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Chameleonic reactivity of α-amino nitrile-derived ureas. Synthesis of highly functionalized imidazolidin-2-one and imidazolidine-2,4-dione derivatives

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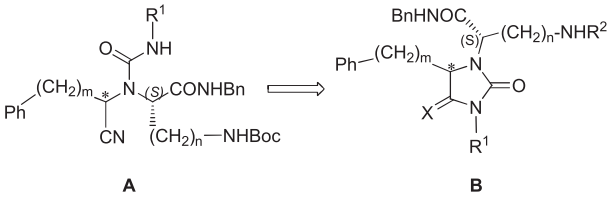
ABSTRACT

The potential of α-amino nitrile-derived ureas for the synthesis of imidazolidin-2-one derivatives has been studied in the context of a medicinal chemistry project focused on the search of antagonists of the thrombin receptor PAR1. In this study α-amino nitrile-derived ureas have shown chameleonic reactivity. Thus, under neutral, basic or mild acid media they cyclize to 4-iminoimidazolidin-2-one derivatives, which tautomerize to 4-amino-2,3-dihydro-1*H*-imidazol-2-ones. This tautomerism triggers epimerization at the C_5 of the imidazolidine ring, as well as its oxidation. However, they give stable highly functionalized hydantoin derivatives under strong acid media, by a no-epimerizing two-step hydrolysis.

1. Introduction

Diverse analogues of α-amino nitrile-derived ureas have been described as inhibitors of the cholesteryl ester transfer protein[1] and diverse enzymes, such as dipeptidyl peptidase IV,[2–4] prolyl oligopeptidases,[5] and cysteine cathepsins,[6,7] as well as agents for neurological disorders,[8] pesticides,[9] and fungicides.[10] On the other hand, α-amino nitrile-derived ureas are intermediates in the synthesis of diverse pharmacologically active hydantoin derivatives from α-amino nitriles.[11–13] In view of these precedents and in the context of a medicinal chemistry project focused on the search of antagonists of the thrombin receptor PAR1,[14,15] by exploring the use of α-amino acid-derived amino nitriles as molecular diversity generators,[16] we have recently described a versatile solvent-free synthesis of basic amino acid-derived *N*-(cyanomethyl)ureas of general formula A.[17] Now, taking into account that hydantoins (imidazolidine-2,4-diones) are included among privileged scaffolds in medicinal chemistry,[18,19] natural products,[20–26] and organic synthesis,[19,27] we have studied and report herein the cyclization of cyanomethylureas **A** to imidazolidin-2-one derivatives **B** (Scheme 1).



Scheme 1. Proposed synthesis of imidazolidin-2-one derivatives **B**.

2. Results and discussion

In general, the synthesis of hydantoins by cyclization of α-amino nitriles involves reaction with isocyanates, followed by in situ acid hydrolysis of the corresponding intermediate *N*-(cyanomethyl) ureas.[11,12,28,29] As we were interested in preserving the Boc protection at the basic side chain of *N*-(cyanomethyl)ureas **A**, the cyclization in acid media was initially excluded and we decided to try it first under neutral or basic reaction conditions. The ornithine derived *N*-(cyanomethyl)urea (*S*)-**1a** (Scheme 2) was chosen for setting up the methodology. The cyclization was initially attempted

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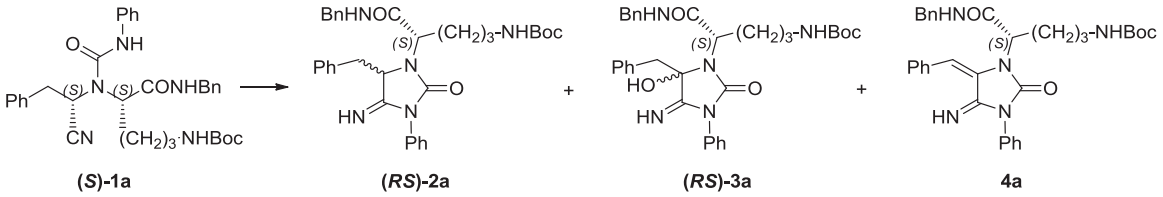


Scheme 2. Cyclization of the *N*-(cyanomethyl)urea (*S*)-**1a** as indicated in Table 1.

