Cyclizations of α-Keto Ester Modified Aspartic Acids in Peptides

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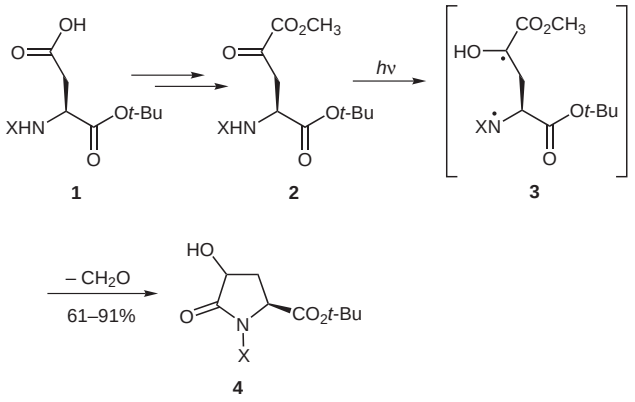
Abstract: Aspartic acid peptides with α-keto ester modification can cyclize to form γ-lactam derivatives. This reaction represents an easy access to conformationally restricted peptidomimetics.

Key words: α-keto ester, cyclizations, γ-lactams, diastereoselectivity, peptidomimetics

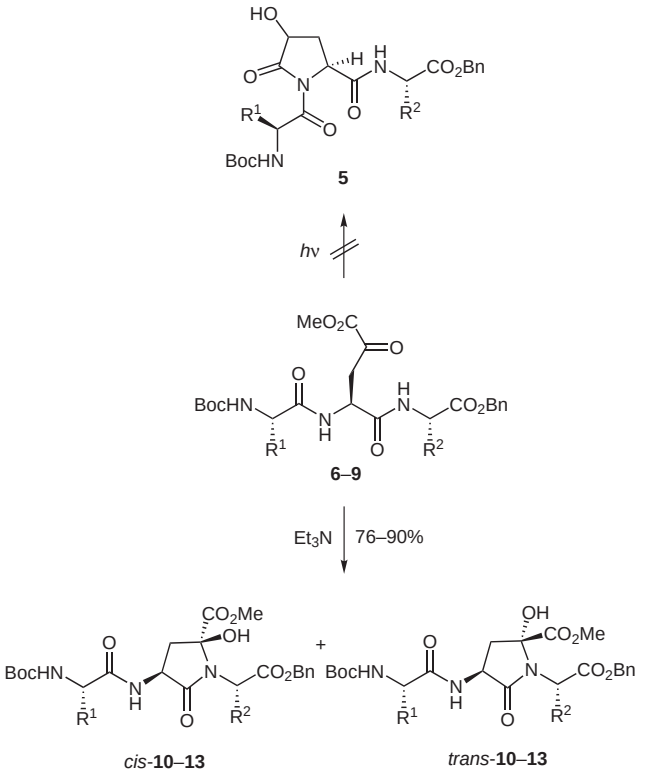
Recently we reported the synthesis of hydroxypyrrolidinones **4** from aspartates **1**.[1] The reaction sequence started with the transformation of the side chain into an α-keto ester **2** and subsequent photocyclization, where diradical **3** is an intermediate (Scheme 1). This new reductive photocyclization was applied to aspartic acid derivatives (X = Boc) and to dipeptides with *N*-terminal amino acids (X = Boc-Gly or Boc-Pro).



Scheme 1 Reductive photocyclization of α-keto ester **2**.

In order to use this cyclization reaction in larger peptides we also attached an amino acid at the *C*-terminal end of the substituted aspartate and were surprised to see, that the photoreaction of tripeptides **6**–**9** did not yield **5** as main product.[2]

However, in the presence of triethylamine, a smooth cyclization to γ-lactams **10**–**13** occurred in 76–90% yield (Scheme 2).[3,4] The *cis*/*trans* ratio of the two diastereomers depended on the size of the side chain of the *C*-terminal amino acid.[5] Thus, with glycine (**6** → **10**) no selectivity was observed, whereas the bulky isopropyl group of valine (**9** → **13**) strongly favored the *cis* diastereomer.



Scheme 2

Variation of the *N*-terminal amino acid had only a small effect on the diastereoselectivity (Table 1).

