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The revisited synthesis of *tert*-butyl pyroglutamate derivatives

Christelle Claverie [a,b], Alina Ghinet [a,b,*], Philippe Gautret [a,b], Chi-Thanh Vuong [c], Benoît Rigo [a,b]

[a] Univ Lille Nord de France, F-59000 Lille, France
[b] UCLille, EA GRIIOT (4481), Laboratoire de pharmacochimie, HEI, 13 rue de Toul, F-59046 Lille, France
[c] Rhodia, 52 Rue de la Haie Coq, 93306 Aubervilliers, France

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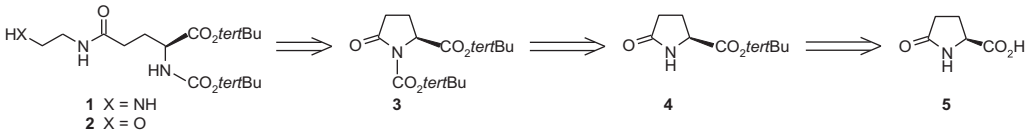
ABSTRACT

The very common protection reactions of scaffolds by introduction of Boc or *tert*-butyl groups on lactams or acids in the pyroglutamic series have been revisited in a green perspective. Particularly, reaction conditions allowing a quantitative yield in substitution of bromine in *tert*-butyl bromide were discovered for the first time, allowing the synthesis of *tert*-butyl pyroglutamate **4**. This synthesis of *tert*-butyl ester by nucleophilic substitution, realized without using concentrated perchloric or sulfuric acid, could be of interest for acid sensitive compounds. On the other hand, we demonstrated that non toxic *N*-methylimidazole and *tert*-butanol can pleasantly replace the problematic toxic 4-dimethylaminopyridine (DMAP) and dichloromethane utilized for the N-carbamoylation of lactam **4**. This environmentally improved route to compound **4** allowed the development of a multi-gram supply of protected *N*-aminoethyl and *N*-hydroxyethyl γ-glutamine **1** and **2**.

1. Introduction

In conjunction with an ongoing program, we needed a convenient multi-gram supply of protected *N*-aminoethyl and *N*-hydroxyethyl γ-glutamine **1** and **2** to be used as future building blocks. A preliminary survey of literature indicated that these amides could be obtained (Scheme 1) by opening the lactam ring of acyl carbamate **3** synthesized from *tert*-butyl ester **4** issued from renewable synthon L-pyroglutamic acid **5**, sometimes called 'the forgotten amino acid'.[1a] The use of a protective group is an important step in synthetic methodology,[1b] and many syntheses of *tert*-butyl esters **3** and **4** have already been described. However, these methods for obtaining **3** and **4** are not really friendly; thus, we examined more environmentally pleasant and efficient protocols for the obtention of these compounds. That led us to discover reaction conditions allowing for the first time the synthesis of *tert*-butyl pyroglutamate **4** from *tert*-butyl bromide in quantitative yield.



Scheme 1. Retrosynthetic pathways for the preparation of amides **1** and **2**.

2. Results and discussion

2.1. Synthesis of *tert*-butyl pyroglutamate 4

The retrosynthetic pathways described in Scheme 1 start from pyroglutamic acid **5**. SciFinder reports about 8000 references for this amidoacid, and many of the described synthetic schemes exploit protected forms of the carboxylic group of **5**. One of these

* Corresponding author. Tel.: +33 (0) 3 28 38 48 58; fax: +33 (0) 3 28 38 48 04; e-mail address: alina.ghinet@hei.fr (A. Ghinet).

