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One-pot synthesis of *N*-substituted pantolactams from pantolactone

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Abstract—*Rac-N*-substituted pantolactams (**5**) are readily obtained in medium to good yields by reaction of *rac*-pantolactone (**1**) with primary amines under acid catalysis, whether at 250°C in a pressure reactor or under microwave irradiation. It appears that the amine can react with pantolactone at the carbonyl carbon atom to give a hydroxyamide (**3**) in a reversible way and at the methylene carbon atom to give a γ-amino acid (**4**). The last one on dehydration would give the corresponding pantolactam (**5**). © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Several years ago we published the enzymatic resolution of 4,4-dimethyl-3-hydroxy-1-phenylpyrrolidin-2-one (*rac-N*-phenylpantolactam, **5a**)[1] and the application of the corresponding enantiomers as chiral auxiliaries in the asymmetric synthesis of several α-substituted carboxylic acids.[2–6] Later on, we described an efficient enantioselective preparation of both enantiomers of **5a** by oxidation of *rac*-**5a** to the corresponding ketolactam, followed by enantioselective reduction with (−)- or (+)-*B*-chlorodiisopinocamphenylborane [(−)- or (+)-DIP-Chloride].[7] The starting *rac*-**5a** used in these works was obtained in good yield (82%) as described by reaction of *rac*-pantolactone with an excess of aniline [about 13 equiv.] in the presence of a catalytic amount of *p*-TsOH (0.02 equiv.) under reflux (about 180°C) for 12 h.[8]

The excellent results obtained with **5a** prompted us to search for other *N*-substituted pantolactams with some added values such as: (a) pantolactams **5** having an amino substituent which would facilitate the separation and recovery of the chiral auxiliary through acid–base washings, and (b) pantolactams **5** having a substituent, such as hydroxyl, that would allow the chiral auxiliary to be anchored to a polymeric support. Herein we report the synthesis of several racemic *N*-substituted pantolactams, several of which bear additional amino or hydroxy groups, through alternative and general procedures, starting from pantolactone and primary amines.

2. Results and discussion

The easiest way to prepare the required *rac*-pantolactams **5** would be the direct reaction of pantolactone (**1**) with primary amines. However, there are many references to reactions of aliphatic and aromatic primary amines with **1** leading to the corresponding hydroxyamides **3** in good yields.[9–14] Moreover, the only additional pantolactams **5** described till now correspond to the unsubstituted (**5g**),[15] the *N*-methyl (**5d**),[16] and the *N*-(*p*-carboxyphenyl) derivatives.[8]

Pantolactams **5d** and **5g** are obtained by reaction of **1** with aqueous methylamine or ammonium hydroxide at high temperature in a closed vessel, while the *N*-(*p*-carboxyphenyl)pantolactam is prepared by a procedure similar to the above mentioned for the preparation of **5a**. Recently, the preparation in low yield of *O*-benzylpantolactam by reaction of *O*-benzylpantolactone with aqueous ammonia in a closed vessel at 230°C has also been described.[17] Pantolactam **5g** has also been prepared by dehydration of the corresponding γ-amino acid.[15]

Initial attempts to prepare new pantolactams **5** were carried out starting from benzylamine. Reaction of **1** with excess benzylamine (**2c**, about 15 equiv.) in the presence of *p*-TsOH (0.05 equiv.) under reflux for 22 h in a similar manner to that used to prepare **5a** allowed us to obtain pure

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5c in 42% yield (Table 1, entry 12). When the reaction was carried out under microwave irradiation using a much lower excess of the amine (2 equiv.) and *p*-TsOH (0.1 equiv.), **5c** was obtained in good yield (59%) with a very short reaction time (5 min) (Table 1, entry 10). Also, lactam **5c** was obtained in 73% yield by reacting **1** with **2c** (1.5 equiv.) catalyzed by *p*-TsOH (0.05 equiv.) in diglyme under reflux for 22 h (Table 1, entry 11).

Moreover, the known hydroxyamide **3c**[10] was prepared quantitatively by reaction of **1** with **2c** (1.4 equiv.) in refluxing methanol for 24 h. To gain insight into the mechanism of formation of **5c**, hydroxyamide **3c** was dissolved in diglyme and heated under reflux in the presence of *p*-TsOH (0.1 equiv.) to give **5c** in 69% yield, some pantolactone (about 14%) being also formed (Table 1, entry 13).

Similarly, the new hydroxyamide **3a**, obtained in 59% yield by reaction of **1** with the lithium derivative of aniline (**2a**, 4 equiv.) in anhydrous THF, heated in refluxing diglyme under *p*-TsOH catalysis for 15 h, gave **5a** (40% yield) and **1** (53% yield), after column chromatography separation of the reaction mixture (Table 1, entry 3).

Curiously, reaction of **1** with excess *n*-heptylamine (**2b**, 14 equiv.) catalyzed by *p*-TsOH (0.02 equiv.) under reflux gave the known hydroxyamide **3b**[9] in only 22% yield, no pantolactam **5b** being observed (Table 1, entry 8). Also, when **3b** was heated in diglyme under reflux using *p*-TsOH as catalyst, a mixture of starting **3b** and pantolactone was obtained (Table 1, entry 7). However, **5b** was isolated in 76% yield on reaction of **1** with **2b** (2 equiv.) catalyzed by *p*-TsOH (0.1 equiv.) under microwave irradiation in a sealed reactor for 10 min (Table 1, entry 6).

Moreover, pantolactam **5b** was obtained in 49% yield (Table 1, entry 5) when **1** was reacted with *n*-heptylamine (**2b**, 2.1 equiv.) in methanol solution under *p*-TsOH catalysis (0.1 equiv.) using more forcing reaction conditions (pressure reactor, 250°C, 4 h: standard conditions). Similarly, reaction of **1** with benzylamine (**2c**) under these conditions gave **5c** in 59% yield (Table 1, entry 9).

These results pointed to a mechanism for the pantolactam formation like that shown in Scheme 1. As expected, the reaction of **1** with a primary amine (**2**) would take place faster at the carbonyl function, probably through the addition–elimination mechanism,[9–14] than at the hindered

Table 1. Products and yields from the reactions of pantolactone **1** and amines **2**, or hydroxyamides **3**, with *p*-TsOH under different reaction conditions

