Synthesis of Conformationally Restricted Amino Acids and Peptides Employing Olefin Metathesis

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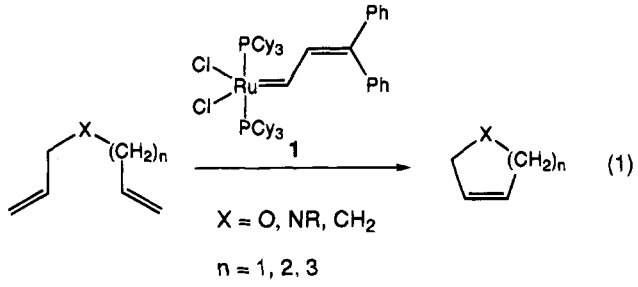
Received February 16, 1995

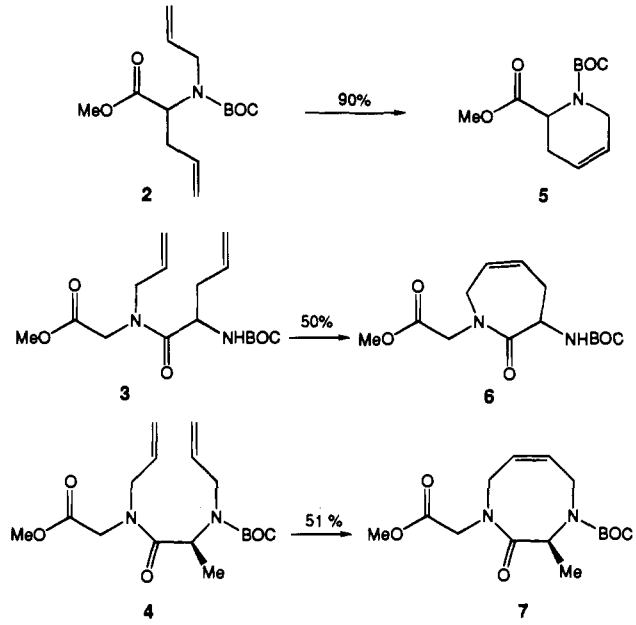
Conformationally restricted peptides and amino acids—peptidomimetics—have assumed a prominent role in drug design and development. Numerous approaches to the design and synthesis of rigidified peptide-like molecules have been described which have been based on side chain modification, amide linkage modification, and de novo synthesis of particular structural motifs.[1] A common theme among many of the strategies applied to date has been the introduction of some cyclic substructure into a peptide-based framework which serves to restrict the conformational space of the molecule. Frequently, such modifications result in increased affinity for a particular biological receptor, with simultaneously diminished sensitivity to cellular peptidases.

Previous reports from these laboratories have demonstrated that the ruthenium complex **1** efficiently catalyzes ring-closing metathesis (RCM) reactions to form five-, six-, seven-, and eight-membered carbocycles and heterocycles (eq 1).[2,3] In addition, the extraordinary functional group tolerance of the catalyst **1** suggested to us that the synthesis of cyclic biomolecules containing multiple heteroatoms and acidic protons might be possible using this strategy. In this communication, we describe the synthesis of several rigidified amino acid and peptide derivatives.



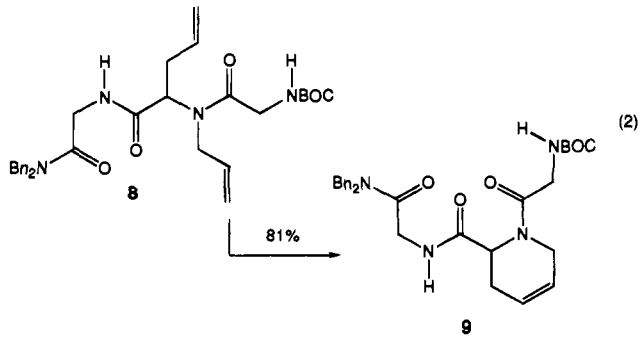
Our initial objective involved the synthesis of simple amino acid derivatives containing various ring sizes, which might subsequently be introduced into peptides, possibly by automated synthesis. Our strategy required introduction of allyl groups at either C_α or the amide nitrogen, depending on the desired ring size. Allyl incorporation at C_α is facilitated by the commercial availability of (+)- and (−)-allylglycine, while amide N-allylation has recently been addressed by Seebach.[4] Assembly of the RCM precursors **2**–**4** then followed in a straightforward fashion employing conventional peptide-coupling techniques.