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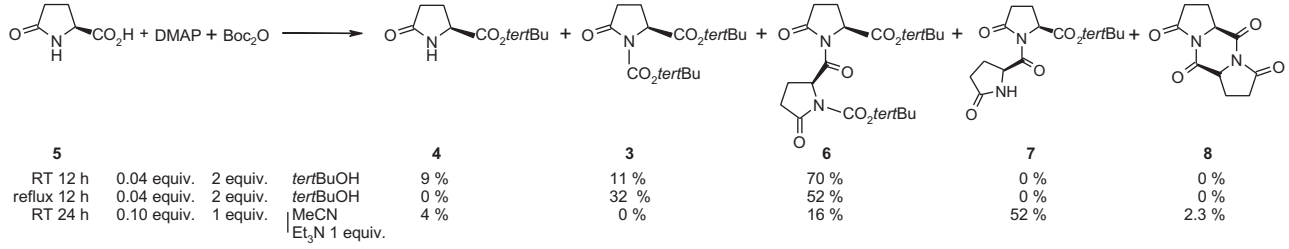
widely utilized compounds is *tert*-butyl pyroglutamate **4**. Mainly, two syntheses are employed to obtain this ester: the general method of reaction of a carboxylic acid with isobutene,[2] catalyzed by great amount of sulfuric acid in dichloromethane or dioxane, furnished with pyroglutamic acid **5** very variable yields of **4** (14–78%).[3] In another method, pyroglutamic acid **5** was reacted with a large amount of *tert*-butyl acetate in the presence of 0.7 equiv of 70% perchloric acid; accordingly, ester **4** was described to be obtained in 31–100% yields.[4] The principal problems concerning these syntheses of *tert*-butyl ester **4** are the nature and the amount of acidic catalyst and solvent, as well as the seemly irreproducible yields. In order to envisage a possible reuse of the acidic catalyst, we attempted to modify this last reaction by stirring pyroglutamic acid **5** and *tert*-butyl acetate in the presence of Nafion® resin (*tert*-butanol was utilized as a co-solvent) for a week at room temperature. However, only low and irreproducible yields (9–30%) of ester **4** were obtained.

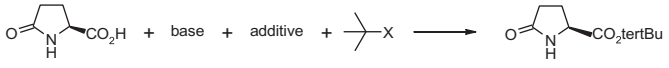
It has been described that carboxylic acids react with Boc_2O in the presence of DMAP to give symmetric anhydrides,[5] which then can react with *tert*-butanol to obtain *tert*-butyl esters, and this method has been utilized with *N*-protected glutamic or pyroglutamic acids, providing good yields of the corresponding ester **3**.[2,6] When we applied this method to pyroglutamic acid **5**, according to the different reaction conditions (Scheme 2), esters **3** and **4** were obtained in low yields, along with dimeric compounds **6**, **7**, and **8**. Diketopiperazine **8** has already been described.[7] On the other side, compounds analogs to *N*-pyroglutamoylpyroglutamic derivatives **6** and **7** have been isolated from the reaction of pyroglutamoyl chloride with amines.[8] Products **6** and **7** can be isolated in good yields (70% and 52%); this needs to be noted as these scaffolds proved to be interesting in the field of pseudopeptide foldamers.[9]

Given these results, although '*with a few exceptions, nucleophilic substitutions at a tertiary carbon have little or no preparative value*,[10]' it was decided to explore the solvolytic displacement of *tert*-butyl halide by the carboxylate anion issued from pyroglutamic acid. A selection of the various reaction conditions employed can be found in Table 1. The temperatures were chosen in order to limit the formation of *iso*butene. The use of *t*-BuOH is often interesting in pyroglutamic chemistry because it is one of the rare and good solvents for this acid. However, triethylamine salt of **5** forms an insoluble mobile oil in many solvents (2-Me-THF, acetone…), and is soluble in CH_2Cl_2 and propylene carbonate. It can be observed that in standard conditions, whatever the solvent and the amine used, the reaction rate is very low without additive (Entries 1–4) and that the bromide is more reactive that the chloride. It was reported in the literature that bismuth carboxylate in CCl_4,[11a] and zinc carboxylate in an excess of carboxylic acid,[11b] react easily with tertiary alkyl halide to give very good yields of *tert*-butyl esters; thus acid **5** was reacted with halide in presence of ZnO,[11b] or $BiCl_3$ and triethylamine. In that case, the reaction mixture in *tert*-butanol became very thick and could not be stirred (Entry 7); with ZnO as additive, the bromide again gave better yields than chloride (Entries 5 and 6), and the 38% of *tert*-butyl pyroglutamate isolated after 36 h (Entry 6) confirms the interest of the presence of zinc additive.[12] However, it was observed that a large part of *tert*-BuBr was hydrolyzed to *tert*-BuOH, thus ZnO was replaced by $ZnCl_2$ (entry 8). In these



Scheme 2. Reaction of pyroglutamic acid with Boc_2O.