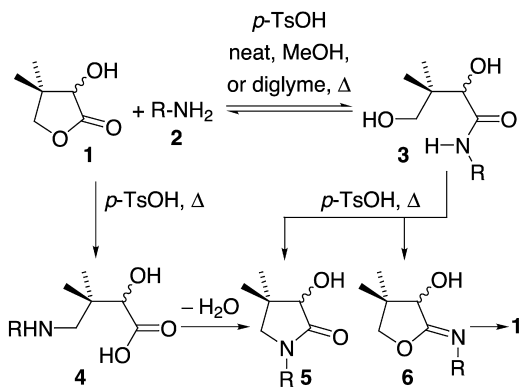
Entry	Starting compounds	Conditions[a] (time/power)	Products (yields)[b]
1	**1**+**2a**	A (4 h)	**5a** (93%)
2	**1**+**2a**	B (10 min/75 W)	**5a** (76%)
3	**3a**	C (15 h)	**1** (53%)[c]+**5a** (40%)[c]
4	**1**+**2a**	D (12 h)	**5a** (82%)[1]
5	**1**+**2b**	A (4 h)	**5b** (49%)
6	**1**+**2b**	B (10 min/75 W)	**5b** (76%)
7	**3b**	C (15 h)	**1** (41%)+**3b** (15%)
8	**1**+**2b**	D (15 h)	**3b** (22%)
9	**1**+**2c**	A (4 h)	**5c** (59%)
10	**1**+**2c**	B (5 min/90 W)	**5c** (59%)
11	**1**+**2c**	C (22 h)	**5c** (73%)
12	**1**+**2c**	D (22 h)	**5c** (42%)
13	**3c**	C (5 h)	**1** (14%)[c]+**5c** (69%)
14	**1**+**2d**	A (4 h)	**5d** (42%)
15	**3d**	A (4 h)	**5d** (39%)
16	**1**+**2e**	A (4 h)	**5e** (10.5%)
17	**1**+**2e**	A (8 h)	**5e** (16%)
18	**1**+**2e**	A (24 h)	**5e** (14%)
19	**1**+**2e**	B (30 min/30 W)	**5e** (11%)
20	**1**+**2f**	A (4 h)	**5f** (52%)
21	**1**+**2f**	B (5 min/120 W)	**5f** (59%)
22	**1**+**2g**	A (4 h)	**3g**+**5g** (19%+19%)[c]
23	**3g**	A (4 h)	**1** (40%)+**3g**+**5g** (9%+9%)[c]
24	**1**+**2h**	A (4 h)	**5h** (24%)
25	**1**+**2i**	A (4 h)	**5i** (34%)
26	**1**+**2i**	A (4 h)[d]	**3i** (72%)
27	**3i**	C (15 h)	**1** (67%)
28	**1**+**2j**	A (4 h)	**5j** (14%)
29	**1**+**2j**	A (8 h)	**5j** (5.5%)
30	**1**+**2k**	A (4 h)	**5k** (23%)
31	**1**+**2k**	B (10 min/150 W)	**5k** (46%)
32	**1**+**2l**	A (4 h)	**5l** (37%)
33	**1**+**2l**	A[e] (4 h)	**7** (24%)
34	**1**+**2l**	B[e] (25 min/90 W)	**7** (25%)

[a] Procedure A: **1**, **2** (2.1 equiv.) (or **3**) and *p*-TsOH·H_2O (0.1 equiv.) in MeOH (2 mL/g **1** or **3**) or ethanol (2 mL/g of **3**), 250°C, pressure reactor. Procedure B: **1**, **2** (2 equiv.) and *p*-TsOH·H_2O (0.1 equiv.), microwave, sealed pyrex vessel. Procedure C: **1**, **2** (1.5 equiv.) (or **3**) and *p*-TsOH·H_2O (0.05 equiv.) in diglyme (4–13 mL/g **1** or **3**), reflux. Procedure D: **1**, **2** (about 15 equiv.) and *p*-TsOH·H_2O (0.05 equiv.), reflux.
[b] Except where otherwise stated, yields refer to isolated products.
[c] Yield calculated from the ^{1}H NMR integration.
[d] This reaction was carried out at 180°C.
[e] In this case, 0.5 equiv. of the amine were used.

neopentyl-type methylene group, although it is known that several better nucleophiles such as the phthalimide[15] and the azide[18] anions react with **1** by attack at the methylene position to give the expected substitution products. Under acid catalysis and at high temperatures, formation of the hydroxyamide **3** could become an easily reversible reaction, as it was recently shown by Pansare and Jain.[19] On the contrary, if the reaction of the primary amine with **1** under acid catalysis at high temperature took place at the hindered methylene group, a γ-amino acid (**4**) would be formed, whose dehydration to **5** could be essentially irreversible.[15] The different behavior observed in the reaction of **1** with *n*-heptylamine vs aniline and benzylamine may be partly due to the lower boiling point (about 30°C) of the first amine (bp 155°C) compared with the other two (bp 184°C). The proposed mechanism is supported by the formation of pantolactone from hydroxyamides **3a** and **3c** under conditions in which **5a** and **5c** were also formed.

Alternatively, pantolactone could be formed from hydroxyamides **3** by acid-catalyzed intramolecular nucleophilic substitution of the hydroxyl group by the amide oxygen atom, followed by hydrolysis of the resulting iminolactones **6** (Scheme 1). Although the formation of pantolactams **5** from hydroxyamides **3** by a similar mechanism cannot be excluded, the low nucleophilic character of the amide nitrogen atom makes this mechanism less likely.

To study the scope of this method, the reactions of **1** with different primary amines were carried out, the results being collected in Table 1. First, the reaction of pantolactone with primary amines in which the amino group is connected to a primary, secondary or tertiary alkyl group was studied. Under these conditions, reaction of pantolactone with a methanolic solution of methylamine gave the expected pantolactam **5d** in 42% yield (Table 1, entry 14). Similarly, when hydroxyamide **3d** was submitted to the same reaction conditions, **5d** was obtained in a similar 39% yield (Table 1, entry 15). The more hindered cyclohexylamine, **2f**, gave lactam **5f** in 52% yield (Table 1, entry 20), while *t*-butylamine, **2e**, gave **5e** in only 16% yield, after 8 h reaction (Table 1, entry 17). Under standard conditions (4 h), the yield was only 10.5% (Table 1, entry 16), and on prolonged heating (24 h), the yield decreased slightly (Table 1, entry 18). In the reactions with *t*-butylamine, the formation of lactam **5g**, probably formed by dealkylation of lactam **5e**, was observed, a fact that could explain the slight decrease of the yield of this reaction at longer reaction times. Comparable yields of **5e** and **5f** (Table 1, entries 19 and 21, respectively) were obtained when these reactions were performed under microwave irradiation, although in these cases, the reaction times were much shorter.



a, R = C_6H_5; **b**, R = *n*-C_7H_{15}; **c**, R = $C_6H_5CH_2$;
d, R = Me; **e**, R = *t*-Bu; **f**, R = cyclohexyl;
g, R = H; **h**, R = CH_2CH_2OH; **i**, R = $CH_2CH_2CH_2NMe_2$;
j, R = 2-pyridyl; **k**, R = *p*-HO-C_6H_4; **l**, R = *p*-H_2N-C_6H_4

Scheme 1. Possible pathways for the formation of pantolactams **5** from pantolactone **1** and amines **2**, or from hydroxyamides **3**.

Reaction of pantolactone with a methanolic solution of ammonia in a pressure reactor under the standard conditions gave a mixture of the corresponding hydroxyamide **3g** and lactam **5g** in low yield which could not be separated by column chromatography or crystallization (Table 1, entry 22). Worthy of note, when hydroxyamide **3g** was submitted to the standard conditions to prepare pantolactams, after column chromatography of the reaction mixture, pantolactone and a mixture of **3g** and **5g** were obtained (Table 1, entry 23).

Then, the reaction was studied with primary aliphatic amines having an extra functionality (an amino or hydroxy group). Thus, reaction of pantolactone with 2-aminoethanol under the standard pressure reactor conditions gave the expected pantolactam **5h** in a low 24% yield (Table 1, entry 24). Apparently, 2-aminoethanol was partially decomposed under these conditions. Similarly, reaction of pantolactone with 3-(dimethylamino)propylamine, **2i**, gave pantolactam **5i** in a moderate 34% yield (Table 1, entry 25). Worthy of note, when the last reaction was carried out under less forcing conditions (180°C), only hydroxyamide **3i** was isolated in high yield (Table 1, entry 26). Moreover, heating hydroxyamide **3i** in the presence of *p*-TsOH in diglyme under reflux, **5i** was not observed, pantolactone **1** being formed instead in high yield (Table 1, entry 27). These results parallel those described above in the case of *n*-heptylamine, and confirmed the need of using forcing conditions to obtain the pantolactams **5**.