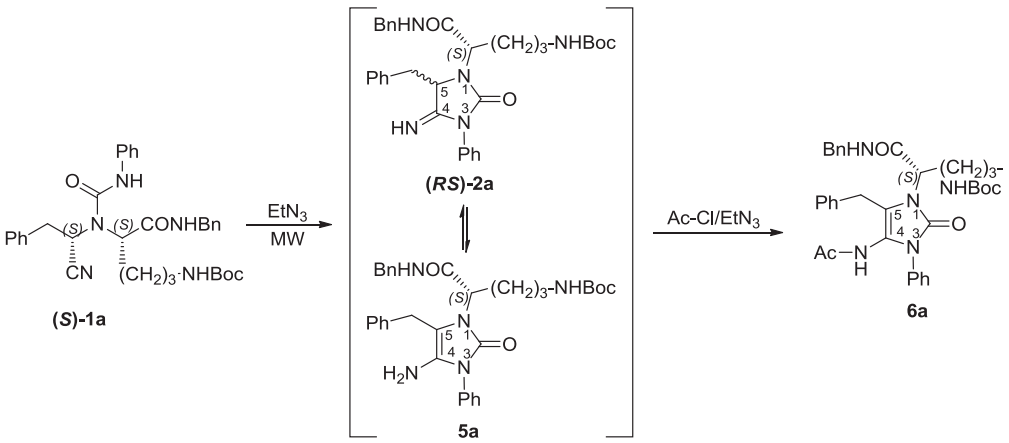
by heating (*S*)-**1a** in refluxing MeOH. As shown in Table 1 (entry 1), after 15 min of reaction, the HPLC-MS analysis of the crude reaction mixture showed the presence of the epimeric mixture of 4-iminoimidazolidin-2-ones (*RS*)-**2a**, as minor products (9%), along with oxidation products,[30,31] the 5-hydroxy-4-iminoimidazolidin-2-ones (*RS*)-**3a** (78%), and the 5-benzylidene-4-iminoimidazolidin-2-one **4a** (13%). To avoid oxidation, the next experiments were carried out under argon and MeOH was replaced by other solvents. In this way, the starting urea (*S*)-**1a** remained unaltered after 2 days in toluene or CH_3CN at 100 °C. Then, we tried to add a catalytic amount of base[32] (10%, Et_3N, K_2CO_3, and Cs_2CO_3), which activated the reaction and decreased the formation of oxidation products. Thus, both Et_3N in toluene and K_2CO_3, or Cs_2CO_3 in CH_3CN led to ≈40% of (*RS*)-**2a** (entries 2–4). The increase of base to 100% and the reaction temperature up to 100 °C, by MW irradiation, in CH_3CN allowed to decrease the reaction time and to increase the yield of the 4-iminoimidazolidin-2-ones (*RS*)-**2a** up to 88% (entry 5). Finally, the improvement was particularly noteworthy when the reaction was carried out without solvent (entries 6 and 7), which yielded quantitatively the desired products (*RS*)-**2a** after 5 min of reaction.

Table 1
Influence of reaction conditions on the synthesis of the 4-iminoimidazolidin-2-ones (*RS*)-**2a** from (*S*)-**1a**

Entry	Base (%)	Solvent	*T* (°C)	*t* (min)	Yield (%)[a]		
					(*RS*)-**2a**	(*RS*)-**3a**	**4a**
1	—	MeOH	75	15	9	78	13
2	Et_3N (10)	Toluene	100	30	44	30	—
3	K_2CO_3 (10)	CH_3CN	80	30	43	25	—
4	Cs_2CO_3 (10)	CH_3CN	80	30	41	29	—
5[b]	Et_3N (100)	CH_3CN	100	15	88	12	—
6[b]	Et_3N (100)	—	100	5	99	—	—
7[b]	K_2CO_3 (100)	—	100	5	99	—	—

[a] Determined by HPLC-MS.
[b] MW irradiation.

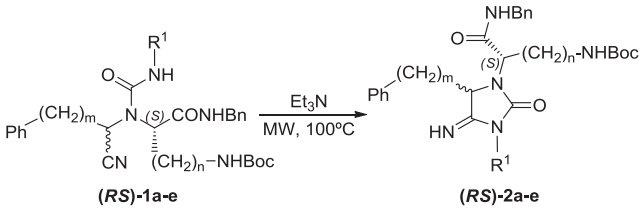
The HPLC-MS analysis of the solvent-free synthesis of (*RS*)-**2a** (Table 1, entries 6 and 7) showed two peaks, at a lower retention time (3.52 and 3.59 min) that the starting *N*-(cyanomethyl)urea (*S*)-**1a** (4.59 min), both with identical $[M+1]^+$ mass to that of this urea. The ^1H NMR spectrum of (*RS*)-**2a** in $CDCl_3$ and in $(CD_3)_2CO$ showed the presence of two isomers, as well as the disappearance of the ureido NH and the appearance of two signals for the 5-H of the imidazolidin-2-one ring at ≈0.45 ppm higher field than the proton in position α to the CN group of (*S*)-**1a**. The imine NH proton could not be observed, probably due to its fast exchange. No significant changes were observed in the signals corresponding to the benzyl amide group, with respect to those of the starting urea (*S*)-**1a**. This fact discarded the alternative cyclization through this group to give an isomeric 6-imino-piperazine-2-one ring. The duplicity of peaks in the HPLC-MS and of signals in the NMR spectra indicated that the cyclization occurred with epimerization at the C_5 due to an equilibrium between the 4-iminoimidazolidin-2-one structure **2a** and its tautomer 4-amino-2,3-dihydro-1*H*-imidazol-2-one **5a** (Scheme 3). The racemization of optically active 5-benzylhydantoins has been explained through a similar tautomerism[33] and Bepary et al. have recently reported the tautomerism of 2-iminoimidazolidin-2-ones.[34] Interestingly, the HPLC-MS analysis of the cyclization of (*S*)-**1a** in MeOH (Table 1, entry 1) showed only one peak at 3.67 min. This fact suggested us that the tautomer equilibrium could be controlled by the solvent and that **5a** could be the main tautomer in MeOH. Then, we attempted to study this tautomer equilibrium by registering the ^1H NMR spectrum of (*RS*)-**1a** in CD_3OD at different times. After 3 h, the cyclization was complete, but, unfortunately, the overlapping of the CD_3OD signals with those of the cyclization products avoided their unequivocal assignment. We also tried to trap the tautomers by acetylation. For that purpose, the cyclization of (*S*)-**1a** was carried out solvent-free and under Ar, by MW heating at 100 °C in the presence of 2 equiv of acetyl chloride and Et_3N. The HPLC-MS analysis of the crude reaction mixture showed the formation of a unique acetylated derivative, to which we assigned the structure of the 4-acetamido-



Scheme 3. Synthesis, tautomerism, and acetylation of the 4-iminoimidazolidin-2-ones (*RS*)-**2a**.

