Catalytic Ring-Closing Metathesis of Dienes: Application to the Synthesis of Eight-Membered Rings

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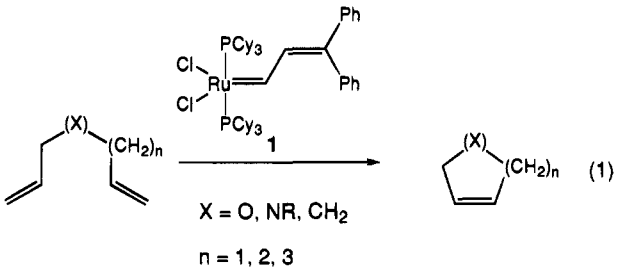
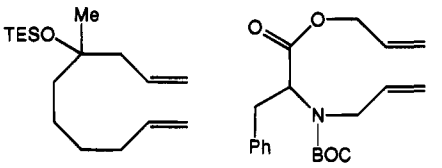
Previous reports from these laboratories have demonstrated that the ruthenium complex **1** efficiently catalyzes ring-closing metathesis (RCM) reactions to form five-, six-, and seven-membered carbocycles and heterocycles (eq 1).[1,2] The synthesis of eight-membered rings, common structural elements in numerous natural products,[3] has proven to be a challenging extension of this methodology. Presumably, the kinetics of ring closure, the strain inherent in many eight-membered rings, and the competing metathesis-based polymerization of reactants and/or products are among the factors contributing to this problem. The subject of this communication is the application of catalyst **1** to the RCM of several eight-membered-ring targets.



(1)

Our initial studies focused on the RCM reactions of acyclic precursors which, upon treatment with catalyst **1**, would afford eight-membered rings. Whereas acyclic diene precursors could successfully undergo RCM to form small (five- to seven-membered) rings, no eight-membered-ring products were observed when acyclic precursors **2** and **3** were subjected to standard RCM conditions. In contrast to the smaller ring analogs, acyclic dienes afforded only dimeric products resulting from intermolecular metathesis reactions, even when the reactions were performed at high dilution or under syringe pump conditions.

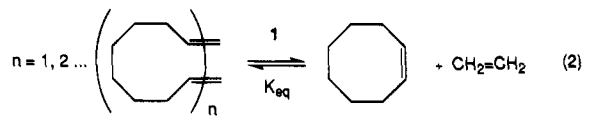
However, we have found that the introduction of a conformational constraint greatly enhances the ability of analogous dienes to undergo RCM to afford eight-membered rings (Table 1).[4] For example, the catechol derivative **4** undergoes rapid RCM to form the eight-membered ring **5** in 75% yield within 3 h at 55 °C (entry 1). Similarly, the *trans*-substituted cyclohexanes **6** and **10** (entries 2 and 4) are good substrates for RCM and afford the bicyclic [6.4.0] systems **7** and **11** in 75% and 60% yields, respectively. Presumably, the incorporation of the olefins which undergo metathesis into systems where they are constrained to be in proximity to one another predisposes the substrates **4**, **6**, and **10** to RCM on entropic grounds.



2 **3**

In contrast, the *cis*-substituted cyclohexane derivatives **8** and **12** were found to be poor substrates for RCM. When these compounds were submitted to the conditions which were found to work well for the *trans*-substituted analogs **6** and **10**, low yields of ring-closed products **9** (33%) and **13** (20%) were obtained. In each case, significant amounts of side products resulting from intermolecular metathesis, in addition to recovered starting material, were obtained.

Because RCM involves an equilibrium between ring-closed and open-chain products (eq 2),[5] it seemed reasonable that the relative ratio of cyclic product to acyclic materials might correlate to the relative free energy changes for given processes (eq 3). Therefore, we sought to calculate the difference in the free energy changes for two reactions which were identical, except in the stereochemical arrangement at the ring junction. Our approach is illustrated by the transformation of **10** to **11** versus **12** to **13** (entries 4 and 5, Table 1). Since the entropy change for each reaction is very similar, the relative difference in the free energy change for the two reactions is manifested primarily in the difference in the enthalpy changes, which in this case is primarily composed of the relative steric energies (SE). Molecular mechanics (MM3) calculations[6] were carried out on compounds **10**–**13**, and the free energy change of entry 5 was found to be 1.8 kJ/mol (0.44 kcal/mol) greater than that for entry 4 (eqs 3–5). The ratio of ring-closed products to open-chain products presumably reflects the greater ring strain encountered in the formation of bicycle **13** relative to **11** upon going from reactant to product.