Finally, the reaction was studied with aromatic amines other than aniline. Reaction of **1** with 2-aminopyridine, **2j**, under standard pressure reactor conditions gave lactam **5j** in only 14% yield (Table 1, entry 28). Increasing the reaction time to 8 h, resulted in a decreased yield of 5.5% (Table 1, entry 29). The low yield of this reaction may be related to the presence of two nucleophilic centers in the 2-aminopyridine and the low nucleophilic character of its primary amino group.

Somewhat better results were obtained in the reaction of **1** with *p*-aminophenol, **2k**. Under the standard pressure reactor conditions, lactam **5k** was obtained in a moderate 23% yield (Table 1, entry 30). However, the yield of this reaction performed under microwave irradiation was much higher (46%, Table 1, entry 31).

Worthy of note, the reaction of **1** with *p*-phenylenediamine, **2l**, gave different products, depending on the pantolactone/diamine ratio. Under the standard pressure reactor conditions (ratio of pantolactone/amine of 1:2), the only

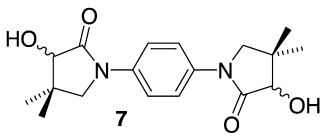


Figure 1. Structure of the bislactam **7**.

isolated product (37% yield) was the monoreaction lactam **5l** (Table 1, entry 32). However, carrying out the reaction with a ratio pantolactone/amine of 2:1, the only isolated product (24% yield) was product **7**, derived from the reaction of each primary amino group of **2l** with pantolactone (Fig. 1, and Table 1, entry 33). A similar result was obtained, when the last reaction was performed under microwave irradiation (Table 1, entry 34). The highly selective formation of **5l** in the reaction of **1** with **2l** in the ratio of 1:2 is in accord with the expected greater nucleophilicity of the *p*-phenylenediamine as compared with its monoacylated derivative **5l**.

3. Conclusion

We have developed two alternative one-pot procedures for the preparation of *N*-substituted pantolactams in low to medium yields starting from pantolactone and primary amines under acid catalysis. In one procedure the reaction is performed in a pressure reactor at 250°C for 4 h, while in the other one the reaction takes place in minutes under microwave irradiation. Work is in progress to convert several of the herein described new racemic pantolactams into the corresponding enantiopure compounds, to study their possible use as chiral auxiliaries suitable to be anchored to a polymeric support or easily recoverable through acid–base washings.

4. Experimental

4.1. General

Melting points were determined in open capillary tubes with a MFB 595010M Gallenkamp melting point apparatus. 300 MHz ^{1}H NMR and 75.4 MHz ^{13}C NMR spectra were recorded on a Varian Gemini 300 spectrometer and 200 MHz ^{1}H NMR spectra on a Varian Gemini 200 spectrometer. The chemical shifts are reported in ppm (δ scale) relative to internal TMS, and coupling constants are reported in Hertz (Hz). For the different compounds, the terms Hα or Hβ are assigned to hydrogen atoms which are *cis* or *trans* relative to the hydroxyl substituent, respectively. IR spectra were run on a FT/IR Perkin-Elmer model 1600 spectrophotometer. Absorption values are expressed as wave-numbers (cm^{-1}); only significant absorption bands are given. Column chromatography was performed on silica gel 60 AC.C (70–200 mesh, SDS, ref 2100027). Thin-layer chromatography (TLC) was performed with aluminum-backed sheets with silica gel 60 F_{254} (Merck, ref 1.05554), and the spots were visualized with UV light and 1% aqueous solution of $KMnO_4$. Pantolactone and all of the hydroxyamides and lactams prepared in this work are racemic. Commercial pantolactone was dried at 25°C/30 Torr for 12 h prior to its use. Analytical grade solvents were used for crystallization, while pure for synthesis solvents were used in the reactions, extractions and column chromatography. NMR spectra were performed at the Serveis Científico-Tècnics of the University of Barcelona, while elemental analyses were carried out at the Mycroanalysis Service of the IIQAB (CSIC, Barcelona, Spain).

4.1.1. 2,4-Dihydroxy-*N*-phenyl-3,3-dimethylbutyramide (3a). A solution of freshly distilled aniline (2.0 mL, 2.04 g, 21.9 mmol, 5.2 equiv.) in anhydrous THF (10 mL) was cooled at −78°C, and 1.6 M *n*-BuLi in hexanes (11.0 mL, 17.6 mmol, 4.2 equiv.) was added dropwise for 50 min. The mixture was warmed to 0°C and was stirred at this temperature for 3 h. To the resulting solution, a cooled solution (−78°C) of pantolactone, **1** (550 mg, 4.23 mmol) in anhydrous THF (1 mL) was added. The reaction mixture was allowed to warm up, was stirred at room temperature for 12 h, and was concentrated in vacuo, to give a black solid residue, which was diluted with water (30 mL) and extracted with AcOEt (3×30 mL). The combined organic extracts were dried over Na_2SO_4, and evaporated at reduced pressure, to give pure hydroxyamide **3a** (556 mg, 59% yield) as a light pink solid: mp 106–107°C (Et_2O); R_f 0.21 (SiO_2, hexane/AcOEt 1:1); IR (KBr) 3326, 3282, 1662, 1652; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (s, 3H) and 1.11 (s, 3H) [3-$(CH_3)_2$], 2.86 (broad s, 1H, 4-OH), 3.55 (broad d, $J\approx$11.0 Hz, 1H) and 3.65 (broad d, $J\approx$11.0 Hz, 1H) (4-H_2), 4.00 (d, J=4.5 Hz, 1H, 2-OH), 4.19 (d, J=4.5 Hz, 1H, 2-H), 7.13 (tt, J=7.5 Hz, J'=1.2 Hz, 1H, 4′-H), 7.34 [ddm, $J\approx J'\approx$8.0 Hz, 2H, 3′(5′)-H], 7.56 [dm, J=8.8 Hz, 2H, 2′(6′)-H], 8.61 (broad s, 1H, CONH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 20.4 (CH_3) and 21.0 (CH_3) [3-$(CH_3)_2$], 39.5 (C, C3), 71.4 (CH_2, C4), 77.7 (CH, C2), 120.1 [CH, C2′(6′)], 124.7 (CH, C4′), 129.0 [CH, C3′(5′)], 136.8 (C, C1′), 171.4 (C, C1). Anal. calcd for $C_{12}H_{17}NO_3\cdot 1/5H_2O$: C, 63.53; H, 7.73; N, 6.17. Found: C, 63.64; H, 7.68; N, 6.17.

4.2. General procedure for the preparation of hydroxyamides 3 from pantolactone, 1

To a solution of pantolactone, **1**, (1 mmol) in MeOH (0.35 mL) at 0°C was added the amine (1.3 equiv.), and the reaction mixture was stirred at room temperature until total conversion of the starting pantolactone was achieved as monitored by TLC (SiO_2). The resulting solution was evaporated at reduced pressure, to give a residue, which consisted of hydroxyamide **3**, pure or slightly impurified by the starting pantolactone, or by the amine, in the cases of the least volatile amines. Purification was carried out as indicated in each example.

