

Synthesis of an Eight-Membered Cyclic Pseudo-Dipeptide Using Ring Closing Metathesis

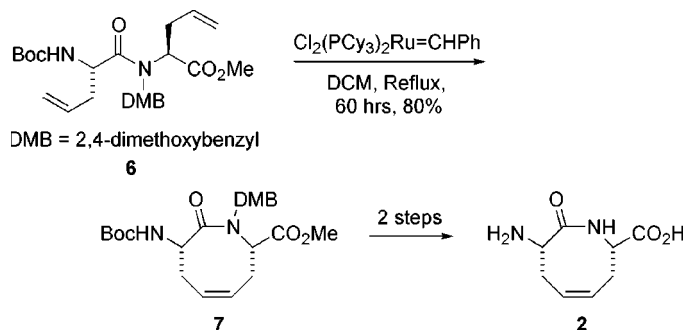
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ABSTRACT



Ring closing metathesis of diallylglycine **6** provided cyclic Z-olefin **7** in 80% yield. The reaction was promoted by substitution of the amide nitrogen with the 2,4-dimethoxybenzyl group allowing for the required cis diallylglycine amide rotamer. Removal of the protecting groups provided cyclic dipeptide **2**, a constrained scaffold useful in peptidomimetic research.

Cyclic, constrained peptide derivatives are useful tools for understanding the structure and function of biologically relevant molecules.¹ The most common unit used to form cyclic peptides and proteins is cystine, which provides a bridging tether that can directly influence biological activity and physical properties. The oxidized cyclic Cys–Cys dipeptide **1** is an eight-membered ring disulfide that is found only infrequently in nature.

Disulfide **1** is of interest because it is conserved in all known nicotinic acetylcholine receptors (nAChRs), and

conformational changes involving **1** are proposed to be the primary switch for ligand-mediated modulation of nAChR activity.² An oxidized Cys–Cys eight-membered ring is found in the catalytic domain of mercuric ion reductase³ and in the bicyclic peptide malformin.^{4,5} The oxidized Cys–Cys motif has also been incorporated into short peptides such as somatostatin⁶ and kemptide.⁷

Peptidomimetics in which the disulfide functionality of cystine has been replaced by two carbon atoms have been prepared in order to increase the chemical stability of a

(1) For examples on the use of peptidomimetic scaffolds, see: (a) Goodman, M.; Ro, S. In *Burger's Medicinal Chemistry and Drug Discovery Volume 1: Principles and Practice*, 5th ed.; Wolff, M. E., Ed.; John Wiley & Sons: 1995; Vol. 1, pp 833–838. (b) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789–12854. (c) Sawyer, T. K. In *Structure-Based Drug Design: Targets, Techniques and Developments*; Veerapandian, P., Ed.; Marcel Dekker: New York, 1997; Vol. 1, pp 559–634. (d) Creighton, C. J.; Zapf, C. W.; Bu, J. H.; Goodman, M. *Org. Lett.* **1999**, *1*, 1407–1409. (e) Hruby, V. J.; Hill, P. S. In *Conformational Analysis of Medium-Sized Heterocycles*; Glass, R. S., Ed.; VCH: New York, 1988; pp 217–60. (f) Ripka, A. S.; Rich, D. H. *Curr. Opin. Chem.* **1998**, 441–452.

(2) Avizonis, D. Z.; Farr-Jones, S.; Kosen, P. A.; Basus, V. J. *J. Am. Chem. Soc.* **1996**, *118*, 13031.

(3) Schiering, N.; Kabsch, W.; Moore, M. J.; Destefano, M. D.; Walsh, C. T.; Pai, E. F. *Nature* **1991**, *352*, 168–171.

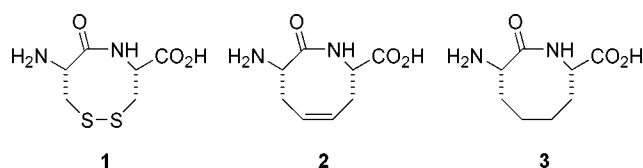
(4) Bodanszky, M.; Stahl, G. L. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *71*, 2791.

(5) Malformin contains cyclic (D) Cys–(D) Cys.

(6) Brady, S. F.; William J. Paleveda, J.; Arison, B. H.; Saperstein, R.; Brady, E. J.; Raynor, K.; Reisine, T.; Veber, D. F.; Freidinger, R. M. *Tetrahedron* **1993**, *49*, 3449–3466.

