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Turn Formation Initiated by a Bissulfoximine Motif: Synthesis and Structural Investigation

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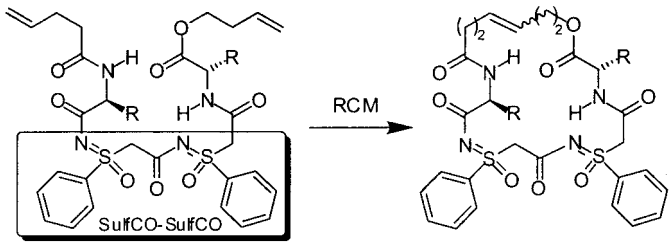
ABSTRACT



Bissulfoximines containing heterochiral SulfCO–SulfCO units may be used as molecular templates, which induce U-shaped conformations in peptidelike structures. The synthesis of such molecules has been investigated, and the structural requirements of this new turn motif have been identified.

Peptides containing unnatural amino acids or structural motifs that mimic original elements of native peptides have attracted much attention as a result of their potential pharmacological properties, including resistance to peptidase degeneration.[1] Much effort has been devoted toward the design and synthesis of modified peptides, which lead to well-defined secondary structures such as helices and sheets. Hence, "foldamers", entirely unnatural oligomers that have a predictable folding behavior, are of particular interest.[2] Because turn elements in proteins play a major role in the recognition of receptors, antibodies, and enzymes,[3] various nonpeptidic turn-forming segments have been developed.[4] Those conformational templates[5] and molecular scaffolds force attached peptide chains to adopt specific secondary structures (e.g., artifical β-sheets). Excellent recent examples have been reported by Gellman,[6] Gennari,[7] and Nowick.[8] In regard to the work described here, Gellman's hairpin formation with β-peptides containing a heterochiral dinipecotic acid segment is particularly noteworthy.[6c,9]

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(2) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173.

(3) (a) Rizo, J.; Gierasch, L. M. *Annu. Rev. Biochem.* **1992**, *61*, 387. (b) Rose, G. D.; Gierash, L. M.; Smith, J. A. *Adv. Protein Chem.* **1985**, *37*, 1.

(4) (a) For reviews on peptide secondary structure mimetics, see: *Tetrahedron* (Symposia-in-Print, no. 50; Kahn, M., Ed.) **1993**, *49*, 3433. (b) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789. (c) For β-turn mimics, see also: Fink, B. E.; Kym, P. R.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 4334 and references therein.

(5) For an early report on a template-nucleated helical conformation, see: Kemp, D. S.; Curran, T. P.; Boyd, J. G.; Allen, T. A. *J. Org. Chem.* **1991**, *56*, 6683.

(6) (a) Fisk, J. D.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **2000**, *122*, 5443. (b) Langenhan, J. M.; Fisk, J. D.; Gellman, S. H. *Org. Lett.* **2001**, *3*, 2559. (c) Chung, Y. J.; Huck, B. R.; Christianson, L. A.; Stanger, H. E.; Krauthäuser, S.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **2000**, *122*, 3995. (d) Woll, M. G.; Lai, J. R.; Guzei, I. A.; Taylor, S. J. C.; Smith, M. E. B.; Gellman, S. H. *J. Am. Chem. Soc.* **2001**, *123*, 11077.

(7) (a) Gennari, C.; Mielgo, A.; Potenza, D.; Scolastico, C. *Eur. J. Org. Chem.* **1999**, 379. (b) Belvisi, L.; Gennari, C.; Mielgo, A.; Potenza, D.; Scolastico, C. *Eur. J. Org. Chem.* **1999**, 389. (c) Belvisi, L.; Gennari, C.; Madder, A.; Mielgo, A.; Potenza, D.; Scolastico, C. *Eur. J. Org. Chem.* **2000**, 695.