4.2.1. *N*-Heptyl-2,4-dihydroxy-3,3-dimethylbutyramide (3b).[9] This compound was prepared following the above general procedure, from a solution of pantolactone, **1** (550 mg, 4.23 mmol) in MeOH (1.5 mL) and *n*-heptylamine (0.75 mL, 583 mg, 5.06 mmol) with a reaction time of 20 h. The colorless oil obtained by evaporation of the reaction mixture consisted of pure hydroxyamide **3b** (1.05 g, quantitative yield): R_f 0.14 (SiO_2, hexane/AcOEt 1:1); IR (NaCl) 3336, 1650; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J=6.9 Hz, 3H, 7′-H_3), 0.91 (s, 3H) and 1.00 (s, 3H) [3-$(CH_3)_2$], 1.22–1.36 (complex signal, 8H, 3′-H_2, 4′-H_2,

5′-H_2 and 6′-H_2), 1.52 (m, 2H, 2′-H_2), 3.15–3.37 (complex signal, 2H, 1′-H_2), 3.49 (s, 2H, 4-H_2), 3.92 (broad s, 1H) and 4.37 (broad s, 1H) (2-OH and 4-OH), 4.01 (s, 1H, 2-H), 6.92 (dd, $J \approx J' \approx 5.7$ Hz, 1H, CONH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.1 (CH_3, C7′), 20.1 (CH_3) and 21.4 (CH_3) [3-(CH_3)$_2$], 22.6 (CH_2, C6′), 26.9 (CH_2), 28.9 (CH_2), 29.5 (CH_2) and 31.7 (CH_2) (C2′, C3′, C4′ and C5′), 39.1 (CH_2, C1′), 39.3 (C, C3), 71.2 (CH_2, C4), 77.4 (CH, C2), 173.1 (C, C1).

4.2.2. *N*-Benzyl-2,4-dihydroxy-3,3-dimethylbutyramide (3c).[10] This compound was prepared following the above general procedure, from a solution of pantolactone, **1** (260 mg, 2.00 mmol) in MeOH (0.6 mL) and freshly distilled benzylamine (0.3 mL, 294 mg, 2.74 mmol, 1.4 equiv.) with a reaction time of 24 h. Evaporation of the reaction mixture afforded a yellowish oil, which solidified on standing, consisting of pure hydroxyamide **3c** (475 mg, quantitative yield): mp 78–79°C (Et_2O/hexane 5:3) [described 101–104°C (*tert*-butyl methyl ether/hexane)][10]; R_f 0.14 (SiO_2, hexane/AcOEt 1:1); IR (KBr) 3379, 3340, 3258, 1642; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.93 (s, 3H) and 1.03 (s, 3H) [3-(CH_3)$_2$], 3.48 (d, J=11.4 Hz, 1H) and 3.55 (d, $J \approx$11.4 Hz, 1H) (4-H_2), 3.1–3.4 (broad signal, 1H) and 3.6–3.9 (broad signal, 1H) (2-OH and 4-OH), 4.09 (s, 1H, 2-H), 4.42 (dd, $J \approx$14.6 Hz, J'=5.8 Hz, 1H) and 4.52 (dd, J=14.6 Hz, J'=5.8 Hz, 1H) (1′-H_2), 7.11 (broad signal, 1H, CONH), 7.22–7.40 (complex signal, 5H, Ar-H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 20.3 (CH_3) and 21.2 (CH_3) [3-(CH_3)$_2$], 39.4 (C, C3), 43.1 (CH_2, C1′), 71.2 (CH_2, C4), 77.4 (CH, C2), 127.4 (CH, C4″), 127.6 [CH, C2″(6″)], 128.6 [CH, C3″(5″)], 137.7 (C, C1″), 173.3 (C, C1).

Note. When the same reaction was carried out in refluxing diglyme (2 mL) for 22 h, hydroxyamide **3c** was obtained in 86% yield.

4.2.3. 2,4-Dihydroxy-3,3,*N*-trimethylbutyramide (3d).[11] This compound was prepared following the above general procedure, from a solution of pantolactone, **1** (1.00 g, 7.69 mmol) in MeOH (3 mL) and 40% aqueous solution of $MeNH_2$ (0.80 mL, 0.32 g, 10.3 mmol) with a reaction time of 3 h. The white solid obtained by evaporation of the reaction mixture consisted of pure hydroxyamide **3d** (1.24 g, quantitative yield): mp 81–82°C (AcOEt); R_f 0.40 (SiO_2, AcOEt/MeOH 9:1); IR (KBr) 3495, 3334, 3230, 1636; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (s, 3H) and 1.04 (s, 3H) [3-(CH_3)$_2$], 2.86 (d, J=5.1 Hz, 3H, NH–CH_3), 3.49 (d, J=11.4 Hz, 1H) and 3.55 (d, J=11.4 Hz, 1H) (4-H_2), 3.0–3.4 (broad signal, 1H) and 3.64 (broad signal, 1H) (2-OH and 4-OH), 4.05 (s, 1H, 2-H), 6.77 (broad s, 1H, N*H*–CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 20.2 (CH_3) and 21.2 (CH_3) [3-(CH_3)$_2$], 25.7 (CH_3, NH–CH_3), 39.3 (C, C3), 71.1 (CH_2, C4), 77.3 (CH, C2), 174.2 (C, C1); Anal. calcd for $C_7H_{15}NO_3$: C, 52.16; H, 9.38; N, 8.69. Found: C, 52.25; H, 9.43; N, 8.73.

4.2.4. 2,4-Dihydroxy-3,3-dimethylbutyramide (3g).[13] This compound was prepared following the above general procedure, from a solution of pantolactone, **1** (3.00 g, 23.1 mmol) in MeOH (9 mL) and 25% aqueous solution of NH_3 (4.2 mL, 61.8 mmol, 2.7 equiv.) with a reaction time of 14 h. The resulting transparent oily residue (3.00 g) was triturated with $CHCl_3$ (5 mL), to afford pure hydroxyamide **3g** (2.84 g, 84% yield) as a white solid: mp 125–127°C (distilled at 140–150°C/0.5 Torr) (described 128–130°C);[13] R_f 0.14 (SiO_2, AcOEt); IR (KBr) 3436, 3397, 3306, 3179, 1683; ^{1}H NMR (300 MHz, CD_3OD) δ 0.94 [s, 6H, 3-(CH_3)$_2$], 3.39 (d, J=11.1 Hz, 1H) and 3.48 (d, J=11.1 Hz, 1H) (4-H_2), 3.89 (s, 1H, 2-H), 4.89 (s, 2-OH, 4-OH and $CONH_2$); ^{13}C NMR (75.4 MHz, CD_3OD) δ 20.8 (CH_3) and 21.3 (CH_3) [3-(CH_3)$_2$], 40.1 (C, C3), 70.3 (CH_2, C4), 77.1 (CH, C2), 179.0 (C, C1).

4.2.5. *N*-[3-(Dimethylamino)propyl]-2,4-dihydroxy-3,3-dimethylbutyramide (3i). This compound was prepared following the above general procedure, from pantolactone, **1** (520 mg, 4.00 mmol) and 3-(dimethylamino)propylamine (0.6 mL, 487 mg, 4.77 mmol), but in refluxing dioxane (5.5 mL) for 5 h. The white solid obtained by evaporation of the reaction mixture consisted of pure hydroxyamide **3i** (892 mg, 96% yield): mp 68–69°C (Et_2O); R_f 0.18 (SiO_2, AcOEt/MeOH/25% aqueous solution of NH_4OH 50:50:0.4); IR (KBr) 3400, 3310, 3084, 1632; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (s, 3H) and 1.00 (s, 3H) [3-(CH_3)$_2$], 1.70 (dddd, $J \approx J' \approx J'' \approx J''' \approx 6.9$ Hz, 2H, 2′-H_2), 2.24 [s, 6H, N(CH_3)$_2$], 2.37 (dd, $J \approx J' \approx 6.9$ Hz, 2H, 3′-H_2), 3.25–3.41 (complex signal, 2H, 1′-H_2), 3.47 (s, 2H, 4-H_2), 3.96 (s, 1H, 2-H), 4.1–5.6 (broad signal, 2H, 2-OH and 4-OH), 7.65 (dd, $J \approx J' \approx 5.7$ Hz, 1H, CONH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 20.2 (CH_3) and 21.6 (CH_3) [3-(CH_3)$_2$], 26.7 (CH_2, C2′), 37.6 (CH_2, C3′), 39.3 (C, C3), 45.2 [CH_3, N(CH_3)$_2$], 57.3 (CH_2, C1′), 71.0 (CH_2, C4), 77.4 (CH, C2), 173.7 (C, C1). Anal. calcd for $C_{11}H_{24}N_2O_3 \cdot 3/4H_2O$: C, 53.74; H, 10.46; N, 11.39. Found: C, 53.74; H, 10.45; N, 11.22.