DFT calculations indicate that the *C*-terminal amino acids in *cis* and *trans* products **11**–**13** adopt preferred 1,3-allylic strain conformations **A** and **B** (Figure 1). The preference of the *cis*-configured γ-lactams **11**–**13** might be caused by an intramolecular hydrogen bond between the OH group and the benzyl ester.[6]

Table 1 Diastereoselectivities of the γ-Lactams **10**–**13**

Educt	R^2	Product	R^1 = H	R^1 = CH_3
			cis/*trans*	*cis*/*trans*
6	H	**10**	57:43	52:48
7	CH_3	**11**	87:13	92:8
8	$CH_2CH(CH_3)_2$	**12**	94:6	
9	$CH(CH_3)_2$	**13**	95:5	90:10

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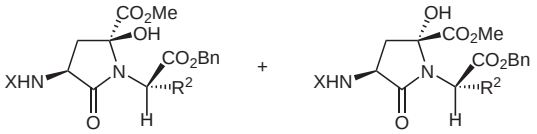
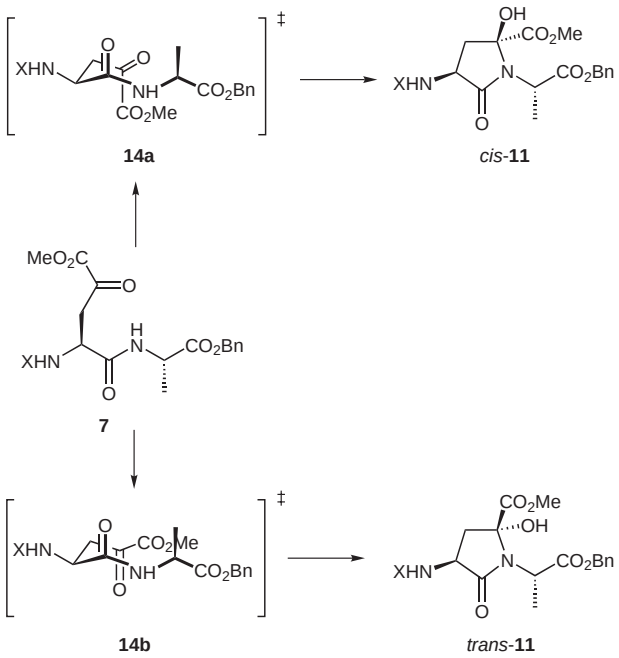


A (*cis*) **B** (*trans*)

Figure 1 Preferred conformations of the γ-lactams **11**–**13**.

Cyclizations also occur under slightly acidic conditions.[7] For example, conversion of α-keto ester **7** with acidic silica gel led to γ-lactam **11**, but with a reversed *cis*/*trans* ratio of 20:80. Subsequent treatment with triethylamine changed the *cis*/*trans* ratio to 87:13. These experiments suggest that the cyclization products under basic conditions, as described in Table 1, are formed under thermodynamic control, whereas acidic silica gel induces kinetic control with the *trans* isomer as preferred product.[8] The favored formation of the *trans* diastereomer under kinetic conditions might be explained by conformations **14b**, in which two carbonyl groups point into opposite directions. Thus, the dipole moment of **14b** should be smaller than that of **14a** (Scheme 3).



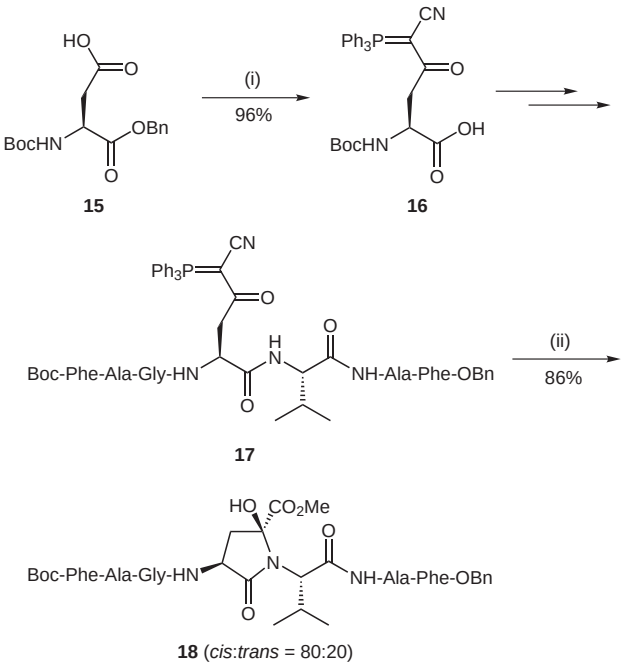
14a *cis*-**11**

7

14b *trans*-**11**

Scheme 3 Transition states of the cyclization.

The cyclization products **10**–**13** are peptidomimetics, which are conformationally restricted because of the γ-lactam structure. The incorporation of lactams in peptides often leads to significantly higher biological activity compared to that of natural peptides.[9] We therefore introduced the γ-lactam moiety into larger peptides by this cyclization strategy. The most efficient way was using the phosphoran-modified aspartic acid **16** as a building block, which could be synthesized in two steps starting from the partially protected aspartic acid **15**. By standard peptide coupling methods in solution, **16** was incorporated into larger peptides, for example heptamer **17**. Ozonolysis in the presence of methanol and cyclization of the obtained α-keto ester with triethylamine finally yielded γ-lactam peptide **18** (Scheme 4). Using the Fmoc-protected derivative of **16** solid-phase peptide synthesis was also possible.



