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Study on induction of stereoselectivity in the Strecker synthesis of basic amino acid-derived α -amino nitriles

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Study on induction of stereoselectivity in the Strecker synthesis of basic amino acid-derived α -amino nitriles

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Dedicated to Professor José Luis García Ruano on the occasion of his 65th birthday

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ABSTRACT

Diverse basic amino acid-derived α -amino nitriles have been synthesized by a modified Strecker reaction, using TMSCN as cyanide source. It has been found that this synthesis is a slow thermodynamically controlled reaction, where it was difficult to induce stereocontrol. Moderate selectivity was induced by thermodynamic control of the reaction in MeOH. The absolute configuration at the generated stereogenic center was assigned by chemical correlation with 2-oxopiperazine derivatives.

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1. Introduction

α -Amino nitriles have been considered key intermediates in organic synthesis since A. Strecker reported the reaction of aldehydes, ammonia and HCN for the synthesis of α -amino acids in 1850.¹ Since then, diverse versions of this reaction, using a carbonylic compound, an amine, and cyanide (or cyanide source), have been one of the most used methods for the synthesis of precursors of α -amino acids.²⁻⁴ During the last years, attention has mainly been focused on the stereocontrol in the Strecker reaction, by using chiral auxiliaries^{2,3,5,6} and, more recently, chiral catalysts.⁵⁻¹²

α -Amino nitriles are versatile intermediates for the synthesis of multiple building blocks.^{5,6} In particular, α -amino acid-derived amino nitriles have shown high potential for molecular diversity generation.¹³ Thus, we have shown their utility in the synthesis of pseudopeptides,^{14,15} and diverse chiral heterocyclic compounds.¹⁶⁻²⁰ In this field, and in the context of a medicinal chemistry project focused on the search of modulators of protein-protein interactions, we required the synthesis of basic amino acid-derived α -amino nitriles of general formula **A** (Scheme 1). Herein, we report the synthesis of these α -amino nitriles via a Strecker reaction of aldehydes **B** with basic amino acid-derived benzyl amides **C**, using trimethylsilyl cyanide (TMSCN) as cyanide source, as well as our efforts to induce stereoselectivity in this synthesis.

Scheme 1. Retrosynthesis of α -amino nitriles **A**

2. Results and discussion

The proposed synthetic scheme required the previous preparation of the basic amino acid-derived benzyl amides **3a-c** (Scheme 2), which were obtained by DCC/HOBt-mediated coupling of the corresponding N_α -Fmoc protected α -amino acid **1a-c** with benzyl amine, followed by Fmoc-removal. Afterwards,

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Scheme 2. Reagents and conditions: (a) BnNH_2 , DCC, HOBT, CH_3CN , rt, 100%; (b) Et_2NH , CH_3CN , rt, 100%; (c) Catalyst and solvent as shown in table 1, 0 °C, 1 h; (d) TMSCN, temperature and time as shown in table 1.

the synthesis of the α -amino nitriles **9** and **11** was undertaken by applying a modified Strecker reaction developed by our group for the synthesis of cyanomethyleneamino pseudopeptides.¹⁴ This involves the ZnCl_2 -catalyzed reaction of one equivalent of an aldehyde with one equivalent of the corresponding N_α -deprotected amino acid or peptide in CH_2Cl_2 at -20 °C for 1 h, followed by *in situ* reaction with trimethylsilyl cyanide (TMSCN) at 0 °C for 24 h. Under these reaction conditions, the HPLC-MS analysis of the crude reaction mixture of the ornithine-derived amino nitriles **9a** showed, along with these compounds, the presence of 10% of the dinitrile **10a**, resulting from over amino acid alkylation. To avoid this side reaction, it was necessary to reduce the proportion of aldehyde equivalents to an 80%. Applying this modification, the proposed α -amino nitriles **9a,b** and **11a,b** were obtained in 60–75 % yield as (1:1) epimeric mixtures at the generated stereogenic center. Only the epimeric mixtures **9a,b** could be chromatographically resolved. Isolated (*R*)- and (*S*)-epimers of **9a,b** were stable at room temperature and epimerization was not observed after more than one month on standing. The difficulties of epimer resolution and the need of optical pure epimers in our medicinal chemistry project moved us to study the possibility of inducing stereoselectivity in the synthesis of the proposed α -amino nitriles **9a-c** and **11a,b**.

In the case of the phenylacetaldehyde derivatives **9a-c**, the intermediate imines **6a-c** could be in equilibrium with their enamine tautomers **7a-c**, which could be stabilized by conjugation of the double bond with the aromatic ring. Considering that the type of reaction intermediate imine or enamine could influence the reaction stereoselectivity, we analyzed the predominant intermediates in the reaction mixtures of the ornithine-derived benzyl amide **3a** with the corresponding aldehyde **4** and **5** after 5 min of heating at 120 °C under microwave irradiation, using ZnCl_2 as catalyst and CDCl_3 as solvent. In the case of the reaction mixture of phenylacetaldehyde (**4**), its ^1H NMR spectrum showed the presence of two pairs of doublets, with a coupling constant of 15 Hz, corresponding to the two enamine protons of *trans*-**7a**, at 5.83 and 6.85 ppm, and *cis*-**7a**, at 6.21 and 7.11–7.50 ppm, in a (1:1) rate. The imine **6a** was not detected in this spectrum. However, in the case of the reaction of 3-phenylpropionaldehyde (**5**), the ^1H NMR spectrum showed the presence of the imine **8a** as the unique reaction intermediate, with the imine proton as a triplet, at 7.66 ppm, coupled (8 Hz) with the multiplet corresponding to the neighboring methylene protons, which appeared at 2.60–2.75 ppm.

