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New strategies towards proline derivatives as conformationally constrained arginine analogues

Nadia Pellegrini, Martine Schmitt,* Sébastien Guery and Jean-Jacques Bourguignon

Laboratoire de Pharmacochimie de la Communication Cellulaire, UMR 7081 CNRS/ULP, Université Louis Pasteur, Faculté de Pharmacie, 74 Route du Rhin, 67401 Illkirch Cedex, France

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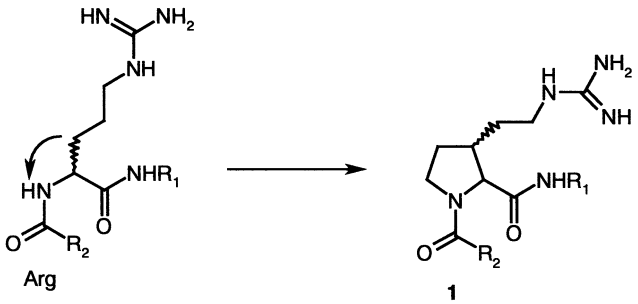
Abstract—The cyano derivatives of 3-functionalized dehydroprolines led to arginine semi–constrained analogues.

The need for selective ligands acting at neuropeptides receptors constitutes an important challenge for medicinal chemists. Starting from the structures of the endogenous ligand, several studies highlighted the specific role played by an arginine residue (neuropeptide FF, neuropeptide Y, thrombin). In addition, substituted arginine derivatives have been described as potent ligands of these receptors (Scheme 1).[1–3]

Proline is a unique natural α-aminoacid inducing specific electronic and geometric features, when compared to alanine. When such a ring is included in the structure of other amino acids, its presence restricts its conformational flexibility, which may efficiently modify binding to its target. In addition, this peptidomimetic compound is expected to be more stable towards metabolic enzymes. The use of proline as a template in order to introduce conformational restrictions has already been described for norleucine, phenylalanine, tyrosine, aspartic acid, glutamic acid and glutamine.[4,5]



Code	Config.	R_1	R_2
BIBP 3236	D	4-OH-Ph-CH_2-	$(Ph)_2CH$-
RF2	L	$PheNH_2$	Ph

Scheme 1.

Several ornithine and arginine semi-rigid analogues have been described in the literature[6–9] in particular *trans*-3-substituted proline.[10] In this latter case, the authors accomplished the synthesis in a seven-step sequence starting from a non commercially available α-unsaturated lactam. In addition, only the *trans* isomer could be obtained.

We now describe a convenient and mild preparation of *cis*- and *trans*-*N*-acyl 3-substituted prolines **1** as semi-rigid BIBP 3236[2] or RF2[1] derivatives (Scheme 1). This method is based on a catalytic hydrogenation of the double bond of a 3-substituted *N*-acyl pyrrole **2** as outlined in Scheme 2. This general strategy has been earlier successfully used by us for the preparation of 3-acetic acid indoline-2-carboxylic acid and of 3-phenyl indoline-2-carboxamides, as semi-rigid glutamic acid and phenylalanine mimetics, respectively.[11]

Retrosynthetically, the dihydropyrrole **2** could be prepared from 3-pyrrolidinone **3** by a two-step procedure including successively a Wittig reaction and a reduction of the corresponding ester into an alcohol (Scheme 2).

Following a literature procedure, the β-keto pyrrolidine **3** was prepared by intramolecular Dieckman-type cyclizations of several *N*-acyl glycinates (Scheme 3).

Keywords: arginines; constrained analogues; Mitsunobu; proline; pyrrolidine.

* Corresponding author. Tel.: +33 390 24 42 31; fax: +33 390 24 43 10; e-mail: schmitt@pharma.u-strasbg.fr

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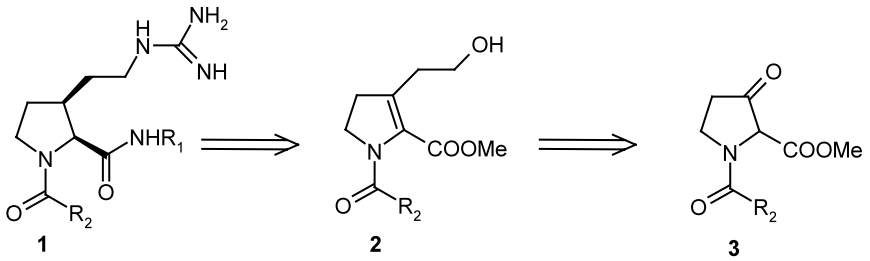
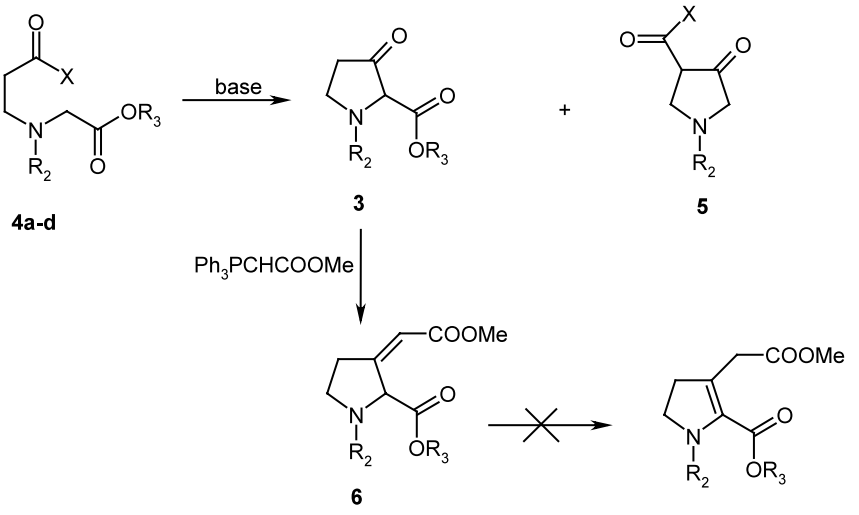