Table 1
Reaction of pyroglutamic acid with *tert*-butyl halides



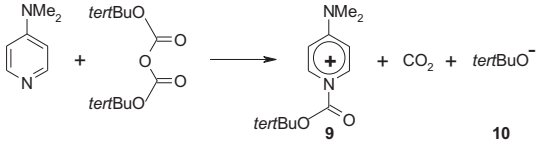
Entry	^{t}BuX (equiv)	Base (equiv)	Additive (equiv)	Temperature °C	Solvent (mL/mol)	Time	Yield[a] %
1	X=Cl (1.25)	Et_3N (1.25)	—	70	THF (200)	7 d	9
2	X=Cl (1.20)	DIPA (1.25)	—	70	THF (200) $CHCl_3$ (50)	8 d	18
3	X=Br (3.00)	Et_3N (3.00)	—	30	MeCN (400)	5 d	35 (isolated)
4	X=Br (3.00)	Py (3.00)	—	40	CH_2Cl_2 (600)	24 h	10
5	X=Cl (1.50)	—	ZnO (0.50)	55	Dioxane (2000)	24 h	4
6	X=Br (1.50)	—	ZnO (1.00)	45	Dioxane (2000)	36 h	38 (isolated)
7[b]	X=Br (1.25)	Et_3N (1.00)	$BiCl_3$ (0.25)	40	*tert*-BuOH(1500)	7 d	5
8	X=Br (1.50)	Et_3N (1.00)	$ZnCl_2$ (0.50)	40	$CHCl_3$ (2500)	48 h	22
9[c]	X=Br (2.00)	Et_3N (2.00)	$ZnBr_2$ (0.50)	40	*tert*-BuOH(1600)	20 h	43 (isolated)
10[d]	X=Br (2.00)	Et_3N (2.00)	$ZnBr_2$ (1.00)	40	CH_2Cl_2 (1000)	20 h	53 (isolated)
11	X=Br (3.00)	Et_3N (3.60)	$ZnBr_2$ (2.50)	40	CH_2Cl_2 (1250)	14 h	**91** (isolated)
12	X=Br (3.00)	Et_3N (3.60)	$ZnBr_2$ (2.50)	40	MeTHF (1250)	48 h	25
13	X=Br (3.00)	Et_3N (3.60)	$ZnBr_2$ (2.50)	40	PC[e] (1250)	15 h	82 (isolated)

[a] Determined by ^{1}H NMR of the reaction mixture.
[b] Very thick mixture.
[c] Formation of a crystallized mass.
[d] 4 Å MS (100 g/mol) was added.
[e] Propylene carbonate.

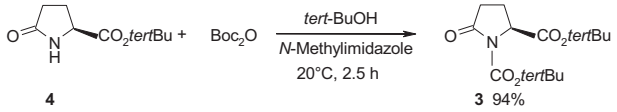
conditions, two secondary reactions occurred: (a) an important amount of *tert*-butyl bromide was transformed in less reactive chloride, and (b) the amount of ester decreased after 48 h of reaction. This indicates that the quantity of base was too low, and that after consumption of all the triethylamine, the zinc halide decomposed the *tert*-butyl ester[13] to give *iso*butene and pyroglutamic acid. Thus, the amounts of Et_3N and of alkyl bromide were increased to 2 equiv and, in *tert*-butanol as solvent (Entry 9), a promising 43% yield of ester **4** was obtained in 20 h. On the other hand, the salts issued from the reaction lead to the formation of an important crystallized mass, prohibiting stirring. Thus, in the next experiments using more base and reagents, dichloromethane was utilized as a better solvent for the salts. Drying the reaction medium with 4 Å MS did not prove to be determinant (Entry 10), but with 3 equiv of halide, 3.6 equiv of triethylamine and 2.5 equiv of zinc dibromide, a quantitative reaction was observed by ^{1}H NMR after 14 h at 40 °C, leading to the isolation of 91% of *tert*-butyl pyroglutamate **4** (Entry 11). The amount of base and additive being optimized, search for a greener solvent was undertaken; disappointing results were obtained with 2-methyl-tetrahydrofuran (Entry 12): this solvent led to the formation of two non-miscible phases, and 24 h were needed to obtain a 25% NMR conversion, which did not increase after 48 h heating at 40 °C. Thus, a more polar green solvent was chosen; gratefully, propylene carbonate[14] furnished a total conversion by ^{1}H NMR to *tert*-butyl pyroglutamate **4**; ethyl acetate/water partition, followed by distillation of the solvent allowed the isolation of 82% of ester **4** and the recovery of 64% of propylene carbonate.