After studying the reaction intermediates, diverse factors that could affect the reaction stereoselectivity were sequentially investigated in parallel for the phenylacetaldehyde- and 3-

phenylpropionaldehyde-derived amino nitriles **9a** and **11a**, respectively. First, we studied the replacement of ZnCl_2 by chiral organocatalysts in the synthesis of **9a**. Among the diverse organocatalysts developed for enantioselective Strecker reactions,^{6,8,11,12} we tried the commercial thiourea **12** (Fig. 1), developed by the Jacobsen group.^{21,22} However, by using up to a 5 mol % of this thiourea, under the described reaction conditions (Table 1, entry 2), neither catalysis nor stereoselectivity was observed. Next, we tried to use Boc-Pro-OH (**13**) as catalyst, which has been described to induce asymmetry in the addition of alkynes to imines.²³ Although 5 and 10 % of excesses in the (*R*)-**9a** epimer were obtained by using 10 and 50 mol %, respectively, of **13** as catalyst (Table 1, entries 3 and 4), this slight excess disappeared under thermodynamic control conditions required for optimizing reaction yield (entry 5).

Fig.1. Organocatalysts used to induce stereocontrol

Table 1
Stereoselectivity results in the synthesis of **9a**

Entry	Catalyst (mol %)	Solvent	T (°C)	t (h)	9a (%) ^a	(<i>R</i>) : (<i>S</i>)
1	ZnCl_2 (100)	CH_2Cl_2	0	24	72	1 : 1
2	12 (5)	Toluene	0	24	42	1 : 1
3	13 (10)	CH_2Cl_2	0	2	56	1.1 : 1
4	13 (50)	CH_2Cl_2	0	2	61	1.2 : 1
5	13 (50)	CH_2Cl_2	0	48	99	1 : 1
6	ZnCl_2 (100)	MeOH	0	2	80	1 : 1
7	ZnCl_2 (100)	MeOH	0	24	80	1 : 2
8	ZnCl_2 (100)	MeOH	rt	2	57	1 : 1.5
9	ZnCl_2 (100)	MeOH	rt	24	48	1 : 2.3
10	13 (50)	MeOH	0	2	82	1.1 : 1
11	13 (50)	MeOH	0	24	94	1 : 1
12	13 (50)	MeOH	rt	2	64	1 : 1.2
13	13 (50)	MeOH	rt	24	79	1 : 1.5
14	13 (50)	MeOH	rt	48	80	1 : 1.9
15 ^b	ZnCl_2 (100)	CH_2Cl_2	120	5 min	51	1 : 1.6
16 ^b	ZnCl_2 (100)	MeOH	120	3 min	40	1 : 2
17 ^b	ZnCl_2 (100)	-	120	5 min	24	1 : 1
18 ^b	-	-	120	5 min	63	1 : 1

^aDetermined by HPLC-MS analysis.

^bCarried out under MW.

In view of the poor results on stereoselectivity obtained with the organocatalysts **12** and **13**, and taking into account several reports that describe the influence of the solvent and temperature/time on the stereoselectivity of the Strecker reaction,^{14,24-26} we studied the influence of these factors on the synthesis of **9a** and **11a**. As shown in Table 1 for **9a**, the replacement of CH_2Cl_2 by MeOH (entries 6-9) under thermodynamic control conditions (higher temperature and reaction time) favored the excess of the (*S*)-**9a** epimer up to a 40 % (entry 9), although with the increase of the reaction temperature the yield decreased due to the formation of complex reaction mixtures of degradation products. The replacement of ZnCl_2 by Boc-Pro-OH (entries 10-14) counteracted, in part, the improvement on stereoselectivity achieved by using MeOH as

solvent, although this replacement significantly decreased the formation of degradation products. Similar stereoselectivity was obtained when the thermodynamic control was induced by increasing the reaction temperature to 120 °C, by MW irradiation (entries 15-16). Under these reaction conditions, product degradation increased and yields were significantly lower. Interestingly, under MW irradiation, the reaction took place even without solvent and without catalyst (entries 17-18), although in these cases stereoselectivity was not observed. Similar results were obtained in the parallel study on stereoselectivity in the 3-phenylpropionaldehyde-derived α -amino nitriles **11a**. This similarity shows that the difference in the type of intermediate imine or enamine does not affect the stereoselectivity. The overall results of these studies have shown the difficulty of inducing stereocontrol in the Strecker synthesis of α -amino nitriles **9a** and **11a**. This synthesis seems to be a very slow thermodynamic controlled reaction, where the solvent MeOH favors the preference of the (*S*)-epimer, that must be slightly more stable than the (*R*). As it is known for the Strecker reaction in aliphatic aldimines with bulky groups,¹² as well as in ketimines,¹⁰ the difficulty in discriminating between the two diastereotopic faces of the intermediate imines **6** and **8** by a catalyst could be due to the presence of the bulky chiral amino acid moiety on the imine nitrogen. Applying the reaction conditions of entry 9, the arginine-derived α -amino nitriles **9c** were obtained in 90 % yield as a (1:3) [(*R*):(*S*)] epimeric mixture, which could not be resolved.

Scheme 3. Configuration assignment in the α -amino nitriles **9a**. Reagents and conditions: (a) H_2 , Pd(C), MeOH, rt, 62 and 72 %; (b) NaOH, (1:1) dioxane/ H_2O , rt, 100 %; (c) $\text{H}_2\text{N-Bn}$, DCC, HOBT, CH_3CN , rt, 95 %.

