, 5 H), 5.01 (1 H, B part of AB system, ^2J = 14.5 Hz), 4.78 (1 H, A part of AB system, ^2J = 14.5 Hz), 3.55 (s, 1 H), 2.79−2.68 (m, 1 H), 2.45−2.25 (m, 2 H), 1.33 (s, 6 H), 1.10 (d, ^3J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.8, 163.5, 137.2, 128.5,

128.3, 127.4, 72.5, 51.7, 35.2, 28.2, 27.1, 27.0, 15.8 ppm. $C_{15}H_{20}N_2O_2$ (260.15): calcd. C 69.20, H 7.74, N 10.76; found C 69.44, H 7.81, N 10.55.

2-Benzyl-6-(1-hydroxy-1-methylethyl)-5-phenyl-4,5-dihydropyridazin-3(2*H*)-one (7c): Colorless oil (10 mg, 10%). IR ($CHCl_3$): $\tilde{\nu}$ = 3430, 1660 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.29−6.61 (m, 10 H), 5.24 (1 H, B part of AB system, ^2J = 14.5 Hz), 4.63 (1 H, A part of AB system, ^2J = 14.5 Hz), 3.88 (dd, ^3J = 7.0, ^3J = 1.5 Hz, 1 H), 3.25 (br. s, 1 H), 2.72 (dd, ^2J = 15.5, ^3J = 7.0 Hz, 1 H), 2.57 (dd, ^2J = 15.5, ^3J = 1.5 Hz, 1 H), 1.33 (s, 3 H), 1.05 (s, 3 H) ppm. ^{13}C NMR (50.5 MHz, $CDCl_3$): δ = 163.4, 160.7, 137.1, 136.7, 129.2, 128.4, 127.7, 127.6, 126.9, 72.9, 51.9, 38.6, 36.6, 29.3, 27.6 ppm. $C_{20}H_{22}N_2O_2$ (322.17): calcd. C 74.51, H 6.88, N 9.93; found C 74.70, H 7.02, N 9.71.

(4*R,5*R**)-2-Benzyl-6-(1-hydroxy-1-methylethyl)-4,5-dimethyl-4,5-dihydropyridazin-3(2*H*)-one (8):** Colorless oil (18 mg, 20%). IR ($CHCl_3$): $\tilde{\nu}$ = 3460, 1660 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.36−7.27 (m, 5 H), 4.95 (d, ^2J = 14.5 Hz, 1 H), 4.73 (d, ^2J = 14.5 Hz, 1 H), 2.49−2.23 (m, 2 H), 1.32 (s, 6 H), 1.02 (d, ^3J = 7.0 Hz, 3 H), 1.01 (d, ^3J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (50.5 MHz, $CDCl_3$): δ = 164.6, 163.2, 137.1, 128.4, 128.3, 127.8, 72.8, 51.6, 39.8, 34.2, 27.3, 27.0, 15.8, 15.2 ppm. $C_{16}H_{22}N_2O_2$ (274.17): calcd. C 70.04, H 8.08, N 10.21; found C 70.25, H 8.21, N 10.05.

Addition of Lithium Bis(trimethylsilyl)amide to 5 and 6. General Procedure: BuLi (1.6 M in hexane, 2.64 mmol, 1.14 mL) was added to a solution of HMDS (1.32 mmol, 0.28 mL) in THF (1 mL) at 0 °C and the solution was stirred for 1 h. A solution of **5** or **6** (0.33 mmol) in THF (1 mL) was added at −78 °C, and the temperature was slowly raised (3 h) to room temp. and stirred for a further 24 h. After addition of H_2O (3 mL), the organic layer was decanted. The aqueous layer was extracted with EtOAc (3 × 3 mL), and the combined organic extracts were dried with $MgSO_4$. Solvent evaporation under reduced pressure afforded a residue, which was purified by column chromatography (hexane/EtOAc, 80:20).

***tert*-Butyl 1-Benzylidenamino-2-methyl-5-oxopyrrolidine-2-carboxylate (9a):** Colorless oil (85 mg, 85%). IR ($CHCl_3$): $\tilde{\nu}$ = 1734, 1691 cm^{-1}. ^1H NMR (200 MHz): δ = 9.35 (s, 1 H), 7.64−7.29 (m, 5 H), 2.54−2.45 (m, 2 H), 2.24−2.20 (m, 1 H), 1.96−1.85 (m, 1 H), 1.54 (s, 3 H), 1.37 (s, 9 H) ppm. ^{13}C NMR (50.5 MHz): δ = 172.3, 172.0, 154.1, 135.0, 130.3, 128.5, 127.4, 81.9, 68.2, 29.8, 29.1, 27.9, 22.9 ppm. $C_{17}H_{22}N_2O_3$ (286.18): calcd. C 67.53, H 7.33, N 9.26; found C 67.51, H 7.40, N 9.28.