2.2. Synthesis of carbamate 3

With ester **4** in hands, synthesis of carbamate **3** can appear trivial. Indeed, the general introduction of a Boc group on amines by using Boc_2O and catalyst (I_2, β-cyclodextrine, $Zn(ClO_4)_2$),[15] was adapted to lactams[16] then to pyroglutamic esters[17] by employing dimethylaminopyridine (DMAP) as an activating agent. In the case of *tert*-butyl pyroglutamate **4**, this reaction was realized in THF[4a] or in MeCN,[4b,e,6b,18] eventually in the presence also of Et_3N[19] with room temperature, furnishing 94% of carbamate **3** after work up, without the need of chromatographic purification (Scheme 4)



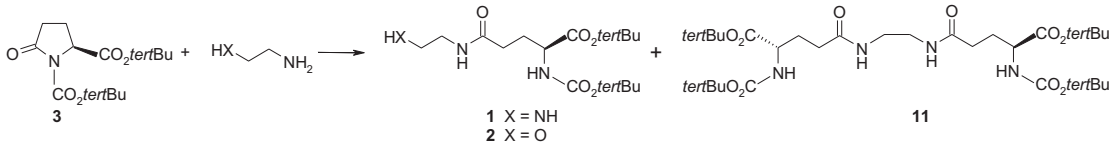
Scheme 3. Reaction of DMAP with Boc_2O.



Scheme 4. Synthesis of carbamate **3**.

2.3. Synthesis of amides 1 and 2

Then, syntheses of amides **1** and **2** were undertaken. As planned in the retrosynthetic approach (Scheme 1) these compounds could be obtained from ring opening of carbamate **3**. Selective cleavage of Boc-acylamides has been described.[24] In the case of *N*-Boc pyroglutamic esters,[16] the nucleophiles utilized were organometals (giving ketones),[20a,25] hydride ions (furnishing alcohols),[4e,19,26] sodium hydroxide (yielding acids).[4c] As for alcohols and amines, they provide esters,[27] and amides,[20b,28] respectively; these last reactions can be catalyzed by trimethylaluminium[29] or by cyanide ion,[30] which forms a more reactive intermediate acylnitrile. Thus, to obtain our targets, ethylenediamine was reacted with *N*-acyl carbamate **3**; no cyanide catalysis was needed, however when reaction mixture was heated at reflux, only 27% of amide **1** were isolated, and 22% of dimer **11** were also obtained. Performing the reaction at room temperature allowed the exclusive formation of aminoamide **1** in 95% yields. The same reaction conditions applied to ethanolamine furnished 66% of amidoalcohol **2** (Scheme 5).



Scheme 5. Synthesis of amides **1** and **2**.

yields ranging from 72 to 100%. In the case of different pyroglutamic esters, other solvents (CH_2Cl_2,[20] DMF/DIPA.[9]…) were also utilized. Dichloromethane or acetonitrile are not very friendly, and DMAP is very toxic. Thus, we though to use greener conditions to obtain ester **3**.