The configuration at the new stereogenic center generated in the α -amino nitriles **9** and **11** was tentatively assigned by chemical correlation. For this purpose, methyl esters (*R*)- and (*S*)-**14a** (Scheme 3) were prepared in a (1:1) ratio, by applying the methodology of entry 1 of table 1, and were chromatographically resolved. Afterwards, each separated epimer

was transformed into the respective 2-oxopiperazine derivative (**R**)- and (**S**)-**15a**, respectively, by 10% Pd (C) catalyzed hydrogenation. The NOE effect observed between the piperazine 3-H and 5-H protons in the NOESY 1D ^1H NMR spectrum of (**R**)-**15a** allowed the assignment of a *cis*-relative disposition to both protons and, therefore, configuration (*R*) to **C**₅. Similarly, the NOE effect between 3-H and 5-CH₂ protons in (**S**)-**15a** allowed the assignment of a 3,5-*trans* relative configuration to this epimer. On the other hand, saponification of (**S**)-**14a**, followed by coupling with benzyl amine, using dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) as coupling reagents, led to a benzyl amide identical to (**S**)-**9a**. From the comparison of the NMR and HPLC data of both epimers **9a** (Table 2), it was observed that the α -H of the basic amino acid appeared at a higher field in the (*R*)-epimer than in the (*S*), while, the 2-H of the amino nitrile appeared at higher field in the (*S*). Furthermore, this epimer showed higher retention time than the (*R*). These differences were used for the tentative assignment of configuration to the other amino nitriles **9b,c** and **11a,b**.

3. Conclusion

In conclusion, the results herein described show that the Strecker synthesis of basic amino acid-derived α -amino nitriles is a slow, thermodynamically controlled reaction, where the solvent MeOH favors the excess of the epimer with the same configuration at the generated chiral center than that of the starting amino acid moiety. The bulkiness of this moiety makes difficult the kinetic stereocontrol of the reaction by using chiral organocatalysts.

4. Experimental

4.1. General

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 F₂₅₄. Silica gel 60 (230-400 mesh) was used for flash chromatography. Analytical RP-HPLC was performed on a Sunfire C₁₈ (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 a (10-100%, 30 min) gradient of CH₃CN (solvent A) and 0.05 % TFA in H₂O (solvent B) as mobile phase. HPLC-MS was performed on a Sunfire C₁₈ (4.6×50 mm, 3.5 μm) column at 30°C, with a flow rate of 1 mL/min. (10-100%, 5 min) Gradient of CH₃CN with 0.08% of formic acid (solvent A) in 0.1% of formic acid in H₂O (solvent B) was used as mobile phase. Electrospray in positive mode was used for ionization. Melting points were taken on a Mettler Toledo M170 apparatus and are uncorrected. Elemental analyses were obtained on a CH-O-RAOID apparatus. Optical rotations were determined in a Perkin Elmer 141 polarimeter. NMR spectra were recorded using Varian Inova 300, Varian Inova o Mercury 400, and Varian Unity 500 spectrometers. The NMR spectra assignment was based on COSY, HSQC, and HMBC spectra. NOESY 1D spectra were carried out at 400 MHz, using a gradient duration of 0.0005 s and mixing times of 0.5 s and 0.70 s.

4.2. General procedure for the synthesis of the α -Fmoc-protected basic amino acid-derived benzyl amides **2a-c**

HOBt (1.35 mg, 10 mmol), DCC (4.13 g, 20 mmol) and BnNH₂ (1.08 g, 1.1 mL, 10 mmol) were successively added to a

solution of the corresponding *N* α -Fmoc-basic amino acid **1a-c** (10 mmol) in CH₃CN (200 mL) under argon and the mixture was stirred at room temperature for 2 h. Then, the precipitated dicyclohexyl urea was filtered off and the filtrate was evaporated to dryness. The residue was dissolved in EtOAc (200 mL) and the solution was successively washed with 1N HCl (50 mL), H₂O (50 mL) and brine (50 mL). The organic extracts were dried over Na₂SO₄ and evaporated to dryness. The residue was purified by flash chromatography, using 10-60% EtOAc in hexane gradient as eluent, to give the corresponding benzyl amide **2a-c**.

4.2.1. Fmoc-Orn(Boc)-NHBN (2a)

White solid (98%). Mp 180-181 °C; [α]_D²⁰ -3.1 (c 1, CHCl₃); HPLC *t*_R min 26.00 min; ^1H NMR (300 MHz, CDCl₃) δ 1.12 (m, 2H, γ -H), 1.40 (s, 9H, Boc), 1.69 (m, 2H, β -H), 3.05 (m, 2H, δ -H), 4.20 [t, 1H, *J* = 7 Hz, CH (Fmoc)], 4.37 (dd, 1H, *J* = 8.5 and 13 Hz, α -H), 4.30-4.50 [m, 4H, CH₂ (Bn) and CH₂ (Fmoc)], 4.68 (m, 1H, *NH*Boc), 5.71 (m, 1H, *NH*Fmoc), 6.93 (m, 1H, *NH*Bn), 7.11-7.83 [m, 13H, Ar (Fmoc and Bn)]. ^{13}C NMR (75 MHz, CDCl₃) δ 26.6 (C _{γ}), 28.3 [3CH₃ (Boc)], 30.5 (C _{β}), 38.8 (C _{δ}), 43.5 [CH₂ (Bn)], 47.2 [CH (Fmoc)], 53.3 (C _{α}), 66.9 [CH₂ (Fmoc)], 79.4 [C (Boc)], 120.0 [2CH (Fmoc)], 125.2, 127.1 [4CH (Fmoc)], 127.6, 127.7 [4CH (Bn)], 128.7 [3CH (Fmoc and Bn)], 137.9 [C (Bn)], 141.3 [2C (Fmoc)], 143.8 [2C, Fmoc], 156.4 [CO (Fmoc)], 156.8 [CO (Boc)], 171.9 (CO). ES-MS *m/z* [M+1]⁺ calcd. for C₃₂H₃₈N₃O₅ 544.27; Found 544.36 (100%). Anal. calcd. for C₃₂H₃₇N₃O₅: C, 70.70; H, 6.86; N, 7.73. Found: C, 70.82; H, 6.96; N, 7.59.