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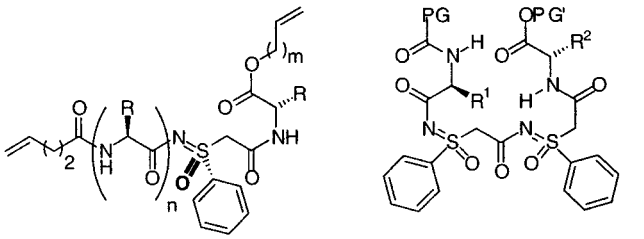


1a: R = CH(Me)Et; n = m = 1
1b: R = CH_2CHMe_2; n = m = 1
1c: R = Me; n = 1; m = 2
1d: R = Me; n = m = 2

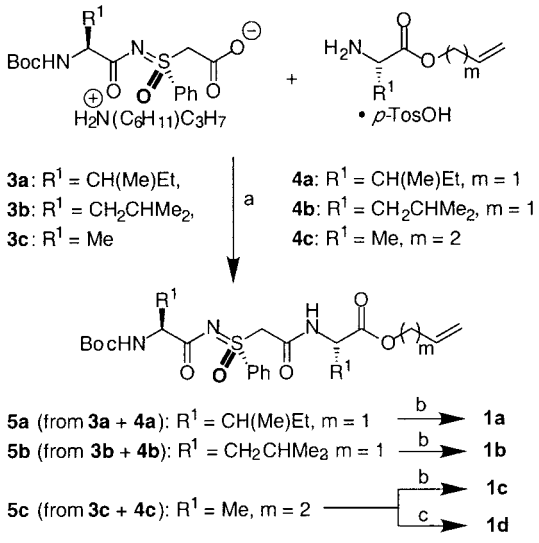
2a: PG = PG' = $(CH_2)_2CH{=}CH_2$; $R^1 = R^2 = Me$
2b: PG = O*t*Bu; R^1 = CH(Me)Et; $R^2 = CHMe_2$; PG' = Bn

Figure 1.

Our investigation was initiated after molecular modeling studies had revealed that a sulfoximidoyl (SulfCO) moiety[10] as in **1** led to a bending of the peptide chain, resulting in an overall L-shaped conformation of the molecule. We then prepared bissulfoximines **2**, containing two consecutive SulfCO-moieties in the peptidelike chain, to investigate whether a sequence of two sulfoximidoyl units would give a turn motif.

The synthesis of the pseudopeptide **1** with one SulfCO group followed a reaction sequence in which the key step was the coupling of *β*-sulfoximidoyl carboxylate **3** with *p*-tosylate salts of protected amino acid esters **4** to give **5** (Scheme 1).[11] Further functionalization of **5** afforded **1a**−**c**

Scheme 1[a]