2,3-dihydro-1*H*-imidazol-2-one **6a**, based on its ^{1}H NMR spectrum in $CDCl_3$. Thus, the 5-H proton of (*RS*)-**2a** had disappeared and the 5-CH_2 protons appeared as an AB system [at 3.72 and 3.79 ppm and J=16.5 Hz, ≈0.5 ppm lower field than the corresponding protons in (*RS*)-**2a**]. However, the acetylated compound **6a** resulted highly unstable and the NMR sample completely decomposed during the ^{13}C NMR registration time (≈8 h). This ^{13}C NMR spectrum showed a complex mixture that could not be assigned. The decomposition was also evident in the HPLC-MS analysis of the recovered NMR sample, which showed the almost complete disappearance of the peak corresponding to **6a** and the appearance of multiple peaks of oxidation products.

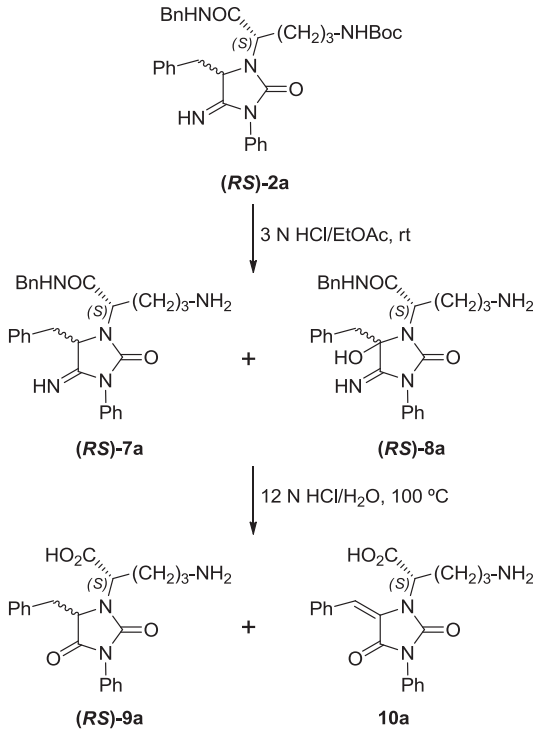
In view of the epimerization observed in the cyclization of (*S*)-**1a**, the versatility of the MW-promoted and base-catalyzed solvent-free cyclization was studied using epimeric mixtures of the *N*-(cyanomethyl)ureas (*RS*)-**1a**–**e** (Scheme 4). In this way, the corresponding 4-iminoimidazolidin-2-ones (*RS*)-**2a**–**e** were obtained in higher than 95% yield. Although the HPLC analysis of the crude reactions showed a high degree of purity, the NMR spectra of (*RS*)-**2a**–**e** showed low resolution, due to the presence of mixtures of epimers and to the high tendency of these 4-iminoimidazolidin-2-ones to oxidation. The assignment of these spectra was based on 2D HSQC and HMBC spectra.



Starting urea				Iminoimidazolidin-2-one	
no.	m	n	R^1	no.	yield
(*RS*)-**1a**	1	3	Ph	(*RS*)-**2a**	97
(*RS*)-**1b**	1	3	Bn	(*RS*)-**2b**	95
(*RS*)-**1c**	1	3	4-MeO-Ph-$(CH_2)_2$	(*RS*)-**2c**	95
(*RS*)-**1d**	1	3	4-F-Ph-$(CH_2)_2$	(*RS*)-**2d**	96
(*RS*)-**1e**	2	4	Ph	(*RS*)-**2e**	95

Scheme 4. Synthesis of the 4-iminoimidazolidin-2-ones (*RS*)-**2a**–**e**.

4-Iminoimidazolidin-2-ones are known to give hydantoins in acid media.[28,33,35] Based on this knowledge, we decided to study the hydrolysis of (*RS*)-**2a**–**e** to the corresponding hydantoin derivatives. We first tried the hydrolysis in acid conditions compatible with the presence of the Boc protection in the basic side chain, such as (0.1–1.0 N) HCl in EtOAc, 20% AcOH in MeOH or (1:1:1) AcOH/MeOH/H_2O at rt. In all cases, the starting 4-iminoimidazolidin-2-ones (*RS*)-**2a** were recovered unaltered. Then, we tried the standard acid conditions for Boc removal, 3 N HCl in EtOAc, and 20% TFA in CH_2Cl_2, at rt. After 30 min, the removal of the Boc group was complete in both cases, but the iminoimidazolidin-2-one ring was unaltered. After 24 h, the HPLC-MS of the crude reaction mixture showed 58% of ring oxidation, but no hydrolysis. Finally, we studied the hydrolysis of (*RS*)-**2a** at 100 °C in concentrated aqueous HCl (12 N). Under these conditions, complete hydrolysis required overnight heating, which besides the hydrolysis of the iminoimidazolidin-2-one ring, also produced the hydrolysis of the benzyl amide group at the basic amino acid residue to carboxylic acid and partial oxidation of the ring (Scheme 5). The mixture of products (*RS*)-**9a** and **10a**, although was identified by their $[M+1]^+$ in the HPLC-MS analysis, could not be separated.