Scheme 2.



Scheme 3.

Table 1.

Entry	Cpd 4	X	R_2	R_3	**3** (%)	**5** (%)
1	a	OEt	Boc	Et	[a]	[a]
2	b	SEt	COOEt	Et	77	–
3	c	-N(OMe)Me	Boc	Et	73	–
4	d	OMe	Bz	*t*-Bu	45	[b]

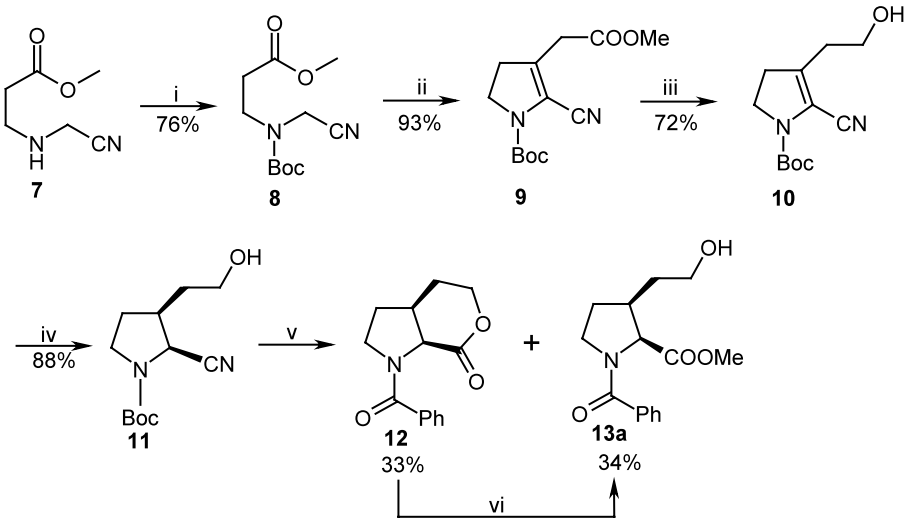
[a] In our hands, regioisomers leading from **4a** could not separated.
[b] Recovery of significant amount of *N*-benzoyl glycinate as the result of retro-Michael addition.

Rapoport et al.[12] described two separable regioisomers (**3** and **5**) which could be obtained by a similar intramolecular cyclization, but in our hands, the separation failed (entry 1 in Table 1). The use of a semi-thiol ester,[13] or of the Weinreb amide,[14] as more electrophilic ester equivalents, was found to be more interesting (entries 2 and 3). We have observed that the introduction of a more bulky ester ($R_3 = t$-Bu, R_2 = Bz, entry 4) altered the regiochemical selectivity. In this case, **3** was obtained in 45% yield accompanied by 55% of starting *N*-benzoyl glycinate as the result of retro-Michael addition.

Treatement of the β-ketoester **3** with Wittig reagent led to the diester **6** in 70% yield. In contrast to the indoline series,[11] this compound still presents an exocyclic double bond, which could not allow a C-2 and C-3 stereocontrol (Scheme 3). Therefore, we planned to replace the ester in position 2 by a cyano group as a more electron-withdrawing group, to favor migration of the double bond into the pyrrolidine ring (Scheme 4).

The cyano ester **7**[12] was first protected as a *N*-Boc derivative. The enol obtained by cyclization using *t*BuOK was trapped with TMSCl. After removal of TMS, the resulting 3-pyrrolidinone reacted with [(methoxycarbonyl)methylene]triphenylphosphorane to afford the expected dihydropyrrole **9** in good yield. It is noteworthy that both the *N*-Boc acyl and cyano groups decreased H-2 proton acidity, which led to the *endo*-cyclic migration of the double bond, as shown by the NMR spectrum.[15] In addition, as endocyclic migration could be efficiently controlled, this approach can be generalized to other 3-substituted proline groups as original semi-constrained α-aminoacids.