Literature described that in these reactions the *tert*-Boc-dimethylaminopyridinium cation **9** acts as an acylating reagent,[21] and that the highly basic *tert*-butoxide anion **10** is involved in the proton abstraction from the lactam ring (Scheme 3).[22] It is known that the greener *N*-methylimidazole can efficiently catalyze some acylation reactions,[23] and we postulated that it could activate the Boc_2O acylation reagent in the same way as DMAP (Scheme 3). Thus this catalyst was chosen, and the carbamoylation of pyroglutamic ester **4** was carried out in the friendly *tert*-butanol solvent. Gratefully, a full NMR conversion was observed after 2.5 h of stirring at

3. Conclusion

Protection of scaffolds by introduction of Boc or *tert*-butyl groups on lactams or acids is very common for synthetic organist chemists. In the case of pyroglutamic acid derivatives, we have revisited these reactions in a green perspective, and obtained very good yields of *tert*-butyl pyroglutamate **4** and the corresponding *N*-Boc derivative **3**. We thought that these results can be extended to many other scaffolds. Particularly the method of synthesis of *tert*-butyl ester by using *tert*-butyl bromide, realized without using sulfuric or perchloric acid, could be of interest for acid sensitive compounds. On the other hand, we demonstrated that non toxic *N*-methylimidazole and *tert*-butanol can pleasantly replace the problematic toxic DMAP and dichloromethane utilized for the N-carbamoylation of this lactam.

4. Experimental section

4.1. General

Starting materials are commercially available and were used without further purification. Melting points were measured on a MPA 100 OptiMelt® apparatus and are uncorrected. NMR spectra were acquired at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR on a Varian 400 MHz Premium Shielded® spectrometer. Chemical shifts (δ) are given in parts per million relative to $CDCl_3$ (7.26 ppm; 77.1 ppm). Splitting patterns are designed as: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; m, multiplet, and sym m, symmetric multiplet. Coupling constants *J* are reported in hertz (Hz). Thin layer chromatographies were realized on Macherey Nagel silica gel plates with a fluorescent indicator and were visualized with UV-lamp at 254 nm and 366 nm. Column chromatographies were performed using a Combi*Flash* Rf Companion (Teledyne-Isco System) and Redi*Sep* packed columns. IR spectra were recorded on a Varian 640-IR FT-IR Spectrometer. Elemental analyses (C, H, N) of new compounds were determined by 'Pôle Chimie Moléculaire', Faculté de Sciences Mirande, Université de Bourgogne, Dijon, France.

*4.1.1. tert-Butyl N^5-(2-aminoethyl)-N^2-(tert-butoxycarbonyl)-α-glutaminate (**1**).* To a stirred solution of carbamate **3** (50.0 g, 0.175 mol) in 1,2-dichloroethane (300 mL) was added via syringe 1,2-ethylene diamine (29.5 mL, 0.438 mol). The resulting solution was stirred at room temperature overnight. Volatiles were removed under reduced pressure. The crude reaction mixture was dissolved in CH_2Cl_2 (300 mL) and washed with water (100 mL). MeOH was added to the organic phase (50 mL) and it was dried (Na_2SO_4) and concentrated under reduced pressure to give the pure product (57.42 g, 86%) as a white solid; mp (CH_2Cl_2/MeOH): 135–136 °C; R_f (CH_2Cl_2/MeOH: 9/1) 0.13; IR ν cm^{-1}: 3385, 2961, 2887, 1719, 1685, 1654, 1152; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 1.39 (s, 9H, (C*H*$_3$)$_3$C), 1.40 (s, 9H, (C*H*$_3$)$_3$C), 1.67–1.77 (m, 1H, C*H*$_2$CH), 1.85–1.94 (m, 1H, C*H*$_2$CH), 2.15 (t, *J*=7.5 Hz, 2H, C*H*$_2$C=O), 2.66 (t, *J*=6.3 Hz, 2H, C*H*$_2$NH$_2$), 3.10–3.15 (m, 2H, C*H*$_2$NH), 3.74–3.80 (m, 1H, C*H*), 4.46 (broad s, 2H, NH$_2$), 7.12 (d, *J*=7.8 Hz, 1H, NHBoc), 7.92 (t, *J*=5.4 Hz, 1H, NHCH$_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.6 (CH_2), 27.9 ($3CH_3$), 28.4 ($3CH_3$), 31.8 (CH_2), 37.3 (CH_2), 39.1 (CH_2), 54.2 (CH), 78.3 (C), 80.5 (C), 155.7 (C), 171.8 (C), 172.2 (C). Anal. Calcd for $C_{16}H_{31}N_3O_5$, $2H_2O$: C, 50.38; H, 9.25; N, 11.02. Found: C, 50.16; H, 9.09; N, 10.94.