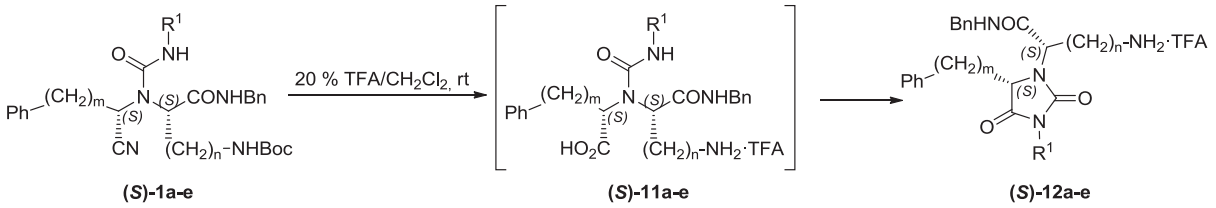
Scheme 5. Acid hydrolysis of the 4-iminoimidazolidin-2-ones (*RS*)-**2a**.

In view of the difficulties to obtain hydantoins by hydrolysis of 4-iminoimidazolidin-2-ones, we turned to study their preparation by direct hydrolysis of the starting *N*-(cyanomethyl)ureas (*S*)-**1a**–**e**. The setting up of reaction conditions was carried out with (*S*)-**1a**. As shown in Table 2, treatment of this urea with 0.1 N solution of HCl in EtOAc for 3 days led almost quantitatively to the Boc-protected 4-iminoimidazolidin-2-ones (*RS*)-**2a** (entry 1), while, increasing the HCl concentration up to 3 N gave a mixture of deprotected iminoimidazolidin-2-ones (*RS*)-**7a** and the hydantoin (*S*)-**12a** (entry 3). As shown in Scheme 6, this compound was the only reaction product when the hydrolysis was carried out in 20% TFA solution in CH_2Cl_2 at rt (entry 4) or in 12 N aqueous HCl at 100 °C (entry 5). In this latter case, neither hydrolysis of the benzyl amide group nor epimerization at C_5 was observed. This different behavior respect to the commented hydrolysis of 4-iminoimidazolidin-2-ones (*RS*)-**2a** suggested that the hydrolysis mechanism was different and that it should not go through the 4-iminoimidazolidin-2-ones (*RS*)-**7a**. To study the process, the TFA-mediated reaction was monitored by HPLC-MS at different times. After 5 h, the starting urea (t_R=5.79 min, $[M+1]^+$=570.46) was completely transformed into the acid (*S*)-**11a** (t_R=3.25 min, $[M+1]^+$=488.46), that is, after 24 h, completely cyclized to the hydantoin (*S*)-**12a** (t_R=3.30 min,

Table 2
Influence of the acid media in the hydrolysis of the *N*-(cyanomethyl)urea (*S*)-**1a**

Entry	Acid	T (°C)	t	Yield (%)[a]		
				(*RS*)-**2a**	(*RS*)-**7a**	(*S*)-**12a**
1	0.1 N HCl/EtOAc	rt	3 days	95	—	—
2	0.3 N HCl/EtOAc	rt	15 min	62	38	—
3	3 N HCl/EtOAc	rt	30 min	—	55	45
4	20% TFA/CH_2Cl_2	rt	24 h	—	—	95[b]
5	12 N HCl/H_2O	100	30 min	—	—	85[b]

[a] Determined by HPLC-MS analysis of the crude reaction. Sunfire C_{18} (4.6×50 mm, 3.5 μm).
[b] Isolated yield.



Scheme 6. Synthesis of the hydantoin derivatives (*S*)-**12a**–**e** by acid hydrolysis of the *N*-(cyanomethyl)ureas (*S*)-**1a**–**e**.

$[M+1]^+$=471.99). This two-step hydrolysis was also monitored by ^{1}H NMR in $CDCl_3$, which confirmed the mechanism. In view of the good results of this methodology, it was applied to the synthesis of the series (*S*)-**12a**–**e** (Scheme 6). These hydantoins derivatives were isolated from the reaction mixtures as TFA salts in higher than 95% yield and were screened as antagonists of the thrombin receptor PAR1 in an assay of human platelet aggregation inhibition.[14] None of them displayed significant activity at 0.1 mg/mL concentration.

3. Conclusions

In conclusion, the results herein described show that *N*-(cyanomethyl)ureas display a chameleonic reactivity that can act as a double-edged sword. Adequately controlled, this reactivity may have high synthetic potentiality. Thus, under neutral, basic or mild acid media they cyclize to 4-iminoimidazolidin-2-one derivatives, which tautomerize to 4-amino-2,3-dihydro-1*H*-imidazol-2-ones. This tautomerism triggers epimerization at the C_5 of the imidazolidine ring, as well as its oxidation. However, under strong acid media, *N*-(cyanomethyl)ureas in a no-epimerizing two-step hydrolysis, through the corresponding carboxylic acids, give stable highly functionalized hydantoin derivatives.

4. Experimental section

4.1. General methods

All reagents were of commercial quality. Solvents were dried and purified by standard methods. Analytical TLC was performed on aluminum sheets coated with a 0.2 mm layer of silica gel 60 F_{254}. Silica gel 60 (230–400 mesh) was used for flash chromatography. Analytical RP-HPLC was performed on a Sunfire C_{18} (4.6×150 mm, 3.5 μm) column, with a flow rate of 1 mL/min, using a tunable UV detector set at 214 and 254 nm and gradient of CH_3CN (solvent A) and 0.05% TFA in H_2O (solvent B) as mobile phase. HPLC-MS was performed on a Sunfire C_{18} (4.6×50 mm, 3.5 μm) column at 30 °C, with a flow rate of 1 mL/min and gradient of 0.1% of formic acid in CH_3CN (solvent A) in 0.1% of formic acid in H_2O (solvent B) was used as mobile phase. Electrospray in positive mode was used for ionization. NMR spectra were recorded using Varian Inova 300, Varian Inova or Mercury 400, and Varian Unity 500 spectrometers. The NMR spectra assignments were based on COSY, HSQC, and HMBC spectra. MW experiments were carried out in sealed vessels in an MW Emrys™ Synthesizer (Biotage AB), with transversal IR sensor for reaction temperature monitoring.