3a: R^1 = CH(Me)Et,
3b: $R^1 = CH_2CHMe_2$,
3c: R^1 = Me

a

4a: R^1 = CH(Me)Et, m = 1
4b: $R^1 = CH_2CHMe_2$, m = 1
4c: R^1 = Me, m = 2

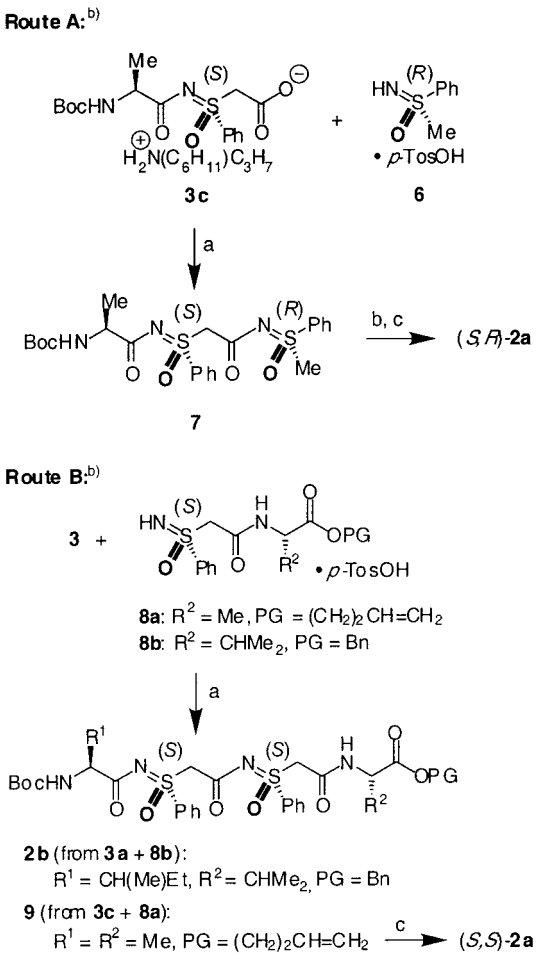
5a (from **3a** + **4a**): R^1 = CH(Me)Et, m = 1 → b → **1a**
5b (from **3b** + **4b**): $R^1 = CH_2CHMe_2$ m = 1 → b → **1b**
5c (from **3c** + **4c**): R^1 = Me, m = 2 → b → **1c**; → c → **1d**

[a] (a) 1.03 equiv of DCC, 0.13 equiv of DMAP; (b) (1) TFA; (2) 1.0 equiv of 4-penten acid, 1.03 equiv of DCC, 1.03 equiv of HOBt; (c) (1) TFA; (2) 1.0 equiv of Boc-Ala-OH, 1.03 equiv of DCC, 1.03 equiv of HOBt; (3) TFA; 1.0 equiv of 4-penten acid, 1.03 equiv of DCC, 1.03 equiv of HOBt.

in up to 50% and **1d** in 8% yield (over five and six steps, respectively).

Two synthetic strategies (routes A and B) were developed for the synthesis of **2** (Scheme 2). Both rely on the coupling

Scheme 2[a]



Route A:[b]

3c + **6**

a

7 → b, c → (*S*,*R*)-**2a**

Route B:[b]

3 + • *p*-TosOH

8a: R^2 = Me, PG = $(CH_2)_2CH{=}CH_2$
8b: $R^2 = CHMe_2$, PG = Bn

a

2b (from **3a** + **8b**):
R^1 = CH(Me)Et, $R^2 = CHMe_2$, PG = Bn

9 (from **3c** + **8a**):
$R^1 = R^2$ = Me, PG = $(CH_2)_2CH{=}CH_2$ → c → (*S*,*S*)-**2a**

[a] (a) 1.03 equiv of DCC, 0.13 equiv of DMAP; (b) (1) lithium cyclohexylisopropyl amide (LCHIPA), CO_2, aq. workup; (2) 1.0 equiv of H-Ala-O$(CH_2)_2CH{=}CH_2$, 1.0 equiv of *p*TosOH; 1.03 equiv of DCC, 0.13 equiv of DMAP; (c) (1) TFA; (2) 1.0 equiv of 4-penten acid, 1.03 equiv of DCC, 1.03 equiv of HOBt. [b] The given absolute configurations refer to those at sulfur only.

of **3** with *p*-tosylate salts of sulfoximines and allow the introduction of sulfur-containg fragments with defined absolute configuration. All four possible diastereomers of **2a** and two diastereomers of **2b** (hetero- and homochiral at sulfur) were synthesized in the course of this study.

Route A involves the buildup of the SulfCO−SulfCO unit through the combination of **3** and sulfoximine **6**[12] prior to peptide chain extensions on both sides. In Scheme 2 the synthesis of **2a** having *S*- and *R*-configuration at the SulfCO units is shown. Analogously, the diastereomer of **2a** with *R*-configuration at both sulfurs was prepared. Route B is more convergent and utilizes the coupling of two sulfoximines of about equal size. As a consequence, only two further steps are required in the synthesis of **2a** after **3** and **8** react to afford **9**. This route was followed in the synthesis of the two diastereomers of **2a** having *S*,*S*-configuration (as shown in Scheme 2) and *R*,*S*-configuration at the sulfur atoms.