Reduction of the methyl ester using $LiBH_4$ and catalytic hydrogenation of the dihydropyrrole ring afforded

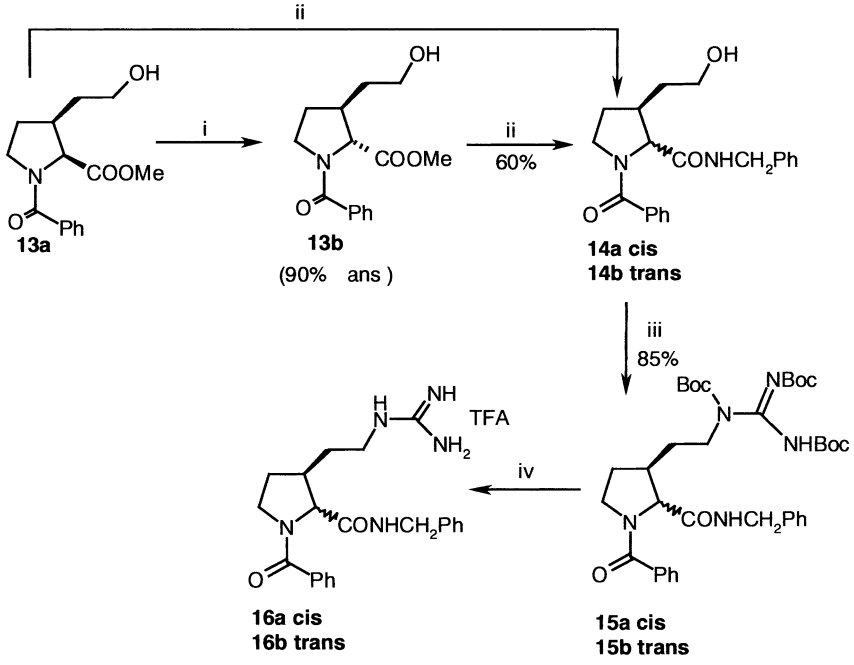


Scheme 4. (i) $(Boc)O_2$, (ii) 1. *t*-BuOk, toluene then TMSCl, 2. H_2O, 3. $Ph_3PCHCOOMe$, toluene, (iii) $LiBH_4$, THF, (iv) H_2/Pd/C/MeOH, (v) 1. HCl (g), MeOH, 2. $PhCOCl/TEA/CH_2Cl_2$, (vi) MeOH, HCl, quantitative.

the *cis*-3-substituted proline **11**, characterized by an AB system in its ^1H NMR, and only one C-2 methine signal in its ^{13}C NMR spectrum. Simultaneous acidic methanolysis of the cyano group and *N*-Boc deprotection followed by direct *N*-acylation gave a mixture of two compounds in 67% overall yield; they were identified as the alcohol ester **13a** and the corresponding lactone **12**. This latter compound generated quantitatively the open derivative **13a** by methanolysis. NOE experiments confirmed the already established *cis* configuration for **13a**. A weak NOE was also observed between H-2 and H-3.

Compound **13a** could be epimerized in a 9:1 ratio into the *trans* isomer **13b** by means of 3.5 equiv. of LDA at −78°C for 3 h[16] (Scheme 5).[17] Conversion of the methyl ester into a *N*-benzylamide was carried out with cyanide anion as catalyst.[18] The resulting amides **14a** and **14b** have been separated by chromatography on silica. Guanidylation of **14a** and **14b** with guanidine tri-Boc using Mitsunobu conditions[19] followed by removal of the protecting groups yielded the guanidines **16a** and **16b** [MS m/z 394.24 $(M+H)^+$].

In conclusion, motivated by the pharmacological interest we may expect for either the *cis* and the *trans* stereomers **16a** and **16b** as arginine semi-rigid derivatives, we developed an efficient method for their preparation. In addition functionalization of position 3 of proline combined with an endocyclic double bond as an efficient method for controlling the configuration at C-2 and C-3 of the pyrrolidine ring will be very useful in the future for building interesting alkaloid analogues.



Scheme 5. (i) LDA/THF, (ii) $PhCH_2NH_2$/NaCN/MeOH, (iii) tri-Boc guanidine/Ph_3P/DEAD/THF, (iv) TFA.

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15. ^{1}H NMR **9**: 3.39 (s, 2H, CH_2COOMe); **6** (R_2 = Boc, R_3 = Et) mixture of rotamers 4.74 (s, 0.63H, NC*H*-COOEt), 4.82 (s, 0.37H, NC*H*COOEt), 6.00 (s, 0.63H, C=C*H*), 6.05 (s, 0.37H, C=C*H*).
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17. Compounds **13a** and **13b** could not be separated. HPLC: **13a** R_{t1} = 14.43 min, **13b** R_{t2} = 14.76 min (Vydac, gradient H_2O/MeOH: 30 min [98/2-0/100], flow: 1 mL/min). ^{1}H NMR **13b**: 2.5 (1H, m, H-3), 4.39 (1H, d, J = 7.5 Hz, H-2); **13a**: 2.7 (1H, m, H-3), 4.72 (1H, d, J = 8.1 Hz, H-2).
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