15 **16** **17**

18 (*cis*:*trans* = 80:20)

Scheme 4 *Reagents and conditions*: (i) a) Ph_3P=CHCN, EDC, DMAP, CH_2Cl_2, 0 °C, 18 h; b) Pd/C, H_2, THF, 20 °C, 18 h; (ii) a) O_3, CH_2Cl_2, MeOH, –78 °C, 30 min; b) Et_3N, CH_2Cl_2, 20 °C, 30 min.

In summary, we report cyclization reactions of α-keto ester modified aspartic acids in peptides. The diastereoselectivity of the obtained γ-lactam peptides highly depends on the amino acid sequence and the reaction conditions. Applied to larger peptides, this cyclization reaction represents an easy access to conformationally restricted peptidomimetics.

Acknowledgment

This work was supported by the Swiss National Science Foundation.

References and Notes

(1) Obkircher, M.; Seufert, W.; Giese, B. *Synlett* **2005**, 1182.
(2) During this reaction at least four different products were formed, with **5** only as a minor component.
(3) **General Cyclization Procedure.**
The α-keto ester modified aspartic acid peptides **6**–**9** were dissolved in 20 mL CH_2Cl_2. After addition of 2 mL Et_3N, the solution was stirred for 30 min at r.t. The solvents were evaporated and the residue purified by column chromatography yielding γ-lactams **10**–**13** as mixture of two diastereomers.
Spectroscopic Data for *cis*-13 (R^1 = H) as an Example. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 6.9 Hz, 3 H), 1.03 (d, *J* = 6.6 Hz, 3 H), 1.45 (s, 9 H), 2.14 (dd, *J* = 13.5, 9.3 Hz, 1 H), 2.74 (dsept, *J* = 9.6, 6.7 Hz, 1 H), 3.01 (dd,

J = 13.5, 8.9 Hz, 1 H), 3.48 (s, 3 H), 3.63 (d, *J* = 9.7 Hz, 1 H), 3.83–3.86 (m, 2 H), 4.53 (m, 1 H), 4.99 (s, 1 H), 5.08 (d, *J* = 12.3 Hz, 1 H), 5.12 (d, *J* = 12.3 Hz, 1 H), 5.34 (br t, 1 H), 7.06 (d, *J* = 5.7 Hz, 1 H), 7.30–7.37 (m, 5 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 20.1 (CH_3), 21.0 (CH_3), 27.8 (CH), 28.4 (CH_3), 39.5 (CH_2), 44.2 (CH_2), 50.3 (CH), 53.6 (CH_3), 61.1 (CH), 67.3 (CH_2), 80.5 (C), 86.5 (C), 128.5 (CH), 128.6 (CH), 128.7 (CH), 135.4 (C), 156.2 (C), 169.7 (C), 170.5 (C), 171.5 (C), 171.5 (C). MS (ESI): *m/z* (%) = 560 (2) [M + K]$^+$, 544 (100) [M + Na]$^+$, 488 (2) [M – *t*-Bu + Na]$^+$. Anal. Calcd for $C_{25}H_{35}N_3O_9$: C, 57.57; H, 6.76; N, 8.06. Found: C, 57.62; H, 6.75; N, 8.01.

(4) To our knowledge, such a cyclization of an amide group into an α-keto ester under basic conditions has been described only with β-lactams leading to six-membered rings: (a) Bryan, D. B.; Hall, R. F.; Holden, K. G.; Huffman, W. F.; Gleason, J. G. *J. Am. Chem. Soc.* **1977**, *99*, 2353. (b) Aszodi, J.; Chantot, J.-F.; Collard, J.; Teutsch, G. *Heterocycles* **1989**, *28*, 1061. (c) Arnoldi, A.; Merlini, L.; Scaglioni, L. *J. Heterocycl. Chem.* **1987**, *24*, 75.

(5) The *cis* and *trans* refer to the relative configuration of the amine and the hydroxy substituent. Assignment of the diastereomers was made on the basis of NOESY experiments.

(6) DFT calculations (B3LYP) indicate that the *cis* diastereomer **A** is thermodynamically slightly more stable than the *trans* diastereomer **B**. Only in the *cis* isomer **A** does an H bond (1.9 Å) between the OH and the benzyl ester exist.

(7) A similar cyclization under acidic conditions has been described recently: Takeuchi, Y.; Nagao, Y.; Toma, K.; Yoshikawa, Y.; Akiyama, T.; Nishioka, H.; Abe, H.; Harayama, T.; Yamamoto, S. *Chem. Pharm. Bull.* **1999**, *47*, 1284.

(8) The preferred formation of *trans* products under slightly acidic conditions was also observed with peptides **6** and **9**. Not only acidic silica gel but also acetic acid could be used.

(9) (a) Freidinger, R. M.; Veber, D. F.; Perlow, D. S.; Brooks, J. R.; Saperstein, R. *Science* **1980**, *210*, 656. (b) Freidinger, R. M. *J. Med. Chem.* **2003**, *46*, 5553.