To probe the expected U-shape conformation of **2**, reactivity studies were performed. Assuming that molecules that were preorganzied by a suitable turn motif would be prone to undergo an intramolecular cyclization, we chose the ring closing metathesis (RCM) reaction[13] with Grubbs' catalyst $Cl_2(PCy_3)_2Ru{=}CHPh$ as an analytical tool.[14] Since it was desired to have a broad basis for comparison, the investigation included compounds **1a**−**d** (with all-*S* configurations) having a single SulfCO unit and various distances between the reacting double bonds, as well as all four diastereomers of bissulfoximine **2a**, resulting from the combination of *R*- and *S*-configurated sulfoximine units. The latter part of this study was considered to be particularly interesting, since we hoped to reveal the importance of the absolute configuration at sulfur with respect to the overall conformation of the molecules. The results of this investigation are summarized in Table 1. *Cyclic products were only obtained from two diastereomers of* ***2a*** *both having heterochiral configurations at sulfur.*[15] Neither **1a**−**d** nor the two diastereomers of **2a** with homochiral sulfur atoms led to cyclized products. These results support the hypothesized presence of a turn motif in **2** and reveal the conformational impact of the sulfur atoms. Hence, it may be concluded that the following two factors are necessary for formation of a U-shaped arrangement: first, the presence of two SulfCO units and second, a heterochiral combination at sulfur.

Table 1. RCM Reactions of **1a**−**d** and **2a**[a]

entry	starting material[b]	ring size of products	yield of cyclized product [%]
1	(*S*)-**1a**	17	0
2	(*S*)-**1b**	17	0
3	(*S*)-**1c**	18	0
4	(*S*)-**1d**	21	0
5	(*S*,*S*)-**2a**	22	0
6	(*R*,*R*)-**2a**	22	0
7	(*S*,*R*)-**2a**	22	37
8	(*R*,*S*)-**2a**	22	40

[a] Use of 15 mol % of $Cl_2(PCy_3)_2Ru{=}CHPh$, DCM, 12 h, 40 °C. [b] The absolute configurations refer to those at sulfur only.

Table 2. Selected ^{1}H NMR Data for **2b** and **9**[a]

entry	compound[b]	δ of H^a [ppm]	δ of H^b [ppm]
1	(*R*,*S*)-**2b**	7.65	5.34
2	(*S*,*S*)-**2b**	7.64	5.05
3	(*S*,*R*)-**2b**	7.82	5.44
4	(*R*,*S*)-**9**	7.80	5.42
5	(*S*,*S*)-**9**	7.79	4.82
6	(*R*,*R*)-**9**	7.81	4.88

[a] Use of 10 mg of peptide in 0.07 mL of $CDCl_3$. [b] The absolute configurations refer to those at sulfur only.

The relevance of the second point was further supported by ^{1}H NMR spectroscopy data of various diastereomers of **2b** and **9** (Table 2). A weak hydrogen bond was identified between H^b and the C=O group of the other peptide chain branch (Figure 2). Whereas in molecules **2b** and **9** with homochiral sulfur atoms these protons resonate in the range of 4.8 to 5.1 ppm (Table 2, entries 2, 5, and 6), the respective chemical shifts in the heterochiral series of **2b** and **9** have values between 5.3 and 5.4 ppm (entries 1, 3, and 4). The downfield shift of the latter protons is indicative for a more pronounced H^b-carbonyl interaction in cases where the two sulfur atoms of the SulfCO−SulfCO unit have opposite absolute configurations. The strong downfield shift of the H^a protons in all isomers of **2b** and **9** (δ = 7.64−7.82 ppm) is analogous to the ones previously observed in studies of structurally related pseudotripeptides.[11b]

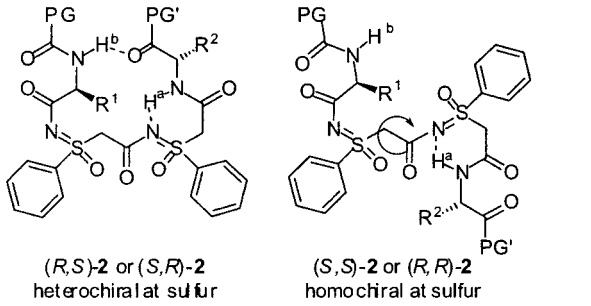


Figure 2.