*4.1.2. tert-Butyl N^2-(tert-butoxycarbonyl)-N^5-(2-hydroxyethyl)-α-glutaminate (**2**).* To a stirred solution of carbamate **3** (50.0 g, 0.175 mol) in 1,2-dichloroethane (300 mL) was added via syringe ethanolamine (17.0 mL, 0.283 mol). The resulting solution was stirred at room temperature overnight. Volatiles were removed under reduced pressure. The crude reaction mixture was purified by flash chromatography (SiO_2, gradient CH_2Cl_2/MeOH from 100/0 to 95/5) to isolate amidoalcohol **2** as a thick yellow oil (65.5 g, 66%), R_f (CH_2Cl_2/MeOH: 9/1) 0.62; IR ν cm^{-1}: 3303, 2977, 2933, 1694, 1647, 1149; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 1.37 (s, 9H, (C*H*$_3$)$_3$C), 1.38 (s, 9H, (C*H*$_3$)$_3$C), 1.65–1.74 (m, 1H, C*H*$_2$CH), 1.82–1.90 (m, 1H, C*H*$_2$CH), 2.12 (t, *J*=7.6 Hz, 2H, C*H*$_2$C=O), 3.08 (dd, *J*=11.9, 5.8 Hz, 2H, C*H*$_2$NH), 3.36 (d, *J*=6.1 Hz, 2H, C*H*$_2$OH), 3.72–3.78 (m, 1H, C*H*), 4.61 (t, *J*=5.5 Hz, 1H, O*H*), 7.10 (d, *J*=7.9 Hz, 1H, NHBoc), 7.77 (t, *J*=5.2 Hz, 1H, NHCH$_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 27.1 (CH_2), 28.1 ($3CH_3$), 28.6 ($3CH_3$), 31.6 (CH_2), 41.9 (CH_2), 54.4 (CH), 60.3 (CH_2), 78.4 (C), 80.7 (C), 155.9 (C), 171.9 (C), 172.0 (C). Anal. Calcd for $C_{16}H_{30}N_2O_6$, H_2O: C, 52.73; H, 8.85; N, 7.69. Found: C, 52.51; H, 9.22; N, 7.32.

*4.1.3. tert-Butyl 1-(tert-butoxycarbonyl)-pyroglutamate (**3**).* *N*-Methylimidazole (0.031 g, 0.378 mmol) and Boc anhydride (0.907 g, 4.16 mmol) were added to a mixture of *tert*-butyl pyroglutamate **4** (0.700 g, 3.78 mmol) in *tert*-BuOH (15 mL) at 30 °C. The solution was stirred 10 min at this temperature, and then at room temperature for 3 h. Solvents were removed under vacuum, the residue was dissolved in ethyl acetate (30 mL), the solution was washed with water (2×10 mL) and the aqueous phases were extracted with ethyl acetate (2×20 mL). The combined organic phases were dried ($MgSO_4$), and the solvent was removed under vacuum. The residue was dissolved in absolute EtOH, and the solution was cooled at 0 °C to give of pure compound **3** (1.013 g, 94%) with the same properties as described in literature.[6b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 9H, (C*H*$_3$)$_3$C), 1.51 (s, 9H, (C*H*$_3$)$_3$C), 1.95–2.05 (m, 1H, CH$_2$C*H*$_2$CH), 2.24–2.35 (m, 1H, CH$_2$C*H*$_2$CH), 2.43–2.53 (m, 1H, C*H*$_2$CH$_2$CH), 2.55–2.66 (m, 1H, C*H*$_2$CH$_2$CH), 4.48 (dd, *J*=9.4, 2.7 Hz, 1H, CH$_2$CH$_2$C*H*).