4.2.2. Fmoc-Lys(Boc)-NHBN (2b)

White solid (99%). Mp 155-156 °C; [α]_D²⁰ -2.6 (c 1.1, CHCl₃); HPLC *t*_R 26.38 min; ^1H NMR (300 MHz, CDCl₃) δ 1.34 (m, 2H, γ -H), 1.41 (s, 9H, Boc), 1.60 (m, 2H, β -H), 1.80 (m, 2H, δ -H), 3.08 (m, 2H, ϵ -H), 4.17 [t, 1H, *J* = 7 Hz, CH (Fmoc)], 4.37 [m, 2H, CH₂ (Fmoc)], 4.38 (m, 1H, α -H), 4.43 [m, 2H, CH₂ (Bn)], 4.61 (m, 1H, *NH*Boc), 5.54 (m, 1H, *NH*Fmoc), 6.52 (m, 1H, *NH*Bn), 7.21-7.77 [m, 13H, Ar (Fmoc and Bn)]. ^{13}C NMR (75 MHz, CDCl₃) δ 22.5 (C _{γ}), 28.4 [3CH₃ (Boc)], 29.6 (C _{β}), 32.0 (C _{δ}), 39.8 (C _{ϵ}), 43.5 [CH₂ (Bn)], 47.2 [CH (Fmoc)], 54.9 [C _{α}], 67.0 [CH₂ (Fmoc)], 79.3 [C (Boc)], 119.9 [2CH (Fmoc)], 125.1, 127.0, 127.7 [6CH (Fmoc)], 127.6, 127.7 [4CH (Bn)], 128.7 [CH (Bn)], 137.8 [C (Bn)], 141.2 [2C (Fmoc)], 143.8 [2C, Fmoc], 156.2 [CO (Fmoc)], 156.3 [CO (Boc)], 171.5 (CO). ES-MS *m/z* [M+1]⁺ calcd. for C₃₃H₄₀N₃O₅ 558.29; Found 558.42 (100%). Anal. calcd. for C₃₃H₃₉N₃O₅: C, 71.07; H, 7.05; N, 7.53. Found: C, 71.13; H, 7.18; N, 7.59.

4.2.3. Fmoc-Arg(Pbf)-NHBN (2c)

White solid (97%). Mp 129-130 °C; [α]_D²⁰ -1.2 (c 0.9, CHCl₃); HPLC *t*_R 27.48 min; ^1H NMR (300 MHz, CDCl₃) δ 1.14, 1.16 [2s, 6H, 2CH₃ (Pbf)], 1.50 (m, 2H, γ -H), 1.70 (m, 2H, β -H), 2.11, 2.50, 2.58 [3s, 9H, 3CH₃ (Pbf)], 2.96 [s, 2H, CH₂ (Pbf)], 3.30 (m, 2H, δ -H), 3.83 (dd, 1H, *J* = 6.5 and 13 Hz, α -H), 4.14 [t, 1H, *J* = 7 Hz, CH (Fmoc)], 4.46-4.51 [m, 4H, CH₂ (Bn) and CH₂ (Fmoc)], 5.71 (m, 1H, *NH*Fmoc), 6.39 (m, 3H, Guanidine Group), 6.52 (m, 1H, *NH*Bn), 7.11-7.83 [m, 13H, Ar (Fmoc and Bn)]. ^{13}C NMR (75 MHz, CDCl₃) δ 12.9, 18.3, 19.7 [3CH₃ (Pbf)], 23.8 [2CH₃ (Pbf)], 25.8 (C _{γ}), 30.7 (C _{β}), 40.6 (C _{δ}), 42.6 [CH₂ (Bn)], 43.8 [CH₂ (Pbf)], 47.5 [CH₂ (Fmoc)], 54.7 (C _{α}), 67.5 [CH₂ (Fmoc)], 86.8 [C (Pbf)], 117.9 [C (Pbf)], 120.4 [2CH (Fmoc)], 125.1 [C (Pbf)], 125.2, 127.5 [4CH (Fmoc)], 127.7, 128.0 [4CH (Bn)], 128.1 [2CH (Fmoc)], 128.9 [CH (Bn)], 132.7 [C (Pbf)], 138.5 [C (Pbf)], 138.8 [C (Bn)], 141.6 [2C (Fmoc)], 144.1 [2C, Fmoc], 156.9 [CO (Fmoc)], 158.0 [C (Guanidine Group)], 172.6 (CO). ES-MS *m/z* [M+1]⁺ calcd. for C₄₁H₄₈N₅O₆S 738.32; Found 738.56 (100%). Anal. calcd. for C₄₁H₄₇N₅O₆S: C, 66.73; H, 6.42; N, 9.49. Found: C, 66.91; H, 6.48; N, 9.37.

4.3. General procedure for the synthesis of the N_α -deprotected basic amino acid-derived benzyl amides **3a-c**

EtNH₂ (7.3 g, 10.4 mL, 100 mmol) was added to a solution of the corresponding N_α -Fmoc-protected benzyl amide **2a-c** (10 mmol) in CH₃CN (200 mL) and the mixture was stirred at room temperature for 3 h. After this time, the precipitate was filtered off and washed with CH₃CN (3×10 mL) and the solution was evaporated to dryness. Flash chromatography of the residue with 0-20% MeOH in EtOAc gradient as eluent yielded the respective N_α -deprotected benzyl amide **3a-c**.