***tert*-Butyl (2*S**,3*R**)-1-Benzylidenamino-2,3-dimethyl-5-oxopyrrolidine-2-carboxylate (9b):** Colorless oil (90 mg, 85%). IR ($CHCl_3$): $\tilde{\nu}$ = 1732, 1712 cm^{-1}. ^1H NMR (200 MHz): δ = 9.41 (s, 1 H), 7.66−7.32 (m, 5 H), 2.01−1.99 (m, 3 H), 1.34 (s, 9 H), 1.19 (s, 3 H), 1.17 (d, ^3J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (50.5 MHz): δ = 171.7, 170.3, 155.1, 134.6, 130.7, 128.6, 27.6, 82.7, 69.9, 44.6, 29.7, 28.0, 21.9, 12.2 ppm. $C_{18}H_{24}N_2O_3$ (316.18): calcd. C 68.33, H 7.65, N 8.85; found C 68.40, H 7.70, N 8.78.

***tert*-Butyl (2*S**,3*S**)-1-Benzylidenamino-2-methyl-5-oxo-3-phenylpyrrolidine-2-carboxylate (9c):** Colorless oil (100 mg, 80%). IR ($CHCl_3$): $\tilde{\nu}$ = 1635 cm^{-1}. ^1H NMR (200 MHz): δ = 9.41 (s, 1 H), 7.93−7.35 (m, 10 H), 3.49 (dd, ^3J = 11.5, ^3J = 8.5 Hz, 1 H), 3.21 (dd, ^2J = 16.5, ^3J = 11.5 Hz, 1 H), 3.81 (dd, ^2J = 16.5, ^3J = 8.5 Hz, 1 H), 1.72 (s, 3 H), 1.25 (s, 9 H) ppm. ^{13}C NMR: δ (50.5 MHz): δ = 169.9, 154.8, 135.5, 134.4, 130.4, 130.0, 128.6, 128.5, 128.0, 127.5, 82.2, 73.3, 46.9, 35.3, 27.8, 22.7 ppm. $C_{23}H_{26}N_2O_3$ (378.19): calcd. C 72.99, H 6.92, N 7.40; found C 73.07, H 6.87, N 7.37.

***tert*-Butyl (2*S**,3*R**,4*S**)-1-Benzylidenamino-2,3,4-trimethyl-5-oxopyrrolidine-2-carboxylate (9d):** Colorless oil (90 mg, 80%). IR ($CHCl_3$): $\tilde{\nu}$ = 1711, 1691cm^{-1}. ^1H NMR (200 MHz): δ = 9.62 (s, 1 H), 7.73−7.39 (m, 5 H), 2.40−2.32 (m, 2 H), 1.67 (s, 3 H), 1.49 (s, 9 H), 1.43 (d, ^3J = 7.0 Hz, 3 H), 1.15 (d, ^3J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (50.5 MHz): δ = 173.6, 170.5, 155.0, 134.8, 130.6, 128.6, 127.5, 82.6, 68.1, 47.1, 31.9, 29.3, 22.7, 14.1, 9.8 ppm. $C_{19}H_{26}N_2O_3$ (330.19): calcd. C 69.06, H 7.93, N 8.48; found C 68.97, H 7.96, N 8.50

***tert*-Butyl 1-Benzylamino-2-methyl-5-oxopyrrolidine-2-carboxylate (10):** Hydrazine hydrate (80%, 0.33 mL) and Pd/C (10%) (200 mg) were added to a solution of **9a** (0.33 mmol, 100 mg) in MeOH (10 mL) . The mixture was stirred at reflux for 24 h. After cooling to room temp., the mixture was filtered through Celite and the solid washed with MeOH (5 mL). The solvent was evaporated under reduced pressure to give an oil which was purified by chromatography (hexane/EtOAc, 70:30). Colorless oil (90 mg, 90%). IR ($CHCl_3$): $\tilde{\nu}$ = 3392, 1685 cm^{-1}. ^1H NMR (200 MHz): δ = 7.37−7.31 (m, 5 H), 4.19 (d, ^2J = 12.0 Hz, 1 H), 3.98 (d, ^2J = 12.0 Hz, 1 H), 2.41 (dd, ^3J = 10.0, ^3J = 6.0 Hz), 2.23−2.11 (m, 1 H), 1.91−1.75 (m, 1 H), 1.44 (s, 9 H), 1.38 (s, 3 H) ppm. ^{13}C NMR (50.5 MHz): δ = 175.9, 172.5, 137.6, 129.2, 128.3, 127.5, 81.9, 67.5, 55.2, 29.7, 29.5, 27.9, 21.9 ppm. $C_{17}H_{24}N_2O_3$ (304.18): calcd. C 67.08, H 7.95, N 9.20; found C 67.51, H 7.40, N 9.28.

