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# Synthesis of Small and Large Fused Bicyclic Compounds by Tandem Dienyne Ring-Closing Metathesis

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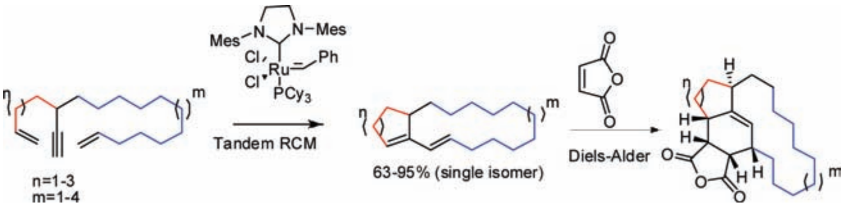
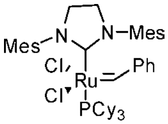
## ABSTRACT



**A tandem ring-closing metathesis reaction using ruthenium catalyst was carried out to synthesize various fused bicyclic compounds containing both small and large rings. Fast ring-closure of the small ring and slow ring-closure of the large ring resulted in the formation of only one isomer. Further manipulation such as the Diels−Alder reaction was carried out to prepare a complex molecule containing multiple rings of different sizes.**

Olefin metathesis (OM) reaction is a powerful tool to create new carbon−carbon double bonds, and numerous organic molecules and polymers are efficiently prepared by OM.[1] Among the various types of OM reactions, ring-closing metathesis (RCM) has attracted the most attention from organic chemists due to its effective synthesis of the various cyclic molecules.[2] In particular, the development of highly active ruthenium carbene catalysts, such as **1**,[3] has led to the broadening of substrate scope for RCM so that it is now routinely used for the synthesis of various natural products and new drugs.[4] Among the various RCM reactions, macrocyclization[5] and tandem RCM to make multiple fused rings[6] enable us to synthesize the molecules with high complexity making this method more versatile. This is demonstrated by recent reports where the tandem RCM of dienyne was successfully carried out for the total synthesis of many natural products.[7] However, this method was so far limited to the synthesis of fused rings comprising small or medium sized only.



**1**

Macrocylization is a very important reaction because many natural products contain large rings. Previously, popular methods for the macrocyclization were Yamaguchi macrolactonization[8] and radical-mediated macrocyclization.[9] However, during the past decade, the macrocyclization by RCM has emerged as a powerful tool because the reaction is highly functional group tolerant with benign reaction conditions.[5] Radical-mediated cascade reactions provide a synthetic

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(1) (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013. (c) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 1, p 2. (d) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117.

(2) (a) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856. (b) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (c) Armstrong, S. K. *J. Chem. Soc. Perkin Trans. 1* **1998**, 371.

(3) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.

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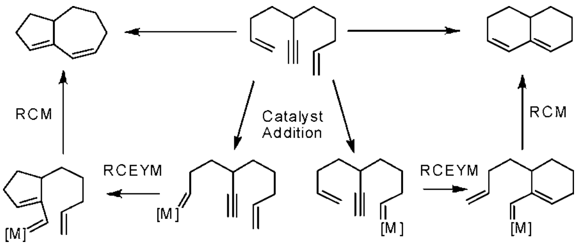
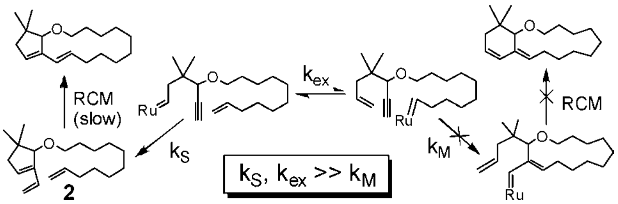
access to the bicyclic compounds comprising both the small and the large rings,[10] but controlling these reactions can be difficult because of problems such as low yield caused by side reactions and the formation of toxic residues. Therefore, a more general method for preparing the small and the large rings in a single reaction would be valuable. We envisioned if the tandem RCM could be implemented as a general and efficient platform for the macrocyclization as well, its synthetic utility would become even greater. Herein, we report the first general method for synthesizing the fused bicyclic compounds comprising both the small and the large rings with high isolated yields by the RCM reaction in a single operation from the corresponding dienynes.

