

Transannular Rearrangement of Activated Lactams: Stereoselective Synthesis of Substituted Pyrrolidine-2,4-diones from Diketopiperazines**

Daniel Farran, Isabelle Parrot, Jean Martinez,* and Georges Dewynter*

A combination of two functional groups in a given molecule often conveys a new reactivity that is not equivalent to that expected if the two functionalities are considered independently. Such combinations can be seen as a unique functionalities in their own right, and their presence could lead to unexpected transformations during the course of otherwise well known reactions. We describe herein the unprecedented reactivity of *N*-carboxy derivatives of 2,5-diketopiperazines (DKPs). The reaction of these derivatives under basic conditions led to novel substituted pyrrolidine-2,4-diones.^[1] This serendipitous C aminoacylation of amino acids could allow the straightforward synthesis of highly valuable pharmacological scaffolds. Analogous structures to those of the pyrrolidine-2,4-dione derivatives are present in various natural and synthetic compounds, such as ascorbic acid,^[2,3] which displays a broad range of well-known biological properties, and tetramic acid,^[4] which exhibits antibacterial and antiviral activities. Furthermore, pyrrolidine-2,4-diones serve as significant intermediates in the synthesis of statins,^[5–11] a key structural motif found in peptidomimetic inhibitors of proteases, such as aspartic proteases.^[13,14] Owing to the lack of a general synthetic route to 3-amino-, 3-alkyl derivatives of pyrrolidine-2,4-diones, the absence of a stereoselective pathway to these compounds,^[15–18] and the significance of such pharmacophore moieties, we became interested in developing a stereoselective ring contraction of bis(*N*-*tert*-butoxycarbonyl)-DKPs (bis-Boc-DKPs) into pyrrolidine-2,4-diones.

DKPs, the smallest cyclic peptides, are not only of interest because of their natural occurrence and pharmacological properties,^[19] but they have also been used widely as scaffolds in asymmetric synthesis and combinatorial chemistry.^[20] However, they are generally not suitable as starting materials in semisynthesis as a result of their high chemical stability and their ready racemization in alkaline media.^[21] We initially planned to prepare bis-Boc derivatives of DKPs to carry out ionic condensation reactions at the 3- and 6-positions by

enolate induction and to enhance the electrophilicity of such substituted lactams. To the best of our knowledge, there are few examples of reactions of Boc-DKPs under basic conditions. In the synthesis of coronamic acid, Bernabé and co-workers reported the opening of a mono-Boc-substituted derivative of a Pro-containing DKP by alkaline hydrolysis,^[22] whereas Nishiyama and co-workers described a modified Sasaki reaction in which a bis-Boc-DKP was alkylidenated with an aldehyde in the presence of potassium *tert*-butoxide with concomitant cleavage of one of the two protecting groups.^[23] We made the unexpected observation that instead of displaying conventional protecting-group behavior, the two Boc moieties on the nitrogen atoms of the heterocycle reacted under certain basic conditions as electron-withdrawing activators to promote the unusual transformation of bis-Boc-DKPs **1** into the corresponding 3-aminopyrrolidine-2,4-dione derivatives **2** and/or **3** (Table 1 and Table 2).

We first examined the reaction with the diprotected 3-alkyl piperazine-2,5-diones **1a–g** (Table 1). Interestingly, in the presence of *t*BuOK, the keto–enol equilibrium of unsymmetrical DKPs was shifted towards enol formation in all cases: A single product was detected and readily identified by ¹H NMR and ¹³C NMR spectroscopy (see the Supporting Information). The aminotetramates **2a–f** were formed in moderate to good yields with excellent enantioselectivities and complete retention of configuration. According to chiral HPLC analysis, the DKPs (3*S*)-**1b**, (3*R*)-**1c**, (3*S*)-**1d**, and

Table 1: Stereoselective ring contraction of unsymmetrical DKPs into 3-aminotetramates.

Entry	1	R	2	Yield [%] ^[a]	ee [%] ^[b]
1	1a	H	2a	72	–
2	1b	Me (<i>S</i>)	2b	60	> 99
3	1c	Me (<i>R</i>)	2c	64	> 99
4	1d	<i>i</i> Pr (<i>S</i>)	2d	82	> 99
5	1e	<i>i</i> Pr (<i>R</i>)	2e	84	> 99
6	1f	<i>s</i> Bu (<i>S</i>)	2f	71	> 95
7	1g	Bn (<i>S</i>)	2g	16	–

[a] Yield of product isolated by flash chromatography. [b] The ee values were determined by HPLC on a chiral phase; see the Supporting Information for details.