4.3.1. H-Orn(Boc)-NHBn (**3a**)

White solid (100%). Mp 96-97 °C; $[\alpha]_D^{20}$ +8.9 (*c* 1.2, MeOH); HPLC *t_R* min 12.76 min; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.05-1.79 (m, 4H, β -H and γ -H), 1.39 (s, 9H, Boc), 2.89 (m, 2H, δ -H), 3.15 (m, 1H, α -H), 3.33 (bs, 2H, NH₂), 4.25 [d, 2H, *J* = 6 Hz, CH₂ (Bn)], 6.80 (m, 1H, *NHBoc*), 7.13-7.40 (m, 5H, Ar), 8.31 (m, 1H, *NHBn*). ¹³C NMR (75 MHz, DMSO-*d*₆) δ 26.5 (*C_{\gamma}*), 28.6 [3CH₃ (Boc)], 32.9 (*C_{\beta}*), 40.7 (*C_{\delta}*), 42.2 [CH₂ (Bn)], 54.9 (*C_{\alpha}*), 77.6 [C (Boc)], 127.7, 128.0, 129.0 [5CH (Bn)], 138.7 [C (Bn)], 155.9 [CO (Boc)], 175.6 (CO). ES-MS *m/z* [M+1]⁺ calcd. for C₁₇H₂₈N₃O₃ 322.21; Found 322.40 (100%). Anal. calcd. for C₁₇H₂₇N₃O₃: C, 63.53; H, 8.47; N, 13.07. Found: C, 63.59; H, 8.56; N, 13.02.

4.3.2. H-Lys(Boc)-NHBn (**3b**)

White solid (100%). Mp 112-113; $[\alpha]_D^{20}$ +6.8 (*c* 1.1, MeOH); HPLC *t_R* 12.89 min; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.32-1.44 (m, 6H, β -H, γ -H and δ -H), 1.30 (s, 9H, Boc), 2.87 (m, 2H, ϵ -H), 3.13 (dd, 1H, *J* = 6.5 and 13 Hz, α -H), 3.31 (m, 2H, NH₂), 4.27 [d, 2H, *J* = 6 Hz, CH₂ (Bn)], 6.73 (d, 1H, *J* = 5.5 Hz, *NHBoc*), 7.11-7.43 (m, 5H, Ar), 8.31 (t, 1H, *J* = 6 Hz, *NHBn*). ¹³C NMR (75 MHz, DMSO-*d*₆) δ 23.0 (*C_{\gamma}*), 23.6 (*C_{\delta}*), 28.6 [3CH₃ (Boc)], 29.8 (*C_{\beta}*), 35.2 (*C_{\epsilon}*), 42.4 [CH₂ (Bn)], 55.1 [*C_{\alpha}*], 77.6 [C (Boc)], 127.7, 128.0, 129.0 [5CH (Bn)], 138.7 [C (Bn)], 155.9 [CO (Boc)], 175.5 (CO). ES-MS *m/z* [M+1]⁺ calcd. for C₁₈H₃₀N₃O₃ 336.22; Found 336.28 (100%). Anal. calcd. for C₁₈H₂₉N₃O₃: C, 64.45; H, 8.71; N, 12.53. Found: C, 64.48; H, 8.78; N, 12.41.

4.3.3. H-Arg(Pbf)-NHBn (**3c**)

White solid (100%). Mp 136-137; $[\alpha]_D^{20}$ +7.4 (*c* 0.1, MeOH); HPLC *t_R* 27.48 min; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.12, 1.15 [2s, 6H, 2CH₃ (Pbf)], 1.07-1.31 (m, 2H, γ -H), 1.51-1.88 (m, 2H, β -H), 2.10, 2.50, 2.58 [3s, 9H, 3CH₃ (Pbf)], 2.95 [s, 2H, CH₃ (Pbf)], 3.06-3.56 (m, 2H, δ -H), 3.84 (dd, 1H, *J* = 6.5 and 13 Hz, α -H), 4.38 [s, 2H, CH₂ (Bn)], 6.44 (m, 3H, Guanidine Group), 7.09-7.42 (m, 5H, Ar), 7.93 (s, 1H, *NHBn*). ¹³C NMR (75 MHz, DMSO-*d*₆) δ 12.9, 18.4, 19.7 [3CH₃ (Pbf)], 23.9 [2CH₃ (Pbf)], 26.0 (*C_{\gamma}*), 32.4 (*C_{\beta}*), 40.9 (*C_{\delta}*), 42.5 [CH₂ (Bn)], 43.6 [CH₂ (Pbf)], 54.7 (*C_{\alpha}*), 86.8 [C (Pbf)], 117.9, 125.0 [2C (Pbf)], 127.7, 128.0, 129.0 [5CH (Bn)], 132.6 [C (Pbf)], 133.4 [C (Pbf)], 138.7 [C (Bn)], 138.9 [C (Pbf)], 157.2 [C (Guanidine Group)], 171.6 (CO). ES-MS *m/z* [M+1]⁺ calcd. for C₂₆H₃₈N₅O₄S 516.26; Found 516.38 (100%). Anal. calcd. for C₂₆H₃₇N₅O₄S: C, 60.56; H, 7.23; N, 13.58. Found: C, 60.63; H, 7.37; N, 13.46.