Synthesis of Pyroglutamates 4. General Procedure: Raney Ni (80% dispersion in H_2O, 10 mL) was added to a solution of compounds **9** (0.33 mmol, 100 mg) in EtOH (10 mL) . The reaction mixture was stirred at reflux for 24 h. At room temp., the solution was filtered and the remaining solid material was washed with EtOH (10 mL). The solvent was evaporated, and the residue was purified by chromatography (hexane/EtOAc, 70:30).

***tert*-Butyl 2-Methyl-5-oxopyrrolidine-2-carboxylate (4a):** Colorless oil (62 mg, 95%). IR ($CHCl_3$): $\tilde{\nu}$ = 3430, 1700 cm^{-1}. ^1H NMR (300 MHz): δ = 5.90 (s, 1 H), 2.52−2.32 (m, 3 H), 2.04−1.97 (m, 1 H), 1.48 (s, 9 H), 1.26 (s, 3 H) ppm. ^{13}C NMR (75 MHz): δ = 176.8, 172.9, 82.3, 62.6, 27.9, 25.9, 22.7, 14.1 ppm. $C_{10}H_{17}NO_3$ (199.12): calcd. C 60.28, H 8.60, N 7.03; found C 60.30, H 8.54, N 7.10.

***tert*-Butyl (2*S**,3*R**)-2,3-Dimethyl-5-oxopyrrolidine-2-carboxylate (4b):** Colorless oil (63 mg, 90%). IR ($CHCl_3$): $\tilde{\nu}$ = 3440, 1705 cm^{-1}. ^1H NMR (200 MHz): δ = 5.13 (s, 1 H), 2.39−1.29 (m, 3 H), 1.38 (s, 9 H), 1.25 (s, 3 H), 1.15 (d, ^3J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (50.5 MHz): δ = = 176.7, 172.8, 82.4, 61.9, 41.2, 30.2, 28.0, 22.7, 13.8 ppm. $C_{11}H_{19}NO_3$ (213.14): calcd. C 61.95, H 8.98, N 6.57; found C 62.05, H 7.09, N 6.49.

***tert*-Butyl (2*S**,3*S**)-2-Methyl-5-oxo-3-phenylpyrrolidine-2-carboxylate (4c):** Colorless oil (82 mg, 90%). IR ($CHCl_3$): $\tilde{\nu}$ = 3430, 1700 cm^{-1}. ^1H NMR (200 MHz): δ = 7.32−7.29 (m, 5 H), 3.79 (dd, ^3J = 10, ^3J = 8.0 Hz, 1 H), 3.00−2.87 (m, 2 H), 1.22 (s, 3 H), 1.16 (s, 9 H) ppm. ^{13}C NMR (50.5 MHz): δ = 177.1, 172.4, 130.0, 128.7, 128.4, 128.0, 127.6, 82.1, 64.2, 43.7, 31.3, 27.8, 22.2 ppm. $C_{16}H_{21}NO_3$ (275.15): calcd. C 69.79, H 7.69, N 5.09; found C 69.89, H 7.78, N 5.01.

***tert*-Butyl (2*S**,3*R**,4*S**)-2,3,4-Trimethyl-5-oxopyrrolidine-2-carboxylate (4d):** Colorless oil (30 mg, 90%). IR ($CHCl_3$): $\tilde{\nu}$ = 3435, 1705 cm^{-1}. ^1H NMR (200 MHz): δ = 2.26−2.13 (m, 2 H), 1.41 (9 H,s), 1.38 (d, ^3J = 7.0 Hz, 3 H), 1.20 (s, 3 H), 1.10 (d, ^3J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (50.5 MHz): δ = 176.6, 173.2, 82.4, 61.5, 43.2, 30.4, 28.9, 22.4, 14.1, 11.4 ppm. $C_{12}H_{21}NO_3$ (227.15): calcd. C 63.41, H 9.31, N 6.16; found C 63.47, H 9.27, N 6.15.

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