4.2. General procedure for the solvent-free synthesis of the 4-iminoimidazolidin-2-ones (*RS*)-2a–e

Et_3N (28 μL, 0.2 mmol) was added under argon to a solution of the corresponding *N*-(cyanomethyl)urea (*RS*)-**1a**–**e** (0.2 mmol) in CH_2Cl_2 (0.50 mL). After 5 min of stirring at rt, the solvent was evaporated under argon stream. The homogeneous mixture was heated at 100 °C by MW irradiation for 5 min. After cooling to rt, the crude reaction was dissolved in EtOAc (10 mL), washed with H_2O (3×3 mL), and brine (3 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography, using 0–15% MeOH in CH_2Cl_2 gradient as eluent, to afford the title compounds (*RS*)-**2a**–**e** as foams that decomposed on standing.

*4.2.1. tert-Butyl [(4S)-4-(5-benzyl-4-imino-2-oxo-3-phenylimidazolidin-1-yl)-5-(benzylamino)-5-oxopentyl]carbamate (RS)-**2a**.* Yield 97%; foam; HPLC-MS (15–95% gradient of A in B for 5 min) t_R 3.55 and 3.61 min; ^{1}H NMR [$(CD_3)_2CO$, 300 MHz] δ 1.26 (s, 9H, Boc), 1.43 (m, 2H),1.96 (m, 2H), 2.91–3.35 (m, 4H), 4.15–4.42 (2m, 3H), 4.50 (t, *J*=5 Hz, 0.5H), 4.68 (t, *J*=5 Hz, 0.5H), 5.96 (br s, 1H), 6.79–7.43 (m, 15H), 7.87 and 7.91 (2t, *J*=6 Hz, 1H); ^{13}C NMR [$(CD_3)_2CO$, 100 MHz] δ 27.2, 27.8, 28.0, 28.4 (CH_2), 28.7 (CH_3), 38.3, 38.8, 40.4, 40.5, 43.5, 43.7 (CH_2), 57.7, 59.4, 60.0, 61.9 (CH), 78.5 (C), 127.7, 127.8, 127.8, 128.3, 128.5, 129.0, 129.1, 129.2, 129.4, 131.0, 131.1 (CH), 136.6, 140.0, 140.1, 141.2 (C), 156.8, 157.8, 170.8, 171.0 (CO). ES-MS *m*/*z* $[M+1]^+$ calcd for $C_{33}H_{39}N_5O_4$ 570.3, found, 570.4.

*4.2.2. tert-Butyl [(4S)-5-(benzylamino)-4-(3,5-dibenzyl-4-imino-2-oxoimidazolidin-1-yl)-5-oxopentyl]carbamate (RS)-**2b**.* Yield 95%; foam; HPLC-MS (15–95% gradient of A in B for 5 min) t_R 3.67 and 3.77 min; ^{1}H NMR [$(CD_3)_2CO$, 400 MHz] δ 1.25 (s, 9H, Boc), 1.38 (m, 2H),1.93 (m, 2H), 2.83–3.25 (m, 4H), 4.12–4.60 (m, 6H), 5.92 (br s, 1H), 6.93–7.22 (m, 15H), 7.74 and 7.86 (2t, *J*=6 Hz, 1H); ^{13}C NMR [$(CD_3)_2CO$, 100 MHz] δ 27.0, 27.8, 27.9, 28.4 (CH_2), 28.6 (CH_3), 37.8, 38.1, 40.3, 40.5, 42.6, 43.5, 43.7, 44.4 (CH_2), 57.8, 59.1, 59.7, 62.0 (CH), 78.5 (C), 127.6, 127.7, 127.8, 128.2, 128.2, 128.4, 129.0, 129.0, 129.1, 129.2, 130.8, 130.9 (CH), 136.4, 140.0, 140.0 (C), 156.8, 158.9, 159.1, 171.0 (CO). ES-MS *m*/*z* $[M+1]^+$ calcd for $C_{34}H_{41}N_5O_4$ 584.3, found, 584.4.

*4.2.3. tert-Butyl [(4S)-4-(5-benzyl-4-imino-3-(4-methoxyphenethyl)-2-oxoimidazolidin-1-yl)-5-(benzylamino)-5-oxopentyl]carbamate carbamate (RS)-**2c**.* Yield 95%; foam; HPLC-MS (15–95% gradient of A in B for 5 min) t_R 3.61 min; ^{1}H NMR [$(CD_3)_2CO$, 300 MHz] δ 1.25 (s, 9H, Boc), 1.33 (m, 2H),1.95 (m, 2H), 2.45, 2.70, 2.98, 3.24, 3.41 (5m, 8H), 3.61 and 3.62 (2s, 3H), 4.05–4.48 (m, 6H), 5.92 (br s, 1H), 6.70 (d, *J*=9 Hz, 2H), 6.93 (dd, *J*=9, 3 Hz, 2H), 7.00–9.19 (m, 12H), 7.68 and 7.82 (2t, *J*=6 Hz, 1H); ^{13}C NMR [$(CD_3)_2CO$, 75 MHz] δ 26.5, 27.0, 28.0, 28.7 (CH_2), 28.9 (CH_3), 33.1, 33.3, 38.6, 38.9, 40.7, 40.9, 43.8, 44.0, 44.1, 44.2 (CH_2), 55.7 (CH_3), 56.9, 57.9, 60.0, 62.2 (CH), 78.8 (C), 114.9, 127.7, 127.9, 127.9, 128.5, 128.6, 128.9, 129.2, 129.3, 129.3, 129.5, 130.7, 130.7, 130.8, 130.9, 131.7 (CH), 136.8, 137.0, 140.3 (C), 157.0, 158.7, 159.5, 159.5, 171.2, 171.3 (CO). ES-MS *m*/*z* $[M+1]^+$ calcd for $C_{36}H_{45}N_5O_5$ 628.3, found, 628.5.