[*] D. Farran, Dr. I. Parrot, Prof. J. Martinez, Prof. G. Dewynter
Institut des Biomolécules Max Mousseron, UMR 5247
Université Montpellier
2, Place Eugène Bataillon, 34095 Montpellier Cedex 5 (France)
Fax: (+33) 4-6714-4866
E-mail: martinez@univ-montp1.fr
georges.dewynter@univ-montp2.fr

[**] We thank Dr. Loïc Toupet of the Groupe Matière Condensée et Matériaux (UMR 6626, Université Rennes 1) for X-ray analysis.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

(3*R*)-**1e** were converted with up to 99% *ee* into the isomers (5*S*)-**2b**, (5*R*)-**2c**, (5*S*)-**2d**, and (5*R*)-**2e**, respectively (Table 1, entries 2–5). We observed a totally regioselective ring contraction. Thus, N1 of the DKP was excluded from the ring system in each case, and the configuration at the C atom bonded to the side chain R of the DKP was retained in the product. In contrast, **2g** was generated in poor yield from the bis-Boc-substituted cyclo(Gly-Phe) **1g**; instead, racemic 3-benzyl-1-(*tert*-butoxycarbonyl)-3-(*tert*-butoxycarbonylamino)pyrrolidine-2,4-dione, which results from the more thermodynamically stable enolate, was the major product (46%; see the Supporting Information).

Encouraged by these results, we decided to apply this rearrangement to symmetrical DKPs (Table 2). We observed the formation from substrates **1h–j** of substituted pyrrolidine-

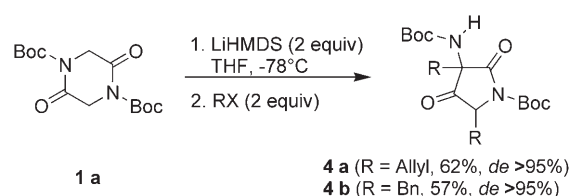
Table 2: Stereoselective ring contraction of symmetrical DKPs into pyrrolidine-2,4-diones.

Entry	1	R	3	Yield [%] ^[a]	<i>de</i> ^[b]
1	1h	Me (<i>S</i>)	3h	66	67
2	1i	<i>i</i> Pr (<i>S</i>)	3i	68	> 95
3	1j	MeO ₂ C(CH ₂) ₂ (<i>S</i>)	3j	29	> 95

[a] Yield of product isolated by flash chromatography. [b] The *de* values were determined by HPLC of the crude product; see the Supporting Information for details.

2,4-diones **3**, in which the two alkyl chains are on the same face of the heterocyclic ring, as shown by NOE experimental data for **3h** and the diastereoisomeric product (see the Supporting Information). Compounds **3** were obtained with good to excellent diastereoselectivity. Thus, the steric effect of the substituents at C3 and C6 appears to be key to the high diastereoselectivity observed. The occurrence of a retro-Michael reaction at the 3-position of the pyrrolidine-2,4-dione is a plausible explanation for the low yield and high diastereoselectivity found for the formation of **2j** from **1j** under basic conditions: A β elimination on the side chain of the glutamate led to the elimination of methyl acrylate. The resulting product with just one MeO₂C(CH₂)₂ side chain was obtained in 42% yield with > 95% *ee*.

To gain access to various functionalized pyrrolidine-2,4-diones, we examined the rearrangement in the presence of an alkylating agent added during the course of the reaction. With two equivalents each of a base and an electrophilic reagent, the bis-Boc cyclo(Gly-Gly) substrate **1a** was converted readily into the dialkylated pyrrolidine-2,5-diones **4a** and **4b** in a diastereoselective manner (Scheme 1). The positions of the side chains were established by ¹H NMR spectroscopic analysis by comparison with reported data for the previously described derivative **4b**.^[18] It was necessary to use LiHMDS instead of *t*BuOK for this reaction.^[24]



Scheme 1. Tandem rearrangement-alkylation of bis-Boc cyclo-(Gly-Gly). HMDS = hexamethyldisilazide. Bn = Benzyl.