Both the results of the reactivity studies and the ^{1}H NMR data can be explained by conformational arrangements of **2** (and **9**) as depicted in Figure 2. A turn is only then initiated when the two stereogenic centers at sulfur have opposite absolute configurations (Figure 2, left). The resulting U-shape of the molecule brings H^b and a distant carbonyl group into proximitry, as indicated by the downfield shift of H^b in the ^{1}H NMR spectrum. Since the H-bond acceptor is an ester and not an amide group the H-bond-induced chemical shift change is relatively small.[16] If PG and PG′ contain terminal double bonds as in **2a**, those may be utilized in RCM

(9) For earlier studies on RCM of diastereomeric peptides, see: (a) Miller, S. J. Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 5855. (b) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606.

(10) Sulfoximines can easily be prepared on a multigramm scale. For a recent review, see: Reggelin, M.; Zur, C. *Synthesis* **2000**, 1.

(11) (a) Bolm, C.; Kahmann, J. D.; Moll, G. *Tetrahedron Lett.* **1997**, *38*, 1169. (b) Bolm, C.; Moll, G.; Kahmann, J. D. *Chem. Eur. J.* **2001**, *7*, 1118.

(12) Sulfoximine **6** is commercially available in both enantiomeric forms. Alternatively, it can easily be synthesized following protocols described in: (a) Johnson, C. R.; Schroeck, C. W. *J. Am. Chem. Soc.* **1973**, *95*, 7418. (b) Fusco, R.; Tericoni, F. *Chem. Ind. (Milano)* **1965**, *47*, 61. (c) Brandt, J.; Gais, H.-J. *Tetrahedron: Asymmetry* **1997**, *8*, 909.

(13) Recent reviews on RCM in organic synthesis: (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012.

(14) For recent examples of the use of RCM in the synthesis of cyclic peptides, see: (a) Reichwein, J. F.; Versluis, C.; Liskamp, R. M. J. *J. Org. Chem.* **2000**, *65*, 6187. (b) Blackwell, H. E.; Sadowsky, J. D.; Howard, R. J.; Sampson, J. N.; Chao, J. A.; Steinmetz, W. E.; O'Leary, D. J.; Grubbs, R. H. *J. Org. Chem.* **2001**, *66*, 5291 and references therein.

(15) The *E*/*Z* ratio was approximately 1.6:1, which is similar to the ones reported for macrocyclizations by RCM. Fürstner, A.; Kindler, N. *Tetrahedron Lett.* **1996**, *37*, 7005.

reactions generating the corresponding cyclic products. In contrast to this scenario, derivatives of **2**, which contain homochiral sulfur atoms, lead to stretched structures (Figure 2, right). Those do not form H^b/O═C hydrogen bonds and hence may not undergo RCM reactions because of the distance between the two reacting sites.

In conclusion, we have described a new turn motif for peptidic structures and demonstrated the importance of the stereogenic sulfur atoms for conformational control. Studies focusing on the biological activities of those sulfoximine-containing peptides are currently in progress.

(16) At the present stage we can neither rigorously exclude structures with H-bonds to the sulfur oxygen nor the formation of β-sheet pattern resulting from interactions between H^a and other remote carbonyl groups. Further studies to clarify these aspects are in progress.

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Supporting Information Available: The preparation and characterization of compounds **1**−**9** and full details of the RCM reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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