4.4. General procedure for the synthesis of α -amino nitriles **9a-c** and **11a,b**

ZnCl₂ (1.36 g, 10 mmol) or Boc-Pro-OH (5 mmol) was added to a -20 °C cooled solution of the corresponding α -amino acid benzyl amide **3a-c** (10 mmol) and aldehyde **4** and **5** (8 mmol) in CH₂Cl₂ or MeOH (100 mL). After 1 h of stirring at -20 °C, TMSCN (1.49 g, 2.09 mL, 15 mmol) was added and the mixture was stirred at the temperature and for the time indicated in Table 1. Then, solvent was evaporated under vacuum. The residue was dissolved in EtOAc (200 mL), washed with H₂O (3×25 mL) and

brine (25 mL), and dried over Na₂SO₄. Evaporation, followed by flash chromatography, using 20-60% EtOAc gradient in hexane as eluent, afforded the protected α -amino nitriles **9a-c** and **11a,b**, whose more significant analytical and spectroscopic data are shown in Tables 2 and 3.

4.5. Synthesis of (S)-methyl 5-[(*tert*-butoxycarbonyl)amino]-2-[(*R*)- and (S)-1-cyano-2-phenylethyl]amino]-pentanoate [(*R*)- and (S)-**14a**]

Triethylamine (250 μ L, 1.8 mmol) was added to a solution of H-Orn(Boc)-OMe·HCl (509 mg, 1.8 mmol) in CH₂Cl₂ (20 mL). After being stirred at rt for 15 min, the reaction mixture was cooled at -20°C. Then, ZnCl₂ (244 mg, 1.8 mmol) and phenylacetaldehyde (173 mg, 330 μ L, 1.44 mmol) were added, and the mixture was stirred at this temperature for 1 h. Afterwards, TMSCN (268 mg, 0.332 mL, 2.7 mmol) was added and the mixture was stirred overnight at 0°C. The reaction mixture was work up as above indicated for the synthesis of amino nitriles **9** and **11**. Flash chromatography, using 20-60% EtOAc gradient in hexane as eluent, allowed the resolution of the two epimers.

(*R*)-**14a**: (182 mg, 27%); HPLC *t_R* 22.24 min; $[\alpha]_D^{20}$ +7.5 (*c* 1, MeOH); ¹H NMR (400 MHz, CDCl₃) δ 1.44 (s, 9H, Boc), 1.54-1.90 (m, 4H, β - and γ -H), 2.99-3.10 (m, 4H, 3- and δ -H), 3.37 (t, *J* = 6 Hz, 1H α -H), 3.71 (dd, *J* = 6 and 1 Hz, 1H, 2-H), 3.74 (s, 3H, OMe), 4.52 (s, 1H, *NH*-Boc), 7.10-7.43 (m, 5H, aromatics); ¹³C NMR (100 MHz, CDCl₃) δ 26.03 (CH₂, *C_{\gamma}*), 28.64 (CH₃, Boc), 30.12 (CH₂, *C_{\beta}*), 40.1 (CH₂, *C_{\delta}*), 40.22 (CH₂, *C₃*), 51.04 (CH, *C₂*), 52.46 (CH₃, OMe), 59.63 (CH, *C_{\alpha}*), 77.9 (C, Boc), 119.48 (CN), 127.81, 128.98, 129.71 (CH, Ph), 135.19 (C, Ph), 156.13 (C, Boc), 174.25 (C, CO₂); ES-MS *m/z* [M+1]⁺ calcd. for C₂₀H₃₀N₃O₄, 376.22; found 376.50 (100%). Anal. calcd. for C₂₀H₂₉N₃O₄: C, 63.98; H, 7.79; N, 11.19. Found: C, 63.97; H, 7.84; N, 11.25.

(*S*)-**14a**: (190 mg, 28%); HPLC *t_R* 22.03 min; $[\alpha]_D^{20}$ -22.9 (*c* 1.2, MeOH); ¹H NMR (400 MHz, CDCl₃) δ 1.44 (s, 9H, Boc), 1.48-1.82 (m, 4H, β - and γ -H), 2.98-3.16 (m, 4H, 3- and δ -H), 3.52 (dd, *J* = 7 and 5 Hz, 1H, α -H), 3.70 (s, 3H, OMe), 3.85 (t, *J* = 7 Hz, 1H, 2-H), 4.58 (s, 1H, *NH*-Boc), 7.17-7.40 (m, 5H, aromatics); ¹³C NMR (100 MHz, CDCl₃) δ 26.43 (CH₂, *C_{\gamma}*), 28.38 (CH₃, Boc), 30.4 (CH₂, *C_{\beta}*), 39.7 (CH₂, *C_{\delta}*), 40.0 (CH₂, *C₃*), 50.5 (CH, *C₂*), 52.1 (CH₃, OMe), 58.7 (CH, *C_{\alpha}*), 77.9 (C, Boc), 119.3 (CN), 127.66, 128.8, 129.3 (CH, Ph), 134.7 (C, Ph), 155.9 (C, Boc), 174.0 (C, CO₂); ES-MS *m/z* [M+1]⁺ calcd. for C₂₀H₃₀N₃O₄, 376.22; found 376.50 (100%). Anal. calcd. for C₂₀H₂₉N₃O₄: C, 63.98; H, 7.79; N, 11.19. Found: C, 64.03; H, 7.92; N 10.98.