To promote the tandem RCM reaction for the synthesis of the fused bicyclic compounds comprising the small and the large rings, we designed a dienyne containing a small and a long tether. However a potential problem of this tandem RCM would be that asymmetric dienynes with two terminal alkenes result in the formation of two different products with different ring sizes (Scheme 1). This is due to a nonselective initiation on both tethered alkenes, which will result in two different bicycles. To prevent this mixture issue, temporal protection was used by replacing one of two terminal alkenes with a disubstituted olefin so that the catalyst would preferentially react with the terminal olefin.[6,11] For the synthesis of the fused bicycles comprising the small and the large rings by the tandem RCM, we expected that the selectivity issue might be eliminated if the rate of initial RCM to form the small ring ($k_{\mathrm{S}}$) is far greater than the rate of macrocyclization ($k_{\mathrm{M}}$) (Scheme 2). Indeed, a model study and $^1$H NMR confirmed that **2** was the major intermediate implying the initial formation of the small ring occurred exclusively without signs of further dimerization or oligomerization when monitored during the first 3 h. This suggests that although catalyst **1** may react with the terminal olefin on the long tether, no productive RCM occurs. Instead, **1** undergoes fast exchange ($k_{\mathrm{ex}}$) ensuring the formation of the small ring as the first RCM event. Then the slow macrocyclization proceeds for a long period of time producing a single isomer in 82% isolated yield. An alternative mechanism for **1** reacting with the alkyne first is less likely due to a more congested environment.

**Scheme 1.** General Pathway for Tandem RCM



**Scheme 2.** Scheme for the Selective Tandem RCM



To expand the scope of the reaction, various substrates were subjected to the tandem RCM for the synthesis of bicyclic[n.3.0] compounds ($n$ = 12−15). Even though the second macro-RCM itself was challenging since there was only one flexible chain, just 5 mol % of **1** in 4 mM toluene at 50−90 °C was sufficient to promote the tandem RCM with good to excellent isolated yields of the bicycles (Table 1). In most cases, stereochemistry of olefins on the macrocycles is exclusively trans. This selectivity is noteworthy since $E/Z$ selectivity still remains as a serious issue in the macro-RCM reactions.[12] For the synthesis of a fused macrolactone (entry 2), changing solvent to 1,2-dichloroethane resulted in better yield than in toluene. Substrates with additional oxygen in the long tether (entries 3−5) gave excellent yields favoring the macrocyclization.[13] A protected amine in the long tether also allowed tandem RCM with high yield (entry 6). A bicycle with a more challenging tetrasubstituted alkene containing bicycle[14] was also prepared in good yield at 90 °C (entry 7). For this compound, small amount of $Z$ isomer ($E/Z$ = 8) of the olefin on the macrocycle was observed.

The compatibility of the tandem RCM for the synthesis of bicyclic[n.4.0] ($n$ = 12, 13) compounds was also

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(5) (a) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942. (b) Fürstner, A.; Kindler, N. *Tetrahedron Lett.* **1996**, *39*, 7005. (c) Lee, C. W.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145. (d) Smith, A. B., III; Kozmin, S. A.; Adams, C. M.; Paone, D. V. *J. Am. Chem. Soc.* **2000**, *122*, 4984. (e) Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2003**, *125*, 9582. (f) Gradilas, A.; Perez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086. (g) Majumdar, K. C.; Rahaman, H.; Roy, B. *Curr. Org. Chem.* **2007**, *11*, 1339.

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(7) For recent applications see (a) Boyer, F.-D.; Hanna, I.; Ricard, L. *Org. Lett.* **2004**, *6*, 1817. (b) Niethe, A.; Fisher, D.; Blechert, S. *J. Org. Chem.* **2008**, *73*, 3088. (c) Siegel, D. S.; Piizzi, G.; Piersanti, G.; Movassaghi, M. *J. Org. Chem.* **2009**, *74*, 9292. (d) For review, see Mori, M. *Adv. Synth. Cat.* **2007**, *349*, 121.

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(9) For review on radical cyclizations, see Castle, S. L.; Srikanth, G. S. C. *Tetrahedron* **2005**, *61*, 10377.

(10) (a) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (b) Curran, D. P. *Synlett.* **1991**, 63. (c) Haney, B. P.; Curran, D. P. *J. Org. Chem.* **2000**, *65*, 2007.