*4.2.4. tert-Butyl [(4S)-4-(5-benzyl-3-(4-fluorophenethyl)-4-imino-2-oxoimidazolidin-1-yl)-5-(benzylamino)-5-oxopentyl]carbamate (RS)-**2d**.* Yield 96%; foam; HPLC-MS (15–95% gradient of A in B for 5 min) t_R 3.67 and 3.72 min; ^{1}H NMR [$(CD_3)_2CO$, 500 MHz] δ 1.26 (s, 9H, Boc), 1.36 (m, 2H),1.92 (m, 2H), 2.35–3.58 (m, 8H), 4.09 (t, *J*=7 Hz, 0.5H), 4.24 and 4.34 (2m, 2.5H), 4.48 (br s, 0.5H), 4.61 (br s,

0.5H), 5.91 (br s, 1H), 6.87 (dd, *J*=9, 3 Hz, 1H), 6.89 (dd, *J*=9, 3 Hz, 1H), 6.97–7.27 (m, 10H), 7.76 and 7.82 (2t, *J*=6 Hz, 1H); ^{13}C NMR [$(CD_3)_2CO$, 125 MHz] δ 25.8, 26.4, 26.5, 26.8 (CH_2), 27.2 (CH_3), 31.4, 31.7, 36.4, 36.9, 38.9, 39.1, 39.2, 39.4, 42.2, 42.4 (CH_2), 56.7, 58.1, 58.3, 60.4 (CH), 77.1, 77.5 (C), 114.3, 114.5, 126.4, 126.5, 126.5, 126.8, 126.9, 126.9, 127.1, 127.4, 127.5, 127.7, 127.8, 127.8, 127.8, 127.8, 127.8, 127.9, 129.5, 129.6, 130.1, 130.1, 130.2 (CH), 133.8, 134.9, 138.5, 138.7 (C), 155.5, 156.4, 160.1, 162.0, 162.1, 169.3, 169.5 (CO). ES-MS *m*/*z* $[M+1]^+$ calcd for $C_{35}H_{42}FN_5O_4$ 616.3, found, 616.5.

*4.2.5. tert-Butyl [(5S)-6-(benzylamino)-5-(4-imino-2-oxo-5-phenethyl-3-phenylimidazolidin-1-yl)-6-oxohexyl]carbamate (RS)-**2e**.* Yield 95%; foam; HPLC-MS (15–95% gradient of A in B for 5 min) t_R 3.57 min; ^{1}H NMR [$(CD_3)_2CO$, 300 MHz] δ 1.25 (s, 9H, Boc), 1.29, 1,38 (2m, 4H), 1.79–2.27 (m, 4H), 2.37–3.01 (m, 6H), 4.34 (m, 4H), 5.84 (br s, 1H), 7.01–7.49 (m, 15H), 7.70 and 7.98 (2t, *J*=6 Hz, 1H); ^{13}C NMR [$(CD_3)_2CO$, 75 MHz] δ 23.2, 27.2 (CH_2), 27.4 (CH_3), 29.6, 33.0, 33.5, 34.4, 34.6, 39.6, 42.4, 42.6 (CH_2), 56.3, 57.2, 58.9, 59.6 (CH), 77.1 (C), 125.3, 125.4, 126.4, 127.0, 127.1, 127.8, 127.8, 127.8, 127.9, 127.9, 128.0, 128.1 (CH), 138.8, 138.9, 139.9, 140.1, 141.0, 141.1 (C), 155.3, 155.7, 156.5, 169.5, 169.7 (CO). ES-MS *m*/*z* $[M+1]^+$ calcd for $C_{35}H_{43}N_5O_4$ 598.3, found, 598.3.

4.3. Cyclization–acetylation of the *N*-(cyanomethyl)urea (*S*)-1a. Synthesis of (*S*)-*tert*-butyl (4-(4-acetamido-5-benzyl-2-oxo-3-phenyl-2,3-dihydro-1*H*-imidazol-1-yl)-5-(benzylamino)-5-oxopentyl)carbamate 6a

Et_3N (8.4 μL, 0.06 mmol) and acetyl chloride (4.3 μL, 0.06 mmol) were added under argon to a solution of the *N*-(cyanomethyl)urea (*S*)-**1a** (17.2 mg, 0.03 mmol) in CH_2Cl_2 (0.50 mL). After 5 min of stirring at rt, the solvent was evaporated under argon stream. The homogeneous mixture was heated at 100 °C by MW irradiation for 25 min. After cooling to rt, the crude reaction mixture was purified by flash chromatography, using 0–5% MeOH in CH_2Cl_2 gradient as eluent, to afford the title compounds **6a** (11 mg, 60%) as a foam that decomposed on standing. HPLC-MS: t_R 5.61 min. ^{1}H NMR (CD_3Cl, 300 MHz) δ 1.06 (m, 2H), 1.34 (s, 9H), 1.80 (s, 3H), 2.00 (m, 2H), 2.80 (m, 2H), 3.70 and 3.82 (2d, *J*=16.5 Hz, 2H), 4.43–4.15 (m, 4H), 6.51 (s, 1H), 7.45–7.05 (m, 15H), 7.99 (s, 1H). The instability of this compound did not allow obtaining its ^{13}C NMR spectrum. ES-MS *m*/*z* $[M+1]^+$ calcd for $C_{35}H_{41}N_5O_5$ 612.31, found, 612.31.