*4.1.4. tert-Butyl pyroglutamate (**4**).* Triethylamine (14.5 g, 0.143 mol) was added to a stirred suspension of L-pyroglutamic acid **5** (5.2 g, 0.040 mol) in propylene carbonate (40 mL). Upon solubilization, zinc bromide (22.5 g, 0.100 mol) was slowly (30 min) added to the stirred solution to give a cloudy suspension (exothermic solubilization; cooling bath), then *tert*-butyl bromide (16.4 g, 0.120 mol) was added all at once. The mixture was heated for 15 h by using an oil bath (40 °C). The solvent was evaporated in part, and then water (150 mL) was added leading precipitation of a crystallized precipitate, which was washed with water (20 mL). The solid was dissolved in ethyl acetate, and the combined aqueous phases were extracted with ethyl acetate (3×40 mL), and then the organic phases were combined, washed with water (3×30 mL), dried ($MgSO_4$) then evaporated under reduced pressure (100 mmHg). Propylene carbonate was distilled under vacuum (0.3 mmHg) Bp=45 °C. Upon cooling, the residue crystallized to give pure product **4** (6.2 g, 82%) with the same properties as described in literature.[4d] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 9H, (C*H*$_3$)$_3$C), 2.13–2.23 (m, 1H, CH$_2$C*H*$_2$CH), 2.29–2.49 (m, 3H, C*H*$_2$C*H*$_2$CH), 4.14 (q, *J*=8.2, 5.5 Hz, 1H, CH$_2$CH$_2$C*H*), 6.23 (broad s, 1H, N*H*).

*4.1.5. tert-Butyl 1-(tert-butoxycarbonyl)-pyroglutamoylpyroglutamate (**6**).* A stirred mixture of pyroglutamic acid **5** (5.0 g, 38.7 mmol), Boc anhydride (16.9 g, 77.4 mmol), and DMAP (0.2 g, 1.6 mmol) in *tert*-BuOH (20 mL) was refluxed for 12 h under nitrogen atmosphere. Upon cooling at room temperature, solvent was removed under vacuum, and the residue was purified by flash chromatography (SiO_2, gradient *n*-heptane/ethyl acetate, 100/0 to 0/100), to give firstly compound **6** as an oil crystallizing in absolute EtOH to provide pure compound **6** (5.3 g, 70%) as a white solid; mp: 128–131 °C; IR ν cm^{-1}: 1794, 1746, 1708, 1225, 1147. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H, (C*H*$_3$)$_3$C), 1.48 (s, 9H, (C*H*$_3$)$_3$C), 2.05–2.15 (m, 2H, 2CH$_2$C*H*$_2$), 2.34–2.76 (m, 6H, 2C*H*$_2$C*H*$_2$), 4.71 (dd, *J*=9.8, 2.7 Hz, 1H, CH$_2$CH$_2$C*H*CO$_2^t$Bu), 5.74 (dd, *J*=9.4, 2.4 Hz, 1H, CH$_2$CH$_2$C*H*CON); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9 (CH_2), 21.7 (CH_2), 27.9 ($3CH_3$), 28.0 ($3CH_3$), 31.0 (CH_2), 31.6 (CH_2), 58.3 (CH), 59.6 (CH), 82.9 (C), 83.3 (C), 149.9 (C), 169.8 (C), 171.5 (C), 173.4 (C), 174.8 (C). Anal. Calcd for $C_{19}H_{28}N_2O_7$: C, 57.56; H, 7.12; N, 7.07. Found: C, 57.48; H, 7.51; N, 6.95. *tert*-Butyl pyroglutamate **4** (0.6 g, 9%) [4d] then Boc ester **3** (1.2 g, 11%) with the same properties as described in literature,[6b] were also isolated after purification by flash chromatography.