4.3. General procedure A for the preparation of lactams 5 from pantolactone, 1, or from hydroxyamides 3, under pressure

All the reactions were carried out in a pressure reactor from a solution of pantolactone, **1** (2.00 g, 15.4 mmol), amine **2** (2.1 equiv.) and *p*-TsOH·H_2O (0.29 g, 1.52 mmol, 0.1 equiv.) in MeOH (4 mL) or from a solution of hydroxyamide **3** (12.4–13.6 mmol) and *p*-TsOH·H_2O (0.1 equiv.) in MeOH or EtOH (4 mL). The reaction mixture is heated at 250°C for 4 h (reaching an internal pressure of 9.5–15 atm), then it is allowed to cool to room temperature and is concentrated in vacuo. Purification of the resulting oily residue through column chromatography (SiO_2, hexane/AcOEt/MeOH mixtures) affords the lactams **5**.

4.4. General procedure B for the preparation of lactams 5 from pantolactone, 1, under microwave irradiation

All the reactions were performed in a sealed cylindrical pyrex vessel using pantolactone, **1** (260 mg, 2.00 mmol), the amine (2 equiv.) and *p*-TsOH·H_2O (34.0 mg, 0.2 mmol, 0.1 equiv.). The mixture is introduced into the monomode reactor, Synthwave 402 Prolabo focused MW 2.45 GHz, at the powers and times indicated in each example. At the end of the reaction, after cooling down the mixture is extracted with AcOEt (3×20 mL), washed with 1 M HCl (2×20 mL), and dried over Na_2SO_4. Removal of the solvent and

purification by column chromatography affords the corresponding lactams **5**.

4.4.1. 3-Hydroxy-4,4-dimethyl-1-phenylpyrrolidin-2-one (5a).[8] *Method 1*. This compound was prepared according to the general procedure A. The resulting brown solid residue (5.10 g) was taken up in CH_2Cl_2 (90 mL) and was washed successively with 5N HCl (2×30 mL), saturated aqueous solution of $NaHCO_3$ (3×20 mL), and water (25 mL). The organic phase was dried over Na_2SO_4 and evaporated at reduced pressure, to afford pure lactam **5a** (2.95 g, 93% yield), as a light brown solid: mp 118–119°C (EtOH); R_f 0.33 (SiO_2, hexane/AcOEt 1:1).

Method 2. This compound was prepared according to the general procedure B, at a power of 75 W and with a reaction time of 10 min. On elution with AcOEt/petroleum ether 2:1, pure lactam **5a** (312 mg, 76% yield) was isolated.

*Method 3. From hydroxyamide **3a** in diglyme under reflux*. A solution of hydroxyamide **3a** (150 mg, 0.67 mmol) and *p*-TsOH·H_2O (9.0 mg, 47.3 μmol, 0.07 equiv.) in diglyme (1 mL) was heated under reflux for 15 h, was allowed to cool to room temperature, and was submitted to column chromatography (SiO_2, hexane/AcOEt mixtures). On elution with hexane/AcOEt 90:10, a mixture of lactam **5a** and pantolactone, **1**, in an approximate ratio of 43:57 (^{1}H NMR) was isolated (54.5 mg of **5a**, 40% yield; 46.5 mg of **1**, 53% yield).

4.4.2. 1-Heptyl-3-hydroxy-4,4-dimethylpyrrolidin-2-one (5b). *Method 1*. This compound was prepared according to the general procedure A. On elution with AcOEt, pure lactam **5b** (1.72 g, 49% yield) was isolated as a yellowish solid: mp 66–68°C (distilled at 80°C/0.5 Torr); R_f 0.36 (SiO_2, AcOEt); IR (KBr) 3260, 1670; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J=6.9 Hz, 3H, 7′-H_3), 1.03 (s, 3H, 4α-CH_3), 1.22 (s, 3H, 4β-CH_3), 1.23–1.34 (complex signal, 8H, 3′-H_2, 4′-H_2, 5′-H_2 and 6′-H_2), 1.49 (m, 2H, 2′-H_2), 2.96 (d, J=9.6 Hz, 1H, 5α-H), 3.08 (d, J=9.6 Hz, 1H, 5β-H), 3.23 (ddd, $J\approx$13.8 Hz, $J'\approx J''\approx$7.2 Hz, 1H) and 3.29 (ddd, $J\approx$13.8 Hz, $J'\approx J''\approx$6.9 Hz, 1H) (1′-H_2), 3.98 (s, 1H, 3-H), 4.07 (broad s, 1H, 3-OH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.1 (CH_3, C7′), 20.2 (CH_3, 4α-CH_3), 22.6 (CH_2, C6′), 24.9 (CH_3, 4β-CH_3), 26.7 (CH_2), 27.1 (CH_2) and 28.9 (CH_2) (C2′, C3′ and C4′), 31.7 (CH_2, C5′), 38.7 (C, C4), 42.8 (CH_2, C1′), 57.0 (CH_2, C5), 77.8 (CH, C3), 174.3 (C, C2). Anal. calcd for $C_{13}H_{25}NO_2$: C, 68.68; H, 11.08; N, 6.16. Found: C, 69.01; H, 11.42; N, 6.23.

Method 2. This compound was prepared according to the general procedure B, at a power of 75 W and with a reaction time of 10 min. On elution with AcOEt/petroleum ether 3:1, pure lactam **5b** (345 mg, 76% yield) was isolated.

*Method 3. Attempted preparation of **5b** from hydroxyamide **3b***. This reaction was carried out as described for the preparation of **5a** (Method 3), from a solution of hydroxyamide **3b** (228 mg, 0.93 mmol) and *p*-TsOH·H_2O (9.0 mg, 47.3 μmol, 0.05 equiv.) in diglyme (1 mL). After removal of the solvent by distillation at 75°C/2 Torr, the remaining oily residue (220 mg), consisting mainly of hydroxyamide **3b** and pantolactone was submitted to column chromatography (SiO_2, hexane/AcOEt mixtures). On elution with hexane/AcOEt 70:30, pantolactone, **1** (49.0 mg, 41% yield; 47% yield based on unrecovered **3b**), and starting **3b** (33.4 mg) were successively isolated.

*Method 4. Attempted preparation of **5b** from pantolactone in refluxing* n-*heptylamine*. A solution of pantolactone, **1** (260 mg, 2.00 mmol) and *p*-TsOH·H_2O (8.0 mg, 42.1 μmol, 0.02 equiv.) in *n*-heptylamine (4.2 mL, 3.26 g, 28.3 mmol, 14 equiv.) was heated under reflux for 15 h, was allowed to cool to room temperature, diluted with CH_2Cl_2 (2 mL), and washed successively with 4N HCl (3×1.5 mL) and with saturated aqueous solution of $NaHCO_3$ (3×1.5 mL). The organic phase was dried over Na_2SO_4 and evaporated at reduced pressure, to give hydroxyamide **3b** (110 mg, 22% yield).