4.4. Acid hydrolysis of the *N*-(cyanomethyl)ureas (*S*)-1a–e. Synthesis of the hydantoin derivatives (*S*)-12a–e

The corresponding *N*-(cyanomethyl)urea (*S*)-**1a**–**e** [0.125 mmol, impurified with 0–30% of the respective epimer (*R*)-**1a**–**e**, due to the difficulty of resolution of the epimeric mixtures (*RS*)-**1a**–**e**] was dissolved in 20% solution of TFA in CH_2Cl_2 (5 mL). After 24 h of stirring at rt, the reaction mixture was evaporated to dryness. The residue was coevaporated with CH_2Cl_2 (3×2 mL) and triturated with cold ethyl ether. The residue was dissolved in H_2O (3 mL) and the solution was lyophilized. In this way, the trifluoroacetates of the hydantoin derivatives (*S*)-**12a**–**e** were obtained as amorphous solids retaining the epimer ratio of the starting urea **1a**-**e** [70–100% of the (*S*)-epimer].

*4.4.1. (2S)-5-Amino-N-benzyl-2-[(S)-5-benzyl-2,4-dioxo-3-phenylimidazolidin-1-yl]pentanamide trifluoroacetate (S)-**12a**.* With ≈28% of the epimer (*R*)-**12a**, yield 96%; foam; HPLC-MS (15–95% gradient of A in B for 5 min) t_R 3.08 min; ^{1}H NMR [CD_3OD, 500 MHz] δ 1.60 (m, 2H), 2.05 (m, 2H), 2.86 (m, 2H), 3.18 (dd, *J*=5, 15.5 Hz, 1H), 3.25 (dd, *J*=5, 15.5 Hz, 1H), 4.16 (t, *J*=8 Hz, 1H), 4.27 and 4.35 (AB system, *J*=15 Hz, 2H), 4.45 (t, *J*=8 Hz, 0.28H), 4.55 (t, *J*=5H, 0.78H), 6.72–7.41 (m, 15H), 8.26 and 8.45 (2t, *J*=6 Hz, 1H); ^{13}C NMR [CD_3OD, 125 MHz] δ 24.2, 26.8, 36.1, 38.7, 38.7, 42.9, 43.0 (CH_2), 57.9, 58.0, 59.2, 60.9, 61.6 (CH), 126.2, 127.0, 127.0, 127.3, 128.1, 128.1, 128.2, 128.2, 128.5, 128.6, 129.3, 131.3 (CH), 134.7, 137.0, 138.1 (C), 156.3, 169.7, 169.7, 171.4, 172.3 (CO). ES-MS *m*/*z* $[M+1]^+$ calcd for $C_{28}H_{30}N_4O_3$ 471.2, found, 471.4; Anal. Calcd for $C_{28}H_{30}N_4O_3 \cdot C_2HF_3O$: C, 61.64; H, 5.35; N, 9.58. Found: C, 61.38; H, 5.46; N, 9.37.

*4.4.2. (2S)-5-Amino-N-benzyl-2-[(S)-3,5-dibenzyl-2,4-dioxoimidazolidin-1-yl]pentanamide trifluoroacetate (S)-**12b**.* With ≈25% of the epimer (*R*)-**12b**, yield 95%; foam; HPLC-MS (15–95% gradient of A in B for 5 min) t_R 3.22 min; ^{1}H NMR [CD_3OD, 500 MHz] δ 1.54 and 1.71 (2m, 2H), 1.90, 2.03, 2.14 (3m, 2H), 2.82 (t, *J*=7 Hz, 2H), 3.14 (m, 2H), 4.09 (t, *J*=8 Hz, 0.75H), 4.17–4.50 (m, 5.25H), 6.83–7.35 (m, 15H); ^{13}C NMR [CD_3OD, 125 MHz] δ 25.6, 28.2, 36.6, 40.1, 43.2, 44.3 (CH_2), 59.3, 63.2 (CH), 128.3, 128.4, 128.4, 128.7, 128.7, 129.0, 129.4, 129.5, 129.6, 129.6, 129.6, 129.9, 130.2, 130.7, 131.1 (CH), 136.0, 137.0, 139.3 (C), 158.7, 159.9, 170.9, 171.2, 173.7, 174.3 (CO). ES-MS *m*/*z* $[M+1]^+$ calcd for $C_{29}H_{32}N_4O_3$ 485.3, found, 485.5; Anal. Calcd for $C_{29}H_{32}N_4O_3 \cdot C_2HF_3O$: C, 62.20; H, 5.56; N, 9.36. Found: C, 62.03; H, 5.49; N, 9.06.