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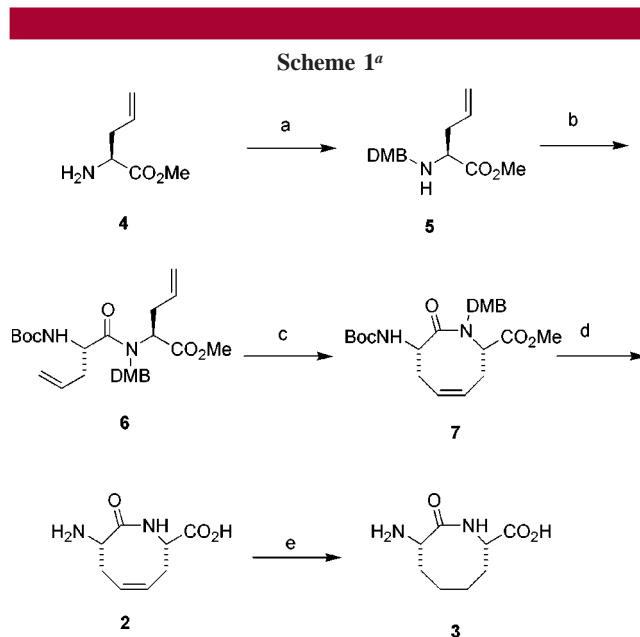
variety of important compounds.⁸ Carbon mimics of **1** such as **2** and **3** have not been specifically evaluated, although one research group attempted to prepare them.⁹



Very recently, the synthesis of a protected variant of **3** was described in 12 chemical steps starting from a derivative of L-serine.¹⁰ In this letter we report the synthesis of **2** and **3** via a sequence of reactions using Grubbs ring closing metathesis (RCM) as the key synthetic step. Eight-membered ring dipeptides such as **2** and **3** may be useful scaffolds¹¹ in peptidomimetic research and for studies involving amide self-association.¹²

Ruthenium-based ring closing metathesis has been used extensively for the preparation of macrocyclic alkenes.^{13,14} Peptidic dienes have also been used as substrates.^{9,15} However, Boc-(S)-allylgly-(S)-allylgly-Oph was found to not be suitable for RCM, which was attributed to a high preference for the trans amide bond rotamer that was incapable of intramolecular reaction.⁹ We have overcome this difficulty by using transient alkylation¹⁶ on the amide nitrogen allowing for the cis amide rotamer to participate in the reaction (see Scheme 1). (S)-Allylglycine methyl ester (**4**) was subjected to reductive amination with 2,4-dimethoxybenzaldehyde to afford derivative **5**. Amide bond formation with Boc-(S)-allylglycine using HATU gave compound **6**.

N-Substituted dipeptide **6** is an excellent substrate for ring closing metathesis because there is a significant amount of the cis amide rotamer in which the alkenes can react intramolecularly. Indeed, inspection of the ¹H NMR (CDCl₃) spectrum of **6** revealed a 3:2 mixture of amide bond rotamers



^a (a) 2,4-Dimethoxybenzaldehyde, NaBH(OAc)₃, >95%. (b) Boc-allylglycine-OH, HATU, HOAT, NEM, 75%. (c) Grubbs catalyst, reflux in DCM, 60 h, 80%. (d) (1) LiOH, MeOH/H₂O, quant; (2) 10% TFA in DCM, 3 h; (3) 1 N HCl and lyophilize, 78%. (e) Pd/C, H₂, quant.

in solution. N-Substitution of a secondary amide to induce a conformational change is an established strategy to improve the yields of certain intramolecular reactions.¹⁷ Ring closing metathesis of **6** provided protected olefin **7** in 80% yield.¹⁸ The olefin geometry of **7** was assigned as cis on the basis of the coupling constant of the olefinic protons (10.6 Hz). The methyl ester of **7** was then hydrolyzed with LiOH, and the Boc and dimethoxybenzyl¹⁹ groups were removed with TFA to afford **2**.²⁰ Alkene **2** was then subjected to hydrogenolysis to yield saturated derivative **3**.