By starting from unsymmetrical DKPs, we were then able to synthesize a range of derivatives **5** with the two side chains R¹ and R² on the same face of the heterocycle (Table 3). The

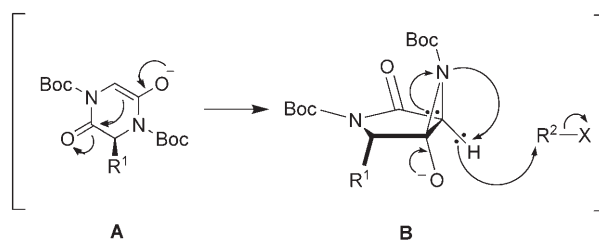
Table 3: Tandem rearrangement-alkylation of unsymmetrical DKPs.

Entry	1	R ² X	5	Yield [%] ^[a]	<i>de</i> ^[b]
1	1e	MeI	5a	60	> 95
2	1e	BnBr	5b	72	> 95
3	1e	EtO ₂ CCH ₂ I	5c	69	> 95
4	1e	CH ₂ =CHCH ₂ Br	5d	76	> 99
5	1e	(CH ₃) ₂ C=CHCH ₂ Br	5e	84	> 95
6	1f	CH ₂ =CHCH ₂ Br	5f	68	> 95

[a] Yield of product isolated by flash chromatography. [b] The ¹³C NMR spectra gave only one set of peaks; see the Supporting Information for details.

tandem rearrangement/alkylation reaction occurred exclusively on the Gly segment of the cyclic peptide. To the best of our knowledge, all substitution patterns accessible by our method have no precedent. Thus, this highly regioselective and diastereoselective tandem rearrangement-alkylation sequence allows the synthesis of highly valuable original scaffolds.

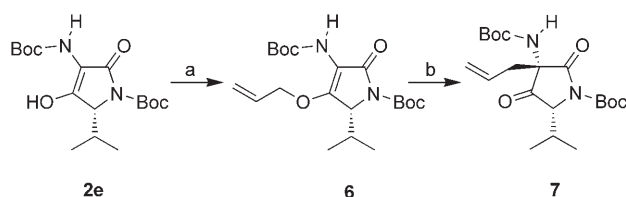
On the basis of X-ray analysis of the DKP **1e**,^[24] the observed strict conservation of the configuration of the starting material during the rearrangement, and the high stereoselectivity of the alkylation, we propose the following mechanism (Scheme 2): Under basic conditions, the kinetic enolate **A** is obtained in a first step from the activated DKP **1**



Scheme 2. Possible intermediates proposed to explain the observed stereoselectivity of the reaction.

without racemization. The transannular attack of **A** at the activated lactam carbonyl group then provides the oxanion **B**, in which the aziridine moiety is located on the less bulky face rather than on the face occupied by the side chain R^1 . In a last step, the opening of the aziridine ring leads to the desired bis-Boc 3-aminopyrrolidine-2,4-dione or the corresponding enol. In the presence of an alkylating reagent R^2-X , the constrained ring system may hinder the attack of **B** at the face of the heterocycle with the Boc-aziridine moiety. The electrophile can only approach the open face of the heterocycle, and the R^1 group is pointed away from the Boc-aziridine moiety. This hypothesis is consistent with the configuration established for compounds **5**. The unexpected rearrangement that we have described seems to be related to well-known conventional transformations, such as the Dieckmann and Gabriel-Colman reactions and the first step of the Dakin-West reaction. In accordance with the postulated mechanism, we propose the name “transannular rearrangement of activated lactams (TRAL)” for this reaction.

To expand the scope of the TRAL reaction, the asymmetric Claisen-like rearrangement described for 3-*O*-allyl-(isopropylidene) ascorbate^[2] was applied to the pyrrolidine-2,4-dione derivative **2e**, following its conversion into **6** by *O* allylation, to give compound **7** in a stereoselective manner (Scheme 3). The TRAL/alkylation and Claisen-like rear-



Scheme 3. Claisen-like rearrangement: a) KOH, allyl bromide, DMSO, 60%; b) microwave, toluene/DMSO, 170 °C, 30 min, 69%.^[25] DMSO = dimethyl sulfoxide.

rangement were both found to be completely diastereoselective reactions. The diastereoselectivity of the sigmatropic rearrangement depends on the structural parameters of the Zimmermann-Traxler chairlike transition state.