Scheme 1



The results of the RCM experiments are shown in Scheme 1.[5] Treatment of the modified amino acid **2** with catalyst **1** under conditions similar to those described in our previous reports (5 mol % **1**, 0.20 M/$CHCl_3$, 25 °C) afforded the dehydropipicolinate **5** in good yield (90%) within 1 h. Substrates **3** and **4**, however, required more stringent conditions, and the isolated yields for the corresponding cyclizations were somewhat lower. Nevertheless, the seven-membered ring **6** can be obtained in 50% yield from acyclic diene **3**, while the eight-membered ring **7** can be obtained in 51% from the acyclic precursor **4**.[6] Each of these latter transformations appears to be limited by the inherent ring strain of the product, which necessitates that the reactions be run at high dilution to minimize competing intermolecular oligomerization processes.[7,8]

We also wished to demonstrate that RCM could be accomplished in the presence of several free amide NH groups. Tripeptide **8**, upon treatment with catalyst **1** under conditions exactly analogous to those applied for the transformation of **2** to **5**, afforded **9** in 81% yield (eq 2), illustrating the tolerance for the catalytic conditions for unprotected peptidic structures.



(1) For an overview of the field, see: (a) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699. (b) *Tetrahedron Symposia-in-Print No. 50* **1993**, *49* (17), 3433. (c) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244. (d) Hruby, V. J.; Al-Obeidi, F.; Kazmierski, W. *Biochem. J.* **1990**, *268*, 249. (e) Toniolo, C. *Int. J. Pept. Protein Res.* **1990**, *35*, 287.

(2) Previous reports on RCM from this laboratory: (a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426. (b) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324. (c) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 3800. (d) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856. (e) Fujimura, O.; Fu, G. C.; Grubbs, R. H. *J. Org. Chem.* **1994**, *59*, 4029. (f) Kim, S. H.; Bowden, N.; Grubbs, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 10801. (g) Miller, S. J.; Kim, S. H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108. For recent applications of RCM to natural product synthesis: (h) Martin, S. F.; Liao, Y.; Rein, T. *Tetrahedron Lett.* **1994**, *35*, 691. (i) Borer, B. C.; Deerenberg, S.; Bieraugel, H.; Pandit, U. K. *Tetrahedron Lett.* **1994**, *35*, 3191. (j) Martin, S. F.; Wagman, A. S. *Tetrahedron Lett.* **1995**, *36*, 1169. (k) Houri, A. F.; Xu, Z.; Cogan, D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 2943. For a review on applications of olefin metathesis in organic synthesis: Grubbs, R. H.; Pine, S. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon; New York, 1991; Vol. 5, Chapter 9.3.

(3) For the preparation and characterization of catalyst **1**: (a) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974. (b) Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858.

(4) Pietzonka, T.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1481.

(5) Compounds were identified on the basis of their ^1H NMR, ^{13}C NMR, IR, and mass spectral characteristics. (See Supplementary Material.)

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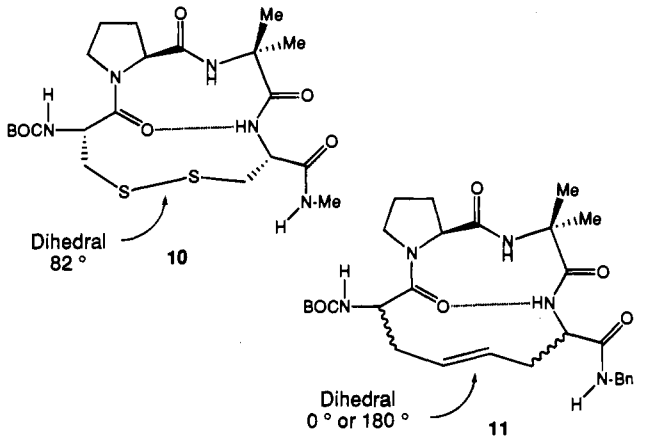
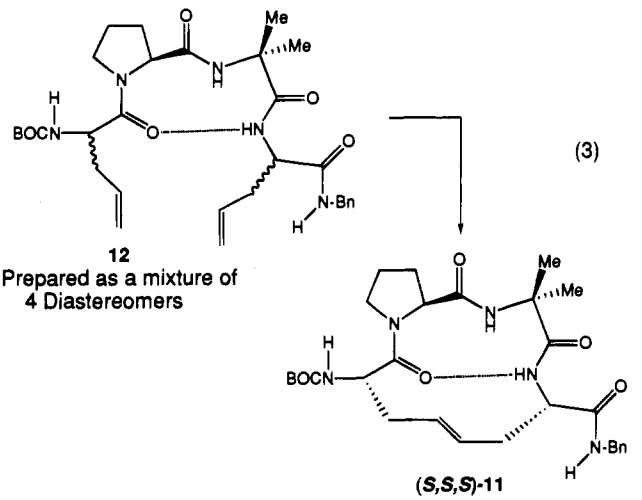


Figure 1. Balaram's disulfide versus the RCM double-bond analog.