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(14) Second generation imidazole/imidazoline Grubbs catalysts: (a) Morgan, J. P.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 3153. (b) Briot, A.; Bujard, M.; Gouverneur, V.; Nolan, S. P.; Mioskowski, C. *Org. Lett.* **2000**, *2*, 1517. (c) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (d) Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674.

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(17) For a recent example, see: Chao, W.; Weinreb, S. M. *Tetrahedron Lett.* **2000**, *41*, 9199. Also while this paper was under peer review Vo-Thanh et al. reported an analogous strategy for the synthesis of medium sized lactams via RCM. See Vo-Thanh, G.; Boucard, V.; Sauriat-Dorizon, H.; Guibe, F. *Synlett* **2001**, *1*, 37–40.

(18) **Experimental procedure** for the ring closing metathesis of **6** to give **7**. Compound **6** (3.0 g, 6.25 mmol) was dissolved in methylene chloride (200 mL) and added to a 5-L round-bottom flask equipped with a condenser containing methylene chloride (1800 mL). Grubbs catalyst (benzylidene bis(tricyclohexylphosphine)dichlororuthenium) (0.514, 0.625 mmol) was added in one aliquot, and the reaction was heated to reflux for 60 h under a stream of dry nitrogen. Upon complete formation of compound **7** (as determined by LCMS and TLC) the solvent was removed by rotary evaporator, and the crude product was purified by flash chromatography (3:1 hexanes/ethyl acetate) to provide a clear, light brown oil (2.25 g, 80% yield): ¹H NMR (300 MHz, CDCl₃, δ) 7.09 (d, 1H, *J* = 8 Hz); 6.40 (m, 2H); 6.20 (d, 1H, *J* = 5 Hz); 5.72 (m, 1H); 5.45 (m, 1H); 4.95 (m, 2H); 4.60 (d, 1H, *J* = 15 Hz); 4.28 (d, 1H, *J* = 15 Hz); 3.80 (s, 3H); 3.80 (s, 3H); 3.44 (s, 3H); 3.00 (m, 1H); 2.70 (m, 2H); 2.35 (ddd, 1H, *J* = 16, 8, 3 Hz); 1.45 (s, 9H). Anal. Calcd for C₂₃H₃₂N₂O₇: C, 61.59; H, 7.19; N, 6.25. Found: C, 61.82; H, 7.20; N, 5.96.

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(20) Characterization of compound **2**·HCl·H₂O: ¹H NMR (300 MHz, CDCl₃, δ) 5.8 (m, 2H); 4.9 (m, 1H); 4.7 (dd, 1H, *J* = 8, 3 Hz); 3.25 (m, 1H); 3.05 (m, 1H); 2.55 (m, 1H); 2.37 (ddd, 1H, *J* = 17, 8, 4 Hz). [α]_D²⁰ = 43.2 (c 1.0, water). Mp > 240 °C. Anal. Calcd: C, 40.26; H, 6.33; N, 11.74; Cl, 14.85; KF H₂O, 7.56. Found: C, 40.33; H, 6.26; N, 11.69; Cl, 14.86; KF H₂O, 7.44.

The method described here for the preparation of **3** involves six chemical steps and an overall yield of 60%. Although we could have used a variety of amide substituents, the 2,4-dimethoxybenzyl group has the advantage of being a model system for the extension of this approach to solid phase using a dialkoxy benzaldehyde resin.²¹

Ring closing metathesis is a versatile reaction that has now been applied to the formation of an eight-membered ring alkene starting from a substrate bearing adjacent allylglycine residues. We obtained olefin **7**, a valuable synthon for further elaboration,²² and we will report on the use of **7** and **2** for that purpose in the future. Incorporation of **2** and **3** into

(21) Polymer-supported ring closing metathesis: Schürer, S. C.; Gessler, S.; Buschmann, N.; Blechert, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3898 and references therein.

peptide chains replacing the oxidized, cyclic Cys–Cys is expected to provide stable and potentially useful peptidomimetic derivatives.

Acknowledgment. We thank Gregory C. Leo, Alexey Dyatkin, and Charles H. Reynolds of our laboratories for helpful discussions and insight. We also thank Prof. Dan Rich (University of Wisconsin, Madison) for useful advice.

Supporting Information Available: NMR data for compounds **2**, **3**, **6**, and **7**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(22) For a notable example, see: White, J. D.; Hrciar, P. *J. Org. Chem.* **2000**, *65*, 9129–9142.