*4.1.6. tert-Butyl 5-oxoprolyl-5-oxoprolinate (**7**) and dihydro-1H,5H-dipyrrolo[1,2-a:1′,2′-d]pyrazine-3,5,8,10(2H,5aH,10aH)-tetrone (**8**).* Triethylamine (4.1 g, 40.6 mmol) was added to a stirred mixture of pyroglutamic acid **5** (5.0 g, 38.7 mmol) and Boc anhydride (8.9 g, 40.6 mmol) in MeCN (30 mL). A yellow solution was obtained, and after stirring the reaction mixture 27 h at room temperature, the solid formed was filtered to recover 0.6 g (12%) of starting pyroglutamic acid **5**. Volatiles were removed under reduced pressure and the residue was dissolved in absolute EtOH. The solid obtained upon cooling at 0 °C for 3 days gave dimer **8** (0.1 g, 2.3%) with the same physico-chemical properties as described in

the literature.[7c] The solvents were evaporated under vacuum, and the residue obtained upon evaporation was purified by automatic flash chromatography, with a gradient *n*-heptane/EtOAc from 100/0 to 80/20 to isolate firstly *tert*-butyl pyroglutamate **4** [4d] (0.28 g, 4%), then Boc ester **6** (1.23 g, 16%) with the same properties as already described, and then acid **7** (3.42 g, 52%) as a white solid; mp (EtOAc/*n*-heptane): 135–137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.48 (s, 9H, C(CH_3)$_3$), 2.33–2.77 (m, 7H, 2$CH_2$$CH_2$CH), 3.07–3.15 (m, 1H, C$H_2$$CH_2$CH), 4.67 (dd, *J*=9.8, 3.1 Hz, 1H, $CH_2$$CH_2$C*H*), 5.15 (sym m, 1H, $CH_2$$CH_2$C*H*), 6.40 (broad s, 1H, N*H*). Anal. Calcd for $C_{14}H_{20}N_2O_5$: C, 56.75; H, 6.80; N, 9.45. Found: C, 57.01; H, 6.92; N, 9.67.

*4.1.7. N^1,N^2-Di[1-tert-Butyl N-(tert-butoxycarbonyl)glutamoyl]ethylenediamine (**11**).* To a stirred solution of carbamate **3** (1.0 g, 3.50 mmol) in 1,2-dichloroethane (2.0 mL) was added via syringe 1,2-ethylene diamine (0.58 mL, 8.76 mmol). The resulting solution was stirred under reflux overnight. After cooling to room temperature the reaction mixture was concentrated under reduced pressure and purified by automatic flash chromatography with a gradient CH_2Cl_2/MeOH from 100/0 to 90/10 to isolate dimer **11**, (244 mg, 22%), light beige solid; mp (CH_2Cl_2/MeOH): 100–103 °C; R_f (CH_2Cl_2/MeOH: 9/1) 0.67; IR ν cm^{-1}: 3373, 3319, 1691, 1525, 1158; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 1.38 (s, 18H, 2(CH_3)$_3$C), 1.39 (s, 18H, 2(CH_3)$_3$C), 1.66–1.76 (m, 2H, CH_2CH), 1.84–1.92 (m, 2H, CH_2CH), 2.12 (t, *J*=7.6 Hz, 4H, 2CH_2C=O), 3.06 (s, 4H, 2CH_2NH), 3.74–3.79 (m, 2H, 2C*H*), 7.10 (d, *J*=7.9 Hz, 2H, 2N*H*Boc), 7.81 (broad s, 2H, 2N*H*CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 27.0 (2CH_2), 28.1 (6CH_3), 28.6 (6CH_3), 32.1 (2CH_2), 38.8 (2CH_2), 54.4 (2CH), 78.4 (2C), 80.7 (2C), 155.9 (2C), 171.9 (2C), 172.0 (2C). Anal. Calcd for $C_{30}H_{54}N_4O_{10}$, MeOH: C, 56.80; H, 8.73; N, 8.88. Found: C, 56.61; H, 9.58; N, 8.60. Aminoamide **1**, (106 mg, 27%) was also isolated, with the same properties as already described.

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