In summary, we have developed an efficient, mild, and exceptionally stereoselective synthesis of dissymmetric pyrrolidine-2,4-diones from DKPs with a high potential for structural diversity. The transannular rearrangement of activated lactams, with or without concomitant alkylation, is a rare tool for the preparation in a single step of a variety of functionalized heterocyclic biomolecules with high stereospecificity. Further studies will be devoted to the extension of

the TRAL reaction to other heterocyclic substrates for the synthesis of a broader range of pharmacological scaffolds, in particular for the synthesis of statine derivatives.

Received: May 15, 2007

Revised: July 7, 2007

Published online: August 23, 2007

Keywords: C–C activation · diastereoselectivity · diketopiperazines · heterocycles · rearrangement

- [1] G. Dewynter, D. Farran, J. Martinez, Patent No. 0753973, deposited March 21, 2007.
- [2] K. Wimalasena, M. P. D. Mahindaratne, *J. Org. Chem.* **1994**, 59, 3427–3432.
- [3] M. G. Kulkarni, S. R. Thopate, *Tetrahedron* **1996**, 52, 1293–1302.
- [4] B. J. L. Royles, *Chem. Rev.* **1995**, 95, 1981–2001.
- [5] P. Catejón, A. Moyano, M. A. Pericas, A. Riera, *Tetrahedron* **1996**, 52, 7063–7086.
- [6] T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1976**, 49, 3287–3290.
- [7] P. Jouin, B. Castro, D. Nisato, *J. Chem. Soc. Perkin Trans. 1* **1987**, 1177–1182.
- [8] S. Klutckko, P. O'Brien, J. C. Hodges, *Synth. Commun.* **1989**, 19, 2573–2583.
- [9] J. Poncet, P. Jouin, B. Castro, L. Nicolas, M. Boutard, A. Gaudemer, *J. Chem. Soc. Perkin Trans. 1* **1990**, 611–616.
- [10] M. Bänziger, J. F. McGarrity, T. Meul, *J. Org. Chem.* **1993**, 58, 4010–4012.
- [11] U. Schmidt, B. Riedl, G. Haas, H. Griesser, A. Vetter, S. Weinbrenner, *Synthesis* **1993**, 216–220.
- [12] R. E. Babine, S. L. Bender, *Chem. Rev.* **1997**, 97, 1359–1472.
- [13] H. Umezawa, T. Aoyagi, H. Morishima, M. Matsuzaki, M. Hamada, T. Takeuchi, *J. Antibiot.* **1970**, 23, 259–262.
- [14] D. J. Maly, L. Huang, J. A. Ellman, *ChemBioChem* **2002**, 3, 16–37.
- [15] L. Rügheimer, *Ber. Dtsch. Chem.* **1888**, 21, 3325–3331.
- [16] S. Kobayashi, L. L. Bryant, Jr., Y. Tsukamoto, T. Saegusa, *Macromolecules* **1986**, 19, 1547–1551.
- [17] J. J. Leban, K. L. Colson, *J. Org. Chem.* **1996**, 61, 228–231.
- [18] C. Pothion, J. A. Fehrentz, A. Aumelas, A. Loffet, J. Martinez, *Tetrahedron Lett.* **1996**, 37, 1027–1030.
- [19] C. J. Dinsmore, D. C. Beshore, *Tetrahedron* **2002**, 58, 3297–3312.
- [20] P. M. Fischer, *J. Pept. Sci.* **2003**, 9, 9–35.
- [21] G. Barany, F. Albericio, *J. Am. Chem. Soc.* **1985**, 107, 4936–4942.
- [22] C. Alcaraz, M. Dolores Fernandez, M. Pilar de Frutos, J. L. Marco, M. Bernabé, C. Foces-Foces, F. H. Cano, *Tetrahedron* **1994**, 50, 12443–12456.
- [23] M. Oba, T. Terauchi, Y. Owari, Y. Imai, I. Motoyama, K. Nishiyama, *J. Chem. Soc. Perkin Trans. 1* **1998**, 1275–1281.
- [24] Details are given in the Supporting Information.
- [25] R. Schobert, J. M. Urbina-Gonzalez, *Tetrahedron Lett.* **2005**, 46, 3657–3660.