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

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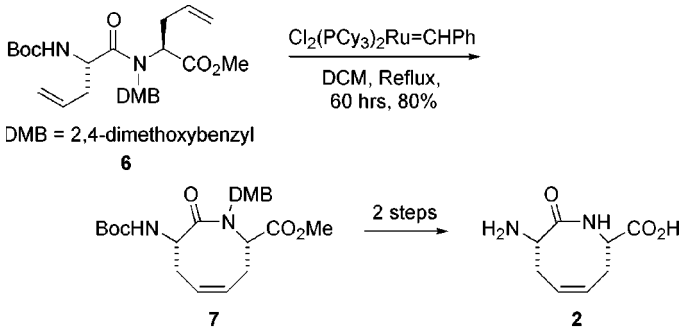
ABSTRACT



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 reductase[3] and in the bicyclic peptide malformin.[4,5] The oxidized Cys−Cys motif has also been incorporated into short peptides such as somatostatin[6] 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Peptidomimetics in which the disulfide functionality of cystine has been replaced by two carbon atoms have been prepared in order to increase the chemical stability of a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 peptididomimetic 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 *Stucture-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.

(7) Prorok, M.; Lawrence, D. S. *J. Am. Chem. Soc.* **1990**, *112*, 8626−8627.

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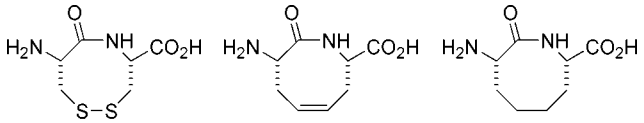
variety of important compounds.[8] Carbon mimics of **1** such as **2** and **3** have not been specifically evaluated, although one research group attempted to prepare them.[9]



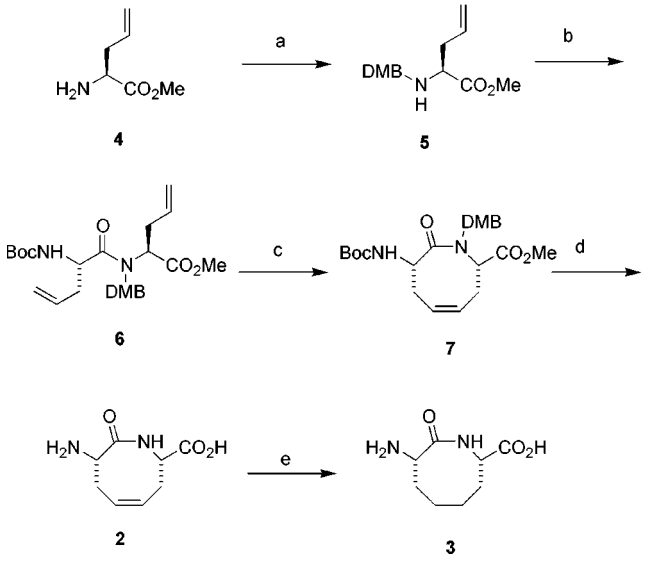
1 **2** **3**

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 scaffolds[11] 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*)-allylglgly-(*S*)-allylglgly-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 alkylation[16] 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 ^{1}H NMR ($CDCl_3$) spectrum of **6** revealed a 3:2 mixture of amide bond rotamers

Scheme 1[a]



[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/H_2O, quant; (2) 10% TFA in DCM, 3 h; (3) 1 N HCl and lyophilize, 78%. (e) Pd/C, H_2, 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 dimethoxybenzyl[19] 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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(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): ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.09 (d, 1H, J = 8 Hz); 6.40 (m, 2 H); 6.20 (d, 1H, J = 5 Hz); 5.72 (m, 1H); 5.45 (m, 1 H); 4.95 (m, 2H); 4.60 (d, 1H, J = 15 Hz); 4.28 (d, 1 H, J = 15 Hz); 3.80 (s, 3H); 3.80 (s, 3H); 3.44 (s, 3 H); 3.00 (m, 1H); 2.70 (m, 2H); 2.35 (ddd, 1 H, J = 16, 8, 3 Hz); 1.45 (s, 9H). Anal. Calcd for $C_{23}H_{32}N_2O_7$: 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·H_2O: ^{1}H NMR (300 MHz, $CDCl_3$, δ) 5.8 (m, 2H); 4.9 (m, 1H); 4.7 (dd, 1H, J = 8, 3 Hz); 3.25 (m, 1 H); 3.05 (m, 1H); 2.55 (m, 1 H); 2.37 (ddd, 1 H, J = 17, 8, 4 Hz). $[\alpha]_D$ = 43.2 (*c* 1.0, water). Mp > 240 °C. Anal. Calcd: C, 40.26; H, 6.33; N, 11.74; Cl, 14.85; KF H_2O, 7.56. Found: C, 40.33; H, 6.26; N, 11.69; Cl, 14.86; KF H_2O, 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 peptide chains replacing the oxidized, cyclic Cys−Cys is expected to provide stable and potentially useful peptidomimetic derivatives.

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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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(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.

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