4.4.3. 1-Benzyl-3-hydroxy-4,4-dimethylpyrrolidin-2-one (5c). *Method 1*. This compound was prepared according to the general procedure A. On elution with hexane/AcOEt 40:60, pure lactam **5c** (2.00 g, 59% yield) was isolated as a yellowish solid: mp 82–83°C (distilled at 81°C/0.4 Torr); R_f 0.38 (SiO_2, AcOEt); IR (KBr) 3317, 1684; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 3H, 4α-CH_3), 1.17 (s, 3H, 4β-CH_3), 2.85 (d, J=9.9 Hz, 1H, 5α-H), 2.96 (d, J=9.9 Hz, 1H, 5β-H), 3.2–3.8 (broad signal, 1H, 3-OH), 4.04 (s, 1H, 3-H), 4.37 (d, J=14.4 Hz, 1H) and 4.52 (d, $J\approx$14.4 Hz, 1H) (1′-H_2), 7.20–7.37 (complex signal, 5H, Ar-H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 20.1 (CH_3, 4α-CH_3), 24.8 (CH_3, 4β-CH_3), 38.5 (C, C4), 46.8 (CH_2, benzyl CH_2), 56.3 (CH_2, C5), 77.8 (CH, C3), 127.7 (CH, Ar–C4), 128.2 [CH, Ar–C2(6)], 128.6 [CH, Ar–C3(5)], 135.6 (C, Ar–C1), 174.6 (C, C2). Anal. calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.33; H, 7.97; N, 6.50.

Method 2. This compound was prepared according to the general procedure B, at a power of 90 W and with a reaction time of 5 min. On elution with AcOEt/petroleum ether 2:1, pure lactam **5c** (258 mg, 59% yield) was isolated.

Method 3. By reaction of pantolactone with benzylamine under reflux. A solution of pantolactone, **1** (240 mg, 1.85 mmol) and *p*-TsOH·H_2O (17.2 mg, 0.09 mmol, 0.05 equiv.) in freshly distilled *n*-benzylamine (3 mL, 2.94 g, 27.4 mmol, 14.8 equiv.) was heated under reflux for 22 h, was allowed to cool to room temperature, was diluted with CH_2Cl_2 (10 mL), and washed successively with 5N HCl (3×5 mL) and saturated aqueous solution of $NaHCO_3$ (3×5 mL). The organic layer was dried over Na_2SO_4 and evaporated at reduced pressure, to give a yellow oil (450 mg), which consisted of lactam **5c** impurified with starting benzylamine (^{1}H NMR). This residue was taken up in AcOEt (15 mL) and was washed successively with 2N HCl (3×10 mL) and water (10 mL). The organic phase was dried over Na_2SO_4 and evaporated at reduced pressure, affording pure lactam **5c** (170 mg, 42% yield).

Method 4. By reaction of pantolactone with benzylamine in diglyme under reflux. A solution of pantolactone, **1** (260 mg, 2.00 mmol), freshly distilled benzylamine (0.3 mL, 294 mg, 2.74 mmol, 1.48 equiv.), and *p*-TsOH·H_2O (19.0 mg, 0.10 mmol, 0.05 equiv.) in diglyme (2 mL) was heated

under reflux for 22 h, was allowed to cool to room temperature, was diluted with water (5 mL), and was extracted with AcOEt (3×10 mL). The combined organic extracts were washed successively with 5N HCl (2×5 mL) and water (2×5 mL), dried over Na_2SO_4, and evaporated at reduced pressure, to give pure lactam **5c** (318 mg, 73% yield).

*Method 5. From hydroxyamide **3c** in diglyme under reflux*. Lactam **5c** was alternatively obtained as described for **5a** (Method 3), from a solution of hydroxyamide **3c** (77.8 mg, 0.33 mmol) and *p*-TsOH·H_2O (6.3 mg, 33.1 μmol, 0.1 equiv.) in diglyme (1 mL) for 5 h. After distillation of the reaction mixture at 60°C/2 Torr, the remaining yellow oily residue (75 mg), consisting of a mixture of lactam **5c**/pantolactone/diglyme in an approximate ratio of 76:12:12 (^{1}H NMR), was submitted to column chromatography (SiO_2, hexane/AcOEt mixtures). On elution with hexane/AcOEt 50:50, pure lactam **5c** (50 mg, 69% yield) was isolated.

4.4.4. 3-Hydroxy-4,4,*N*-trimethylpyrrolidin-2-one (5d).[16] *Method 1*. This compound was prepared according to the general procedure A. On elution with AcOEt, pure lactam **5d** (0.93 g, 42% yield) was isolated as a yellowish solid: mp 86–87°C (AcOEt/pentane 1:1) [described 75°C (AcOEt/petroleum ether)];[16] R_f 0.20 (SiO_2, AcOEt); IR (KBr) 3318, 1700; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 3H, 4α-CH_3), 1.22 (s, 3H, 4β-CH_3), 2.87 (broad s, 3H, N–CH_3), 2.96 (d, *J*=9.9 Hz, 1H, 5α-H), 3.12 (d, *J*=9.9 Hz, 1H, 5β-H), 3.4–3.9 (broad signal, 1H, 3-OH), 3.96 (d, *J*=0.6 Hz, 1H, 3-H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 20.3 (CH_3, 4α-CH_3), 24.9 (CH_3, 4β-CH_3), 30.0 (CH_3, N–CH_3), 38.4 (C, C4), 59.4 (CH_2, C5), 77.4 (CH, C3), 174.8 (C, C2). Anal. calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.68; H, 9.28; N, 9.76.

Method 2. Lactam **5d** was alternatively prepared through the general procedure A, starting from a solution of hydroxyamide **3d** (2.00 g, 12.4 mmol) and *p*-TsOH·H_2O (0.24 g, 1.26 mmol, 0.1 equiv.) in EtOH (4 mL). On elution with AcOEt, pure lactam **5d** (0.70 g, 39% yield) was isolated as a yellowish solid.

4.4.5. 1-*tert*-Butyl-3-hydroxy-4,4-dimethylpyrrolidin-2-one (5e). *Method 1*. This compound was prepared according to the general procedure A with a reaction time of 8 h. On elution with AcOEt, pure lactam **5e** (0.45 g, 16% yield) was isolated as a yellowish solid: mp 117–119°C (AcOEt); R_f 0.47 (SiO_2, AcOEt); IR (KBr) 3332, 1674; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 3H, 4α-CH_3), 1.20 (s, 3H, 4β-CH_3), 1.38 [s, 9H, N–C(CH_3)$_3$], 2.90 (broad s, 1H, 3-OH), 3.06 (d, *J*=9.6 Hz, 1H, 5α-H), 3.10 (d, *J*≈9.6 Hz, 1H, 5β-H), 3.84 (s, 1H, 3-H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 19.6 (CH_3, 4α-CH_3), 24.6 (CH_3, 4β-CH_3), 27.5 [CH_3, N–C(*C*H_3)$_3$], 38.2 (C, C4), 54.0 [C, N–*C*(CH_3)$_3$], 55.0 (CH_2, C5), 78.2 (CH, C3), 174.3 (C, C2). Anal. calcd for $C_{10}H_{19}NO_2$·0.1H_2O: C, 64.21; H, 10.35; N, 7.49. Found: C, 64.12; H, 10.67; N, 7.49.

Method 2. This compound was prepared according to the general method B, at a power of 30 W, with a reaction time of 30 min, and using 8 equiv. of amine. On elution with AcOEt/petroleum ether 2:1, pure lactam **5e** (40.7 mg, 11% yield) was isolated.