*4.4.3. (2S)-5-Amino-N-benzyl-2-[(S)-5-benzyl-3-(4-methoxyphenethyl)-2,4-dioxoimidazolidin-1-yl]pentanamide trifluoroacetate (S)-**12c**.* With ≈30% of the epimer (*R*)-**12c**, yield 97%; foam; HPLC-MS (15–95% gradient of A in B for 5 min) t_R 3.23 min; ^{1}H NMR [CD_3OD, 500 MHz] δ 1.52 and 1.68 (2m, 2H), 1.87, 1.96, 2.06 (3m, 2H), 2.40 (t, *J*=8 Hz, 0.6H), 2.49 (m, 1.4H), 2.81 (t, *J*=7.5 Hz, 1.4H), 2.94–2.09 (m, 2H), 3.12 (m, 0.6H), 3.31–3.51 (m, 2H), 3.63 and 3.64 (2s, 3H), 3.99 (m, 1.4H), 4.16–4.32 (m, 2.6H), 6.70 (m, 2H), 6.91 (m, 2H), 7.02 (m, 2H), 7.09 (m, 2H), 7.14–7.21 (m, 4H), 7.34 (m, 2H); ^{13}C NMR [CD_3OD, 125 MHz] δ 25.6, 28.2, 33.7, 37.2, 40.1, 41.1, 44.3 (CH_2), 55.7 (CH_3), 59.2, 63.2 (CH), 115.0, 115.0, 128.3, 128.4, 128.7, 129.4, 129.6, 129.6, 129.9, 130.2, 130.7, 130.8, 130.8, 131.0 (CH), 136.4, 139.5, 159.9 (C), 158.5, 171.3, 173.7 (CO). ES-MS *m*/*z* $[M+1]^+$ calcd for $C_{31}H_{36}N_4O_4$ 529.3, found, 529.4; Anal. Calcd for $C_{31}H_{36}N_4O_4 \cdot C_2HF_3O$: C, 61.67; H, 5.80; N, 8.72. Found: C, 61.47; H, 5.89; N, 8.45.

*4.4.4. (2S)-5-Amino-N-benzyl-2-[(S)-5-benzyl-3-(4-fluorophenethyl)-2,4-dioxoimidazolidin-1-yl]pentanamide trifluoroacetate (S)-**12d**.* With ≈25% of the epimer (*R*)-**12d**, yield 97%; foam; HPLC-MS (15–95% gradient of A in B for 5 min) t_R 3.31 min; ^{1}H NMR [CD_3OD, 500 MHz] δ 1.53 and 1.70 (2m, 2H),1.87, 1.98, 2.08 (3m, 2H), 2.44–2.59, 2.49 (m, 2H), 2.82 (t, *J*=7.5 Hz, 1.5H), 2.96–3.10 (m, 2H), 3.13 (m, 0.5H), 3.35–3.53 (m, 2H), 4.02 (m, 1.4H), 4.17–4.34 (m, 2.6H), 6.87 (m, 2H), 7.01 (m, 3H), 7.10 (m, 2H), 7.19 (m, 5H), 7.34 (m, 2H); ^{13}C NMR [CD_3OD, 125 MHz] δ 24.1, 26.8, 32.3, 35.7, 38.7, 39.5, 42.9 (CH_2), 57.8, 61.7 (CH), 114.6, 114.8, 126.9, 127.0, 127.3, 127.9, 128.1, 128.2, 128.5, 128.7, 129.3, 129.5, 130.1, 130.1 (CH), 133.7, 134.9, 135.3, 138.0, 162.6 (C), 157.1, 169.8, 172.2 (CO). ES-MS *m*/*z* $[M+1]^+$ calcd for $C_{30}H_{33}FN_4O_3$ 517.3, found, 517.4; Anal. Calcd for $C_{30}H_{33}FN_4O_3 \cdot C_2HF_3O$: C, 60.95; H, 5.43; N, 8.88. Found: C, 60.65; H, 5.27; N, 8.69.

*4.4.5. (S)-6-Amino-N-benzyl-2-[(S)-2,4-dioxo-5-phenethyl-3-phenylimidazolidin-1-yl]hexanamide trifluoroacetate (S)-**12e**.* Yield 97%; foam; HPLC-MS (15–95% gradient of A in B for 5 min) t_R 3.26 min; ^{1}H NMR [CD_3OD, 500 MHz] δ 1.38 (m, 2H), 1.60 (m, 2H), 2.00 (q, *J*=8 Hz, 2H), 2.12 and 2.21 (2m, 2H), 2.51 and 2.72 (2m, 2H), 2.79 (t, *J*=7 Hz, 2H), 4.26–4.36 (m, 4H)), 7.07–7.38 (m, 15H; ^{13}C NMR [CD_3OD, 125 MHz] δ 24.5, 28.2, 30.7, 31.2, 33.3, 40.4, 44.3 (CH_2), 59.3, 61.8 (CH), 127.3, 127.8, 127.8, 128.4, 128.7, 129.3, 129.4, 129.4, 129.5, 129.6, 129.6, 129.6, 129.6, 130.0 (CH), 133.1, 139.7, 141.8 (C), 157.7, 171.4, 173.4 (CO). ES-MS *m*/*z* $[M+1]^+$ calcd for $C_{30}H_{34}N_4O_3$

499.3, found, 499.3; Anal. Calcd for $C_{30}H_{34}N_4O_3 \cdot C_2HF_3O$: C, 62.74; H, 5.76; N, 9.15. Found: C, 62.85; H, 5.83; N, 8.89.

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Supplementary data

^{1}H NMR and ^{13}C NMR spectra of compounds (*RS*)-**2a**–**e**, **6a**, and (*S*)-**12a**–**e**. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.03.082.

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