Our next objective was to synthesize a covalently stabilized β-turn using a RCM strategy. β-Turns are key secondary structural elements in peptides that have been implicated in numerous biological recognition events.[9] One reasonable approach to the problem is the replacement of cysteine residues in known β-turns which are stabilized by disulfide bridges. Incorporation of allylglycines in the place of the cysteines creates the possibility of replacing the disulfide bridge with a carbon–carbon double bond. Ring-closing metathesis in this setting becomes a laboratory analogy for biological oxidation reactions, with carbon–carbon bonds serving as surrogates for disulfide bridges. Balaram has reported the disulfide-stabilized β-turn **10**, and this substrate stimulated us to attempt to prepare the analogous tetrapeptide olefin **11** (Figure 1).[10] Because disulfide bridges possess different dihedral angle requirements relative to olefins,[11] it was unclear at the outset of our study that (*S*)-allylglycine would be the optimal stereoisomer for replacement of the (*l*)-cysteine. Thus, in our initial study of this system, we prepared a statistical mixture of the four stereoisomers of acyclic diene **12**.

When a mixture of the four diastereomers was treated with catalyst **1** (20 mol %, 0.002 M/CH_2Cl_2, 40 °C), a single macrocycle **11** diastereomer was obtained (eq 3). The majority of the reaction mixture was composed of unreacted dienes. Molecular models suggested that the tetrapeptides derived from either (*R*)-allylglycine or (*S*)-allylglycine were the most reasonable cyclization candidates. Synthesis of the (*R,S,R*) and (*S,S,S*) acyclic tetrapeptides **12** was then accomplished. When (*S,S,S*)-**12** was subjected to the reaction conditions, (*S,S,S*)-**11** was obtained in 60% yield, and the product was identical to that obtained from the analogous experiment on the mixture. In contrast, under the same conditions the (*R,S,R*) acyclic tetrapeptide was recovered unchanged.



It is noteworthy that the stereoisomer which undergoes cyclization possesses the absolute and relative configuration which is directly analogous to the disulfide. While the reasons for this are not fully understood, it is possible that the system benefits in part from an element of preorganization, such as the illustrated hydrogen bond, which facilitates the cyclization. Indeed, Balaram has shown that both **10** and the corresponding acyclic (bis)benzyl thioether possess the illustrated hydrogen bond. While this stabilization may facilitate ring closure for the "natural" configuration of **12**, it may lead to destabilizing transannular interactions in the ring-closed diastereomeric analogs of **11** which make the macrocyclizations prohibitive.[12]

In summary, we have prepared a variety of conformationally constrained amino acids and peptides employing olefin metathesis methodology made possible by catalyst **1**. In addition, we have illustrated that replacement of cysteine residues with allylglycine units facilitates the synthesis of covalently stabilized β-turn mimetics.

Acknowledgment. This research was generously supported by a grant from the NIH. S.J.M. is grateful to the NSF for a postdoctoral fellowship. In addition, Professor Andrew G. Myers and Dr. Jim Gleason are gratefully acknowledged for providing samples of optically pure (L)- and (R)-allylglycine, as well as for helpful discussions. Professor Barbara Imperiali is also acknowledged for helpful discussions.

Supplementary Material Available: Characterization data for compounds in addition to a representative procedure for RCM reactions (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(6) See ref 2g.

(7) We have discussed this issue in more detail in ref 2g.

(8) Attempts to form five-membered dehydroproline derivatives from appropriate *N*(-allyl)vinylglycine derivatives have been unsuccessful with catalyst **1**. Olefin isomerization to form α,β-unsaturated compounds is the predominant pathway in this case.

(9) For discussions of β-turns in proteins, see: (a) Rizo, J.; Gierasch, L. M. *Annu. Rev. Biochem.* **1992**, *61*, 387. (b) Rose, G. D.; Gierasch, L. M.; Smith, J. A. *Adv. Protein Chem.* **1985**, *37*, 1. For a review of β-turn mimetics, see ref 1b.

(10) Ravi, A.; Balaram, P. *Tetrahedron* **1984**, *40*, 2577.

(11) The disulfide dihedral angle in **10** has been shown to be 82° with right-handed chirality in the solid state. Ravi, A.; Prasad, B. V.; Balaram, P. *J. Am. Chem. Soc.* **1983**, *105*, 105.

(12) A. H. Hoveyda and co-workers have recently prepared a 14-membered ring using an RCM strategy employing a Mo-based catalyst in the context of a synthesis of Sch 38516 (ref 2k). In this case, the presence of an (*E*)-amide in addition to the presence of three stereogenic centers in the macrocyclization precursor may restrict the number of possible conformations available to the acyclic chain, facilitating ring closure.