4.4.6. 1-Cyclohexyl-3-hydroxy-4,4-dimethylpyrrolidin-2-one (5f). *Method 1*. This compound was prepared according to the general procedure A. After addition of CH_2Cl_2 (10 mL) to the resulting brown oily residue (4.43 g), pure lactam **5f** (0.95 g) precipitated as a light brown solid, which was separated by filtration in vacuo. The filtrate was evaporated at reduced pressure and the resulting residue was submitted to column chromatography (SiO_2, AcOEt), affording an additional crop of **5f** (0.76 g, 52% total yield) as a yellowish solid: mp 174–175°C (sublimed at 110°C/0.5 Torr); R_f 0.31 (SiO_2, AcOEt); IR (KBr) 3267, 1662; ^{1}H NMR (300 MHz, CD_3OD) δ 0.95 (s, 3H, 4α-CH_3), 1.15 (s, 3H, 4β-CH_3), 1.28–1.53 (complex signal, 5H), 1.58–1.72 (complex signal, 3H) and 1.75–1.86 (complex signal, 2H) (2′-H_2, 3′-H_2, 4′-H_2, 5′-H_2 and 6′-H_2), 3.03 (d, *J*=9.9 Hz, 1H, 5α-H), 3.07 (d, *J*=9.9 Hz, 1H, 5β-H), 3.82 (m, 1H, 1′-H), 3.90 (s, 1H, 3-H), 4.89 (s, OH); ^{13}C NMR (75.4 MHz, CD_3OD) δ 20.3 (CH_3, 4α-CH_3), 24.7 (CH_3, 4β-CH_3), 26.4 ($2CH_2$) and 26.6 (CH_2) (C3′, C4′ and C5′), 30.5 (CH_2) and 31.1 (CH_2) (C2′ and C6′), 39.7 (C, C4), 52.1 (CH, C1′), 53.6 (CH_2, C5), 79.5 (CH, C3), 175.2 (C, C2). Anal. calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.08; H, 10.08; N, 6.63.

Method 2. This compound was prepared according to the general procedure B, at a power of 120 W and with a reaction time of 5 min. On elution with AcOEt/petroleum ether 2:1, pure lactam **5f** (249 mg, 59% yield) was isolated.

4.4.7. 3-Hydroxy-4,4-dimethylpyrrolidin-2-one (5g).[15] *Method 1*. This compound was prepared according to the general procedure A. On elution with AcOEt, a mixture of lactam **5g** and hydroxyamide **3g** in an approximate ratio of 1:1 (^{1}H NMR) [0.80 g; 374 mg of **5g**, 19% yield; 426 mg of **3g**, 19% yield] was isolated as a yellowish solid. Spectroscopic data of **5g**, deduced from the spectra of the mixture with **3g**: ^{1}H NMR (200 MHz, DMSO-d_6) δ 0.85 (s, 3H, 4α-CH_3), 1.03 (s, 3H, 4β-CH_3), 2.76–2.94 (complex signal, 2H, 5α-H and 5β-H), 3.63 (m, 1H, 3-H), 5.30 (m, 1H, 3-OH), 7.54 (broad s, 1H, 1-H); ^{13}C NMR (50.3 MHz, DMSO-d_6) δ 20.4 (CH_3, 4α-CH_3), 25.0 (CH_3, 4β-CH_3), 40.0 (C, C4), 51.0 (CH_2, C5), 76.8 (CH, C3), 175.8 (C, C2).

Method 2. Lactam **5g** was alternatively prepared through the general procedure A, starting from a solution of hydroxyamide **3g** (2.00 g, 13.6 mmol) and *p*-TsOH·H_2O (0.27 g, 1.42 mmol, 0.1 equiv.) in MeOH (4 mL). On elution with AcOEt, pantolactone, **1** (0.71 g, 40% yield), and a mixture of lactam **5g** and starting **3g** in an approximate ratio of 1:1 (^{1}H NMR) [340 mg; 159 mg of **5g**, 9% yield] were successively isolated.

4.4.8. 3-Hydroxy-1-(2-hydroxyethyl)-4,4-dimethylpyrrolidin-2-one (5h). This compound was prepared according to the general procedure A. On elution with AcOEt/MeOH 98:2, pure lactam **5h** (0.63 g, 24% yield) was isolated as a yellowish solid: mp 76–79°C (distilled at 125°C/0.5 Torr); R_f 0.15 (SiO_2, AcOEt/MeOH 3:2); IR (KBr) 3392, 1684; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 3H, 4α-CH_3), 1.23 (s, 3H, 4β-CH_3), 1.84 (broad signal, 1H, 2′-OH), 3.07 (d,

$J\approx$9.9 Hz, 1H, 5α-H), 3.23 (d, $J\approx$9.9 Hz, 1H, 5β-H), 3.40 (ddd, J=14.2 Hz, $J'=J''$=5.4 Hz, 1H) and 3.46 (ddd, J=14.2 Hz, $J'=J''$=5.1 Hz, 1H) (1′-H_2), superimposed 3.36–3.50 (1H, 3-OH), 3.77 (broad dd, $J\approx J'\approx$5.2 Hz, 2H, 2′-H_2), 4.00 (s, 1H, 3-H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 20.2 (CH_3, 4α-CH_3), 24.8 (CH_3, 4β-CH_3), 38.9 (C, C4), 46.2 (CH_2, C1′), 58.3 (CH_2, C5), 59.9 (CH_2, C2′), 77.8 (CH, C3), 175.6 (C, C2). Anal. calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.40; H, 8.94; N, 8.42.

4.4.9. 1-[3-(Dimethylamino)propyl]-3-hydroxy-4,4-dimethylpyrrolidin-2-one (5i). *Method 1*. This compound was prepared according to the general procedure A. On elution with AcOEt/MeOH/25% aqueous solution of NH_4OH 80:20:0.7, pure lactam **5i** (1.11 g, 34% yield), was isolated as a brown oil: R_f 0.14 (SiO_2, AcOEt/MeOH/25% aqueous solution of NH_4OH 5:5:0.04); IR (NaCl) 3336, 1687; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 3H, 4α-CH_3), 1.21 (s, 3H, 4β-CH_3), 1.68 (m, 2H, 2′-H_2), 2.19–2.29 (m, 2H, 3′-H_2), 2.21 [s, 6H, N(CH_3)$_2$], 2.99 (d, J=9.6 Hz, 1H, 5α-H), 3.09 (d, J=9.6 Hz, 1H, 5β-H), 3.31 (dd, $J\approx J'\approx$7.2 Hz, 2H, 1′-H_2), 3.5–4.0 (broad signal, 3-OH), 3.94 (s, 1H, 3-H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 20.2 (CH_3, 4α-CH_3), 24.9 (CH_3, 4β-CH_3), 25.4 (CH_2, C2′), 38.7 (C, C4), 41.0 (CH_2, C3′), 45.4 [CH_3, N(CH_3)$_2$], 56.9 (CH_2) and 57.1 (CH_2) (C5 and C1′), 77.8 (CH, C3), 174.3 (C, C2). Anal. calcd for $C_{11}H_{22}N_2O_2\cdot 1/5H_2O$: C, 60.63; H, 10.36; N, 12.86. Found: C, 60.68; H, 10.42; N, 13.16.

Note. When the above reaction was carried out heating at 180°C, hydroxyamide **3i** (2.56 g, 72% yield) was obtained instead of lactam **5i**.

*Method 2. Attempted preparation of **5i** from hydroxyamide **3i** in diglyme under reflux*. In an attempted synthesis of lactam **5i** from a solution of hydroxyamide **3i** (1.00 g, 4.31 mmol) and *p*-TsOH·H_2O (84.0 mg, 0.44 mmol, 0.1 equiv.) in diglyme (7 mL) in a similar way to that described for **5a** (Method 3), pantolactone, **1** (373 mg, 67% yield) was obtained instead.