(2)

$$\Delta G(\text{entry 5}) - \Delta G(\text{entry 4}) = [\Delta H(\text{entry 5}) - \Delta H(\text{entry 4})] - [T\Delta S(\text{entry 5}) - T\Delta S(\text{entry 4})] \quad (3)$$

$$\Delta H(\text{entry 5}) - \Delta H(\text{entry 4}) = [\text{SE}(\mathbf{13}) - \text{SE}(\mathbf{12})] - [\text{SE}(\mathbf{11}) - \text{SE}(\mathbf{10})] \quad (4)$$

(1) 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. For recent applications of RCM to natural product synthesis: (g) Martin, S. F.; Liao, Y.; Rein, T. *Tetrahedron Lett.* **1994**, *35*, 691. (h) Borer, B. C.; Deerenberg, S.; Bieraugel, H.; Pandit, U. K. *Tetrahedron Lett.* **1994**, *35*, 3191. 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.

(2) 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.

(3) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757.

(4) Compounds were identified on the basis of their ^{1}H NMR, ^{13}C NMR, IR, and mass spectral characteristics (see supplementary material). Representative experimental procedure: Ruthenium catalyst **1** (FW 925.1, 0.08 equiv, 21 mg) in C_6H_6 (10 mL) was added through a cannula to a solution of **4** (FW 190, 1.0 equiv, 0.28 mmol, 55 mg, Table 1, entry 1) in C_6H_6 (10 mL, 0.015 M). The resulting light brown solution was placed in a 55 °C oil bath. After 3 h, the starting material was converted to compound **5** (TLC R_f = 0.25, 25% CH_2Cl_2/hexanes). The solution was concentrated under reduced pressure and purified by flash chromatography (25% CH_2Cl_2/hexanes) to afford the product **5** as a colorless, volatile oil (35 mg, 75% yield).

(5) For a discussion of the thermodynamics of ring-opening polymerizations with implications for RCM, see: Ivin, K. J. *Makromol. Chem., Macromol. Symp.* **1991**, *42/43*, 1.

(6) The Macromodel program was generously provided by Professor W. C. Still, Columbia University. For each structure 1000–5000 conformations were generated by MonteCarlo conformational searching. Subsequent minimizations of each conformation were carried out using the MM3 force field in the batch minimization mode.

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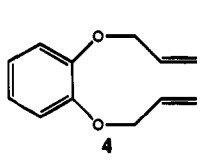
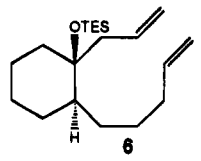
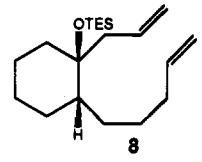
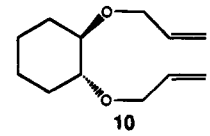
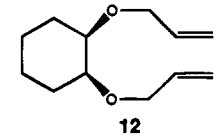
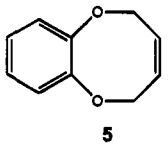
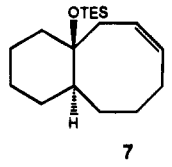
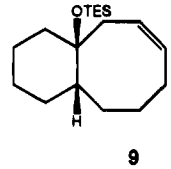
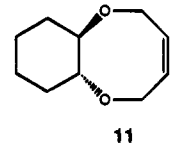
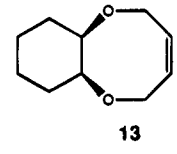
Table 1. Catalytic RCM Synthesis of Eight-Membered Rings

Entry	1	2	3	4	5
Substrate	 **4**	 **6**	 **8**	 **10**	 **12**
Product	 **5**	 **7**	 **9**	 **11**	 **13**
Conditions (Yield)	8 mol% **1**, 3 h, 55 °C, 75%, C_6H_6 (0.015 M)	5 mol% **1**, 4 h, 25 °C, 75%, C_6H_6 (0.010 M)	5 mol% **1**, 20 h, 25 °C, 33%, C_6H_6 (0.010 M)	8 mol% **1**, 2 h, 55 °C, 60%, C_6H_6 (0.015 M)	8 mol% **1**, 2 h, 55 °C, 20%, C_6H_6 (0.015 M)

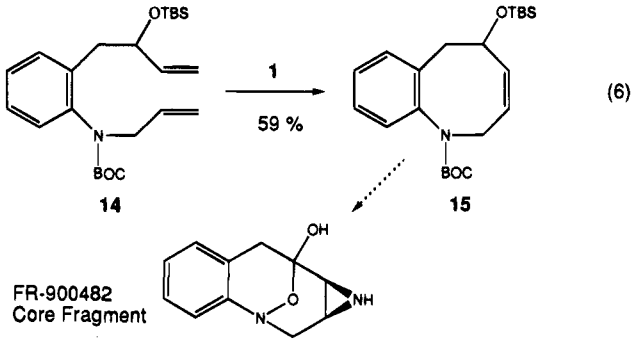
$$\Delta G(\text{entry 5}) - \Delta G(\text{entry 4}) = (119.6 - 109.0) - (112.9 - 104.1) = 1.8 \text{ kJ/mol} \quad (5)$$