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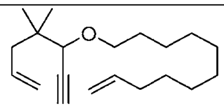
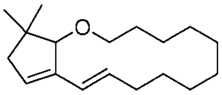
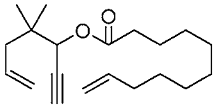
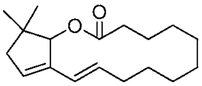
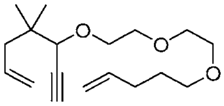
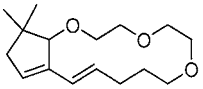
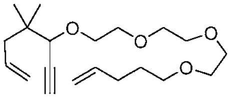
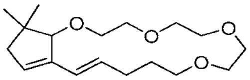
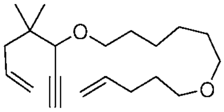
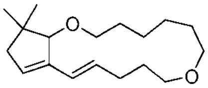
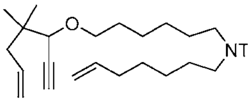
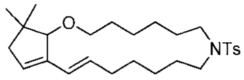
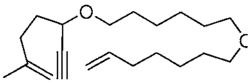
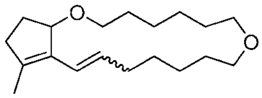
(12) (a) Busca, P.; Etheve-Quelquejeu, M.; Valréy, J.-M. *Tetrahedron Lett.* **2003**, *44*, 9131. (b) Kim, Y. J.; Lee, D. *Org. Lett.* **2004**, *6*, 4351. (c) Conrad, J. C.; Eelman, M. D.; Silva, J. A. D.; Monfette, S.; Parnas, H. H.; Snelgrove, J. L.; Fogg, D. E. *J. Am. Chem. Soc.* **2007**, *129*, 1024.

(13) (a) Fürstner, A. *Top. Catal.* **1997**, *4*, 285. (b) Delgado, M.; Martin, J. D. *J. Org. Chem.* **1999**, *64*, 4798.

(14) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310.

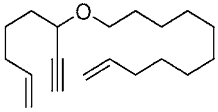
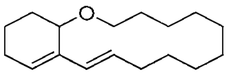
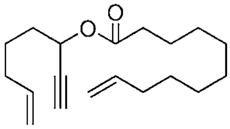
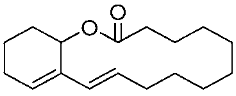
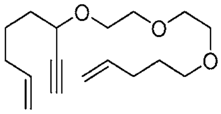
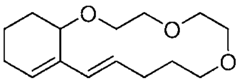
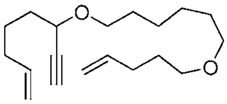
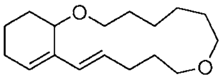
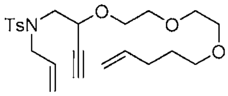
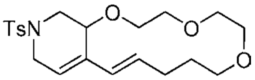
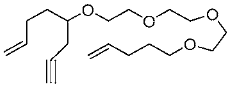
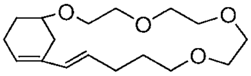
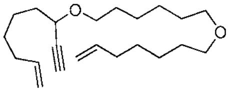
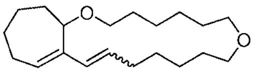
**Table 1.** Tandem RCM for the Formation of Bicycles Comprising Five-Membered Rings[a]

| entry | substrate | temp (°C) | product (yield %) |
|---|---|---|---|
| 1 |  | 70 | <br>(82) |
| 2[b] |  | 55 | <br>(77) |
| 3 |  | 55 | <br>(91) |
| 4 |  | 55 | <br>(89) |
| 5 |  | 55 | <br>(95) |
| 6 |  | 70 | <br>(87) |
| 7[c] |  | 90 | <br>(77) |

[a] General reaction conditions: under Ar atmosphere, substrate in 4 mM toluene is added with 5 mol % **1**, and the solution was heated to 55−90 °C for 24 h. [b] 1,2-DCE as solvent. [c] Mixture of *E*/*Z* = 8 observed by $^1$H NMR.

investigated, and the similar results were obtained (Table 2). Generally, these reactions required higher temperature or higher catalyst loading than examples in Table 1. Also the product yields were slightly lower but still produced only *E* olefins on the macrocycles (entries 1−5). A substrate with a protected amine on its six-membered ring also underwent tandem RCM (entry 5). Interestingly, the tandem RCM affording a bicyclic[15.3.1] compound was also successful even though the product contained a bridgehead olefin on the six-membered ring (entry 6). This is attributed to a reduction in the strain exerted by the flexible macrocycle. A fused bicyclic compound containing a seven-membered ring was also synthesized as a mixture of *E*- and *Z*-isomers (25: 1) (entry 7). However, it required a more dilute condition to suppress the competing dimerization. Furthermore, the tandem RCM was slower than that in the previous examples because the formation of the initial seven-memebered ring was much slower than that of the five and the six-membered rings. As a result, a total of 15 mol % of **1** was added in three portions for 3 days (5 mol % each for a day).