4.4.10. 3-Hydroxy-4,4-dimethyl-1-(2-pyridyl)pyrrolidin-2-one (5j). This compound was prepared according to the general procedure A. On elution with AcOEt, a mixture of lactam **5j**, pantolactone and starting 2-aminopyridine in an approximate ratio of 3:1:0.7 (^{1}H NMR) (0.54 g) was isolated, from which pantolactone and 2-aminopyridine were mostly removed by distillation at 70–80°C/1 Torr. The residue, consisting of almost pure lactam **5j** (0.43 g, 14% yield) was obtained as a yellowish solid: mp 110–111°C (isopropanol); R_f 0.52 (SiO_2, AcOEt); IR (KBr) 3365, 1690; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 3H, 4α-CH_3), 1.34 (s, 3H, 4β-CH_3), 2.83 (broad d, $J\approx$2.4 Hz, 1H, 3-OH), 3.56 (dd, J=11.1 Hz, $J'\approx$0.5 Hz, 1H, 5α-H), 4.00 (d, J=11.1 Hz, 1H, 5β-H), 4.16 (d, J=2.4 Hz, 1H, 3-H), 7.07 (ddd, J=7.2 Hz, J'=4.8 Hz, J''=0.9 Hz, 1H, 5′-H), 7.72 (ddd, J=8.4 Hz, J'=7.2 Hz, J''=2.0 Hz, 1H, 4′-H), superimposed in part 8.36 (ddd, J=4.8 Hz, J'=2.0 Hz, J''=0.9 Hz, 1H, 6′-H), 8.38 (ddd, J=8.4 Hz, $J'=J''$=0.9 Hz, 1H, 3′-H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 19.9 (CH_3, 4α-CH_3), 24.5 (CH_3, 4β-CH_3), 37.8 (C, C4), 55.7 (CH_2, C5), 79.0 (CH, C3), 114.7 (CH, C3′), 119.8 (CH, C5′), 137.8 (CH, C4′), 147.5 (CH, C6′), 151.2 (C, C2′), 174.4 (C, C2). Anal. calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.85; N, 13.58. Found: C, 63.83; H, 7.03; N, 13.26.

4.4.11. 3-Hydroxy-1-(4-hydroxyphenyl)-4,4-dimethylpyrrolidin-2-one (5k). *Method 1*. This compound was prepared according to the general procedure A. On elution with AcOEt, a mixture of lactam **5k** and starting pantolactone (2.40 g) in an approximate ratio of 3:1 (^{1}H NMR) was isolated. This mixture was taken up in MeOH (75 mL), heated under reflux, treated with active charcoal, and filtered through a short pad of Celite™. The resulting filtrate was evaporated under reduced pressure to give a solid residue (1.67 g), which was triturated with $CHCl_3$ (9 mL), affording pure lactam **5k** (0.77 g, 23% yield) as a light brown solid: mp 185–186°C (acetonitrile); R_f 0.46 (SiO_2, AcOEt); IR (KBr) 3308, 3265, 1666 (C=O st); ^{1}H NMR (300 MHz, CD_3OD) δ 1.06 (s, 3H, 4α-CH_3), 1.24 (s, 3H, 4β-CH_3), 3.38 (d, $J\approx$9.9 Hz, 1H, 5α-H), 3.55 (d, $J\approx$9.9 Hz, 1H, 5β-H), 4.06 (s, 1H, 3-H), 4.88 (s, 3-OH and 4′-OH), 6.78 [dm, $J\approx$9.0 Hz, 2H, 3′(5′)-H], 7.35 [dm, $J\approx$9.0 Hz, 2H, 2′(6′)-H]; ^{13}C NMR (75.4 MHz, CD_3OD) δ 20.3 (CH_3, 4α-CH_3), 24.6 (CH_3, 4β-CH_3), 39.5 (C, C4), 59.5 (CH_2, C5), 79.5 (CH, C3), 116.3 [CH, C3′(5′)], 123.5 [CH, C2′(6′)], 132.5 (C, C1′), 156.2 (C, C4′), 174.9 (C, C2). Anal. calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.31; H, 7.00; N, 6.47.

Method 2. This compound was prepared according to the general procedure B, at a power of 150 W, with a reaction time of 10 min, and using 3 equiv. of amine in xylene (8 mL). On elution with AcOEt/petroleum ether 1:1, pure lactam **5k** (203 mg, 46% yield) was isolated.

4.4.12. 1-(4-Aminophenyl)-3-hydroxy-4,4-dimethylpyrrolidin-2-one (5l). This compound was prepared according to the general procedure A. On elution with AcOEt, pure lactam **5l** (1.25 g, 37% yield) was isolated as a light brown solid: mp 206–207°C (sublimed at 185°C/1 Torr); R_f 0.45 (SiO_2, AcOEt); IR (KBr) 3446, 3360, 1684; ^{1}H NMR (300 MHz, CD_3OD) δ 1.05 (s, 3H, 4α-CH_3), 1.24 (s, 3H, 4β-CH_3), 3.35 (d, J=9.6 Hz, 1H, 5α-H), 3.53 (d, $J\approx$9.6 Hz, 1H, 5β-H), 4.05 (s, 1H, 3-H), 4.89 (s, OH and NH_2), 6.72 [dm, $J\approx$9.0 Hz, 2H, 3′(5′)-H], 7.25 [dm, $J\approx$9.0 Hz, 2H, 2′(6′)-H]; ^{13}C NMR (75.4 MHz, CD_3OD) δ 20.4 (CH_3, 4α-CH_3), 24.6 (CH_3, 4β-CH_3), 39.5 (C, C4), 59.6 (CH_2, C5), 79.5 (CH, C3), 116.4 [CH, C3′(5′)], 123.4 [CH, C2′(6′)], 131.2 (C, C1′), 146.7 (C, C4′), 174.8 (C, C2). Anal. calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.28; H, 7.44; N, 12.91.

4.4.13. Stereoisomeric mixture of (+)-, (−)-, and *meso*-3-hydroxy-1-[4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)phenyl]-4,4-dimethylpyrrolidin-2-one (7). *Method 1*. This compound was prepared according to the general procedure A, but with 0.5 equiv. of the amine. On elution with AcOEt, pure bis-lactam **7** (0.62 g, 24% yield) was isolated as a light brown solid: mp 253–254°C (acetonitrile); R_f 0.28 (SiO_2, AcOEt); IR (KBr) 3458, 3384, 3326, 1712, 1689, 1666; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.92 (s, 6H, 4α-CH_3), 1.16 (s, 6H, 4β-CH_3), 3.40 (broad d, J=9.3 Hz, 2H, 5α-H), 3.51 (broad d, J=9.3 Hz, 2H, 5β-H), 3.96 (d, J=5.7 Hz, 2H, 3-H), 5.71 (d, J=5.7 Hz, 3-OH), 7.63 (s, 4H, Ar-H); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ 20.3

(CH_3, 4α-CH_3), 24.3 (CH_3, 4β-CH_3), 37.6 (C, C4), 56.6 (CH_2, C5), 77.6 (CH, C3), 119.4 (CH, Ar–CH), 135.8 (C, Ar–C), 173.3 (C, C2). Anal. calcd for $C_{18}H_{24}N_2O_4 \cdot 1/2H_2O$: C, 63.33; H, 7.38; N, 8.21. Found: C, 63.35; H, 7.31; N, 8.32.

Method 2. This compound was prepared according to the general procedure B, at a power of 90 W, with a reaction time of 25 min, and using 0.5 equiv. of amine in DMF (10 mL). On elution with AcOEt, pure bis-lactam **7** (83.0 mg, 25% yield) was isolated.

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