Despite the small magnitude of this difference, the implication for the relative equilibrium constants is in fact significant. The exact values of K_{eq} cannot be calculated, but a difference 0.4 kcal/mol could translate to a difference between one K_{eq} which is on the order of 1.4 ($\Delta G \sim -0.2$ kcal/mol, favorable for RCM) and one which is 0.71 ($\Delta G \sim 0.2$ kcal/mol, favorable for ring opening).[7,8] Interestingly, this analysis is quite consistent with our experimental results, where the *trans*-fused bicycle **11** is isolated in 60% yield, while the *cis*-fused counterpart **13** is isolated in only 20% yield.

It is significant to note that this analysis is not rigorously accurate because the system does not actually reach equilibrium (the catalyst becomes sequestered by small amounts of oligomeric materials and decomposes over time), nor are the entropy changes rigorously equivalent.[9] However, it is of interest in the sense that the differences in the calculated strain energies may be used to predict the relative facility of given RCM reactions within a stereoisomeric pair.

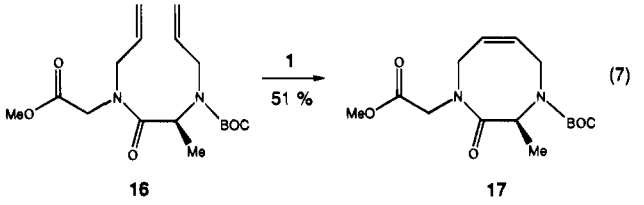
Finally, we wished to demonstrate the application of RCM to some targets of biomedical importance. For example, Kishi[10] and Fukuyama[11] have demonstrated that suitably functionalized structures related to **15** can be converted to the anticancer agents mitomycin and FR-900482 (eq 6). To test the application of RCM to this structure class, compound **14** was prepared in four steps (see supplementary material for details) and subjected to RCM. When **14** was treated with catalyst **1** (10 mol %, 0.0025 M, 60 °C, 24 h), compound **15** was obtained in 59% yield.[12]

In addition, we are pursuing RCM as a means of synthesizing conformationally constrained peptides. An example of this strategy is illustrated in eq 7 where in the bis(*N*-allyl) dipeptide **16** has been prepared and subjected to RCM (eq 7). When **16** was treated with complex **1** (10 mol %, 0.005 M, 60 °C, 24 h), the cyclic dipeptide **14** was isolated in 51% yield. The cyclization is of particular interest when considered in comparison to the *N,O*-bis(allyl) amino ester **3**, which fails to undergo RCM under the conditions investigated. In the case of **16**, the equilibrium among the possible rotamers facilitates



(6)

the production of a rotamer which is conformationally disposed toward RCM.



(7)

In summary, this paper has presented our results concerning the application of complex **1** to the RCM reaction to prepare eight-membered rings. Unlike the application of **1** to the RCM of smaller rings, the present study reveals that eight-membered rings are more demanding in terms of both the amount of catalyst employed and the reaction conditions necessary to obtain good results (concentration, reaction time, temperature). However, we have found that a number of eight-membered-ring substrate classes are amenable to synthesis in reasonable yield by RCM. Defining the parameters which influence the cyclization reaction and extending this reaction to systems of bioorganic importance are among our current objectives.

Acknowledgment. This research was generously supported by a grant from the NIH. S.J.M. is grateful to the NSF for a postdoctoral fellowship. The authors wish to thank Mr. SonBinh Nguyen for providing generous quantities of catalyst **1**.

Supplementary Material Available: Characterization of compounds **4**–**17** in addition to details concerning the synthesis of the RCM precursors (31 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.

JA9433378

(7) For a more rigorous and general treatment of ring–chain equilibria in ring-opening metathesis, see: Chen, Z.-R.; Claverie, J. P.; Grubbs, R. H.; Kornfield, J. A. Submitted to *Macromolecules*.

(8) Analogous calculations were performed on compounds **6**–**9**, and a similar result was obtained.

(9) Attempts to purge ethylene from the system have not resulted in significant enhancements of yields or rates.

(10) Kishi, Y. *J. Nat. Prod.* **1979**, *42*, 549 and references therein.

(11) Fukuyama, T.; Xu, L.; Goto, S. *J. Am. Chem. Soc.* **1992**, *114*, 383.

(12) Professor Stephen Martin of the University of Texas has informed us that he is applying a similar approach to the total synthesis of FR-900482.