4.6. Synthesis of (3*S*,5*R*)- and (3*S*,5*S*)-3-[3-(*tert*-butoxycarbonyl)-aminopropyl]-5-phenylmethyl-2-oxopiperazine [(*R*)- and (S)-**15a**]

10% Pd(C) (40 mg) was added to a solution of the corresponding amino nitrile **14a** (150 mg, 0.4 mmol) in MeOH (25 mL), and the mixture was hydrogenated at 1 atm of H₂ and rt for 24 h. Afterwards, the mixture was filtered through celite and this was washed with methanol (3×50 mL). The filtrates were evaporated, the residue was dissolved in toluene (10 mL) and heated at 100°C for 24 h. Then, the solvent was removed under reduce pressure, and the residue was purified by flash chromatography, using 20-60% EtOAc gradient in hexane as eluent.

Table 2More significant analytical and spectroscopic data of α -amino nitriles **9a-c**

Compd ^a	(<i>R</i>)- 9a	(<i>S</i>)- 9a ^b	(<i>R</i>)- 9b	(<i>S</i>)- 9b	(<i>RS</i>)- 9c ^c	
R ¹	Boc	Boc	Boc	Boc	C(NH ₂)N-Pbf	
n	3	3	4	4	3	
Config (*)	(<i>R</i>)	(<i>S</i>)	(<i>R</i>)	(<i>S</i>)	(<i>R</i>)	(<i>S</i>)
Molecular formula	C ₂₆ H ₃₄ N ₄ O ₃	C ₂₆ H ₃₄ N ₄ O ₃	C ₂₇ H ₃₆ N ₄ O ₃	C ₂₇ H ₃₆ N ₄ O ₃	C ₃₅ H ₄₄ N ₆ O ₄ S	
Yield (%)	28	35	29	32	85	
HPLC <i>t</i> _R (min) ^d	23.3	23.7	23.7	24.1	5.14	5.48
[α] _D ²⁰	+7.5 (c 1, MeOH)	+21.3 (c 0.9, MeOH)	+9.2 (c 1.2, MeOH)	+27.1 (c 1, MeOH)	-	-
MS [M+1] ⁺						
Calculated	451.26	451.26	465.28	265.28	645.31	
Found	451.48	451.48	465.56	465.56	645.46	
¹ H NMR ^e						
2-H	3.73	3.49	3.79	3.48	3.81	3.48
3-H	2.96	2.83-3.14	2.91-3.13	2.94, 3.09	2.85-3.05	
J _{2,3}	7	7	7	6	7	6
Amino acid						
α -H	3.28	3.37	3.25	3.33	3.34	3.36
β -H	1.56-1.71	1.09-1.89	1.53-1.85	1.73-1.86	1.40-1.85	
γ -H	1.44-1.57	1.09-1.89	1.53-1.85	1.48-1.63	1.40-1.85	
δ -H	2.97-3.15	2.83-3.14	1.14-1.38	1.62-1.74	3.05-3.26	
ϵ -H			2.91-3.13	2.99-3.16	-	
NH-R ²	4.55	4.65	4.53	4.62	6.10-6.40	
NH-Bn	6.96	6.74	7.05	6.70	6.95-7.38	7.50
CH ₂ (Bn)	4.35	3.99, 4.25	4.3, 4.48	3.96, 4.28	4.33	4.03, 4.24
J _{NH,CH₂ (Bn)}	6	6	6.5	6	6	6
¹³ C NMR ^f						
CN	119.8	119.9	119.2	119.6	120.1	120.4
C ₂	51.6	51.1	51.1	51.2	51.3	51.8
C ₃	39.9	39.8	39.2	39.9	39.9	
Amino acid						
C _{α}	60.4	60.6	60.9	61.2	60.4	61.1
C _{β}	30.9	33.8	29.8	29.8	31.1	31.1
C _{γ}	26.5	24.9	22.3	22.7	25.7	26.0
C _{δ}	39.8	39.5	32.6	32.8	41.0	
C _{ϵ}	-	-	38.7	39.4	-	-
CO	173.1	172.4	172.7	172.5	174.0	173.3
CH ₂ (Bn)	43.8	42.8	43.4	42.7	43.7	43.3
C(NH)NH	-	-	-	-	156.7	

^aFoams, satisfactory analysis for C, H, N.^bm.p = 120-121 °C (Hexane/EtOAc).^c(*R*):(*S*) Epimer ratio = 1:3.^dSunfire C₁₈ (4.6×150 mm, 3.5 μ m), 10-100% gradient of A in B for 30 min, except for (*RS*)-**9c**, where 50-70% gradient of A in B for 8 min was used.^eSpectra registered at 300 or 400 MHz in CDCl₃, assigned with the help of COSY and HSQC spectra.^fSpectra registered at 75 or 100 MHz in CDCl₃, assigned with the help of HMBC and HSQC spectra.

Table 3
More significant analytical and spectroscopic data of α -amino nitriles **11a,b**

Compd ^a	(RS)-11a^b		(RS)-11b^b	
R ¹	Boc		Boc	
n	3		4	
Config (*)	(R)	(S)	(R)	(S)
Molecular formula	C ₂₇ H ₃₆ N ₄ O ₃		C ₂₈ H ₃₈ N ₄ O ₃	
Yield (%)	72%		70%	
HPLC <i>t</i> _R (min) ^c	24.1	24.3	24.5	24.8
MS [M+1] ⁺				
Calculated	465.28		479.29	
Found	465.50		479.50	
¹ H NMR ^d				
2-H	3.51	3.40	3.53	3.29-3.41
3-H		2.66-2.91		1.88-2.20
4-H		2.98-3.13		2.63-2.88
J _{2,3}	7	7	7	7
Amino acid				
α -H	3.32	3.46	3.23	3.29-3.41
β -H		1.46-1.81		1.68-1.85
γ -H		3.13-3.24		1.31-1.52
δ -H		1.94-2.15		1.52-1.67
ϵ -H		-		2.98-3.14
NH-R ²		4.76		4.68
NH-Bn		7.04		7.08-7.21
CH ₂ (Bn)		4.35, 4.40		4.36, 4.42
J _{NH,CH₂} (Bn)		6		4
¹³ C NMR ^e				
CN	119.8	119.7	120.0	119.8
C ₂		49.1, 49.3		49.4, 49.6
C ₃		31.7		32.0
C ₄		34.7, 35.1		34.9, 35.3
Amino acid				
C _{α}	60.2	59.5	61.6	60.8
C _{β}		30.8		30.1
C _{γ}		26.2, 26.6		22.6, 22.9
C _{δ}		39.2, 39.4		33.2, 33.2
C _{ϵ}		-		39.8
CO	173.3	172.8	173.5	172.9
CH ₂ (Bn)	43.4	43.1	43.6	43.3