**Table 2.** Tandem RCM for Larger Rings[a]

| entry | substrate | temp (°C) | product (yield %) |
|---|---|---|---|
| 1 |  | 90 | <br>(65) |
| 2[b, c] |  | 70 | <br>(83) |
| 3 |  | 55 | <br>(64) |
| 4 |  | 55 | <br>(69) |
| 5[d] |  | 90 | <br>(71) |
| 6[b] |  | 70 | <br>(69) |
| 7[e] |  | 100 | <br>(63) |

[a] General reaction conditions: under Ar atmosphere, substrate in 4 mM toluene is added with 5 mol % **1**, and the solution was heated to 55−100 °C for 24−48 h. [b] 10 mol % catalyst used. [c] 1,2-DCE as solvent. [d] 8 mol % catalyst used. [e] Substrate concentration lowered to 2 mM and 15 mol % catalyst used. Mixture of *E*/*Z* = 25 observed by $^1$H NMR.

The products of enyne metathesis reaction undergo further transformation such as Diels−Alder reaction.[15] However, there have been no reports of the Diels−Alder reaction with the fused bicycles produced by the tandem dienyne RCM reaction because the Diels−Alder reaction in this case is prevented by conformational strain where the fused bicyles with *Z*-olefin on the small rings adopts only a *s*-trans conformation.[16] We anticipated that our products with *E* olefins might adopt a *s*-cis conformation as well if the macrocycle is sufficiently flexible. (Scheme 3) Indeed, the Diels−Alder reaction with maleic anhydride at 90 °C produced a tetra-cyclic compound comprising three small rings and one large ring in 76% isolated yield. An NOE study revealed that the Diels−Alder adduct showed a single diastereomer with endo selectivity, and the dienophile

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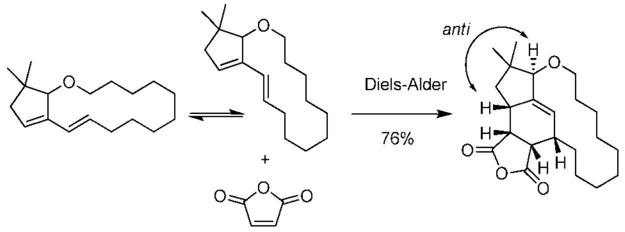
(15) (a) Heerding, D. A.; Takada, D. T.; Kwon, C.; Huffman, W. F.; Samaren, J. *Tetrahedron Lett.* **1998**, *39*, 6815. (b) Rosillo, M.; Dominquez, G.; Casarrubios, L. *J. Org. Chem.* **2004**, *6*, 2084. (c) Lee, H. Y.; Kim, H. Y.; Tae, H. *Org. Lett.* **2003**, *5*, 3439.

(16) For example of Diels-Alder reaction on non-fused bicyclic ring compound, see Aldegunde, M. J.; Codesido, E. M.; Castedo, L.; Granja, J. R. *Tetrahedron Lett.* **2006**, *47*, 6587.

**Scheme 3.** Diels-Alder Reaction of the Tandem RCM Product



approached away from the more hindered alkoxy tether.[17] This is the first example of the Diels–Alder reaction from the fused bicyclic compounds, and this method is potentially useful for the rapid construction of highly complex molecules.

In conclusion, the tandem RCM produced various fused bicycles comprising both the small and the large rings in a single reaction. The advantages of this method are generality and selectivity to produce the fused bicycles with the 5 to 7-membered small rings and the 14 to 17-membered macrocycles in a highly predictive manner. The resulting fused rings contain a 1,3-diene linked by the flexible tether so that further manipulation such as the Diels–Alder reaction was possible. This method can be applicable for the rapid synthesis of complex organic molecules, especially those containing the multiple rings of different sizes.

**Acknowledgment.** The financial support from the Korea Research Fund (Grants 20090069339) and BK21 is acknowledged.

**Supporting Information Available:** Details of the experimental procedure with characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) For similar stereochemistry assignation, see Regás, D.; Alfonso, M. M.; Rodríguez, M. L.; Palenzuela, J. A. *J. Org. Chem.* **2003**, *68*, 7845.