^aFoams, satisfactory analysis for C, H, N.

^b(R):(S) Epimer ratio = 1:1.

^cSunfire C₁₈ (4.6×150 mm, 3.5 μ m), 10-100% gradient of A in B for 30 min.

^dSpectra registered at 300 or 400 MHz in CDCl₃, assigned with the help of COSY and HSQC spectra.

^eSpectra registered at 75 or 100 MHz in CDCl₃, assigned with the help of HMBC and HSQC spectra.

(R)-15a: (86 mg, 62%); HPLC-MS *t*_R 3.03 min; ¹H NMR (400 MHz, CDCl₃) δ 1.44 (s, 9H, Boc), 1.29-1.96 (m, 4H, β - and γ -H), 2.74 (d, J = 7 Hz, 2H, 5-CH₂) 3.01-3.26 (m, 5H, 5-, 6- and δ -H), 3.43 (dd, J = 4 and 7 Hz, 1H, 3-H), 4.95 (s, 1H, NH-Boc), 6.28 (s, 1H, 1-H), 7.06-7.40 (m, 5H, aromatics); ¹³C NMR (100 MHz, CDCl₃) δ 25.9(CH₂, C _{γ}), 29.3 (CH₃, Boc), 29.7 (CH₂, C _{β}),

39.9 (CH₂, 5-CH₂), 40.2 (CH₂, C _{γ}), 47.8 (CH₂, C₆), 53.8 (CH, C₅), 58.5 (CH, C₃), 79.1 (C, Boc), 126.9, 128.4, 129.0 (CH, Ph), 141.6 (C, Ph), 155.9 (C, Boc), 172.7 (C, C₂); ES-MS *m/z* [M+1]⁺ calcd. for C₁₉H₃₀N₃O₃, 348.22; found 348.42 (100 %). Anal. calcd. for C₁₉H₂₉N₃O₃: C, 65.68; H, 8.41; N, 12.09. Found: C, 65.72; H, 8.63; N 11.97.

(S)-15a: (98 mg, 71%); HPLC-MS t_R 2.88 min; 1H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 9H, Boc), 1.30-1.90 (m, 4H, β - and γ -H), 2.70 (d, $J=7$ Hz, 2H, 5- CH_2), 2.93-3.08 (m, 3H, α - and δ -H), 3.17-3.28 (m, 2H, 5- and 6-H), 3.41 (dd, $J=4$ and 9 Hz, 1H, 3-H), 4.76 (bs, 1H, NH -Boc), 6.82 (bs, 1H, 1-H), 7.11-7.27 (m, 5H, aromatics); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5 (CH_2 , C_7), 27.4 (CH_3 , Boc), 28.2 (CH_2 , C_β), 38.05 (CH_2 , 5- CH_2), 39.1 (CH_2 , C_7), 46.4 (CH_2 , C_6), 47.4 (CH , C_5), 55.3 (CH , C_3), 78.0 (C, Boc), 125.8, 127.7, 128.0 (CH, Ph), 136.5 (C, Ph), 154.9 (C, Boc), 171.9 (C, C_2); ES-MS m/z $[M+1]^+$ calcd. for $C_{19}H_{30}N_3O_3$, 348.22; found 348.42 (100 %). Anal. calcd. for $C_{19}H_{29}N_3O_3$: C, 65.68; H, 8.41; N, 12.09. Found: C, 65.68; H, 8.43; N 11.99.

4.7. Synthesis of (S)-N-benzyl-5-[(*tert*-butoxycarbonyl)-amino]-2-[(S)-1-cyano-2-phenylethylamino]-pentanamide [(S)-9a] from (S)-14a

1N NaOH solution (0.4 ml, 0.4 mmol) was added to a solution of (S)-14a (49 mg, 0.13 mmol) in (1:1) 1,4-dioxane/water mixture (2 mL) and the mixture was stirred at room temperature for 30 min. Then, the reaction mixture was acidified to pH 3 with 1N HCl, the organic solvent was evaporated and the aqueous phase was extracted with EtOAc (3 $\times$ 25 mL). The combined organic phases were dried over Na_2SO_4 and evaporated to dryness. The residue (47 mg, 0.13 mmol) was dissolved in acetonitrile (5 mL). To this solution, HOBt (18 mg, 0.13 mmol), DCC (55 mg, 0.27 mmol) and $BnNH_2$ (14 mg, 15 μ L, 0.13 mmol) were successively added at rt. After 2 h, the precipitated dicyclohexyl urea was filtered off and the filtrate was evaporated to dryness. The residue was dissolved in EtOAc (25 mL). This solution was washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4 and evaporated to dryness. Flash chromatography of the residue provided a product (56 mg, 95 %) identical to (S)-9a, whose synthesis by the Strecker reaction is above described.

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