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Synthesis of oxacyclic dienes via ring-closing enyne metathesis: difference in construction of eight-membered rings

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ABSTRACT

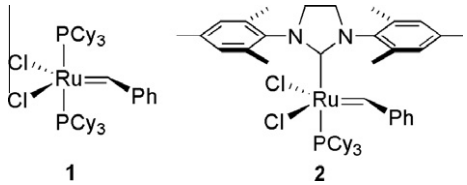
A series of oxacyclic diene compounds, especially eight-membered products bearing a single oxygen atom which have not been reported previously, were successfully synthesized via ring-closing enyne metathesis using the second-generation Grubbs catalyst. In contrast to the construction of the five-membered rings, completely opposite substrate selectivity that methyl substituted internal alkyne showed much higher reactivity than terminal alkyne was observed in building eight-membered ring derivatives.

Ruthenium-catalyzed enyne metathesis with regard to Grubbs catalyst **1** and **2** (Scheme 1)[1,2] has become a powerful strategy to construct various 1,3-diene compounds that are not easily synthesized by common methods.[3] The reaction process involves in intermolecular cross[4] or intramolecular ring-closing enyne metathesis. The latter offers a more convenient access to various five-, six- and seven-membered cyclic diene compounds, including carbocycles, heterocycles, β-lactams, unnatural amino acids, carbohydrates and other biologically active compounds.[5,6] Importantly, ring-closing enyne metathesis has been elegantly used and become a crucial step in the total synthesis of many natural products.[7,8]

However, the construction of eight-membered rings via ring-closing enyne metathesis is thought to be relatively difficult due to unfavorable entropy loss. As a result, rare reports concerned the synthesis of this kind of compounds.[9–11] It was reported that bicyclic compounds containing eight-membered ring could be built by tandem metathesis of dienynes.[9] Alternatively, cyclic structure or more than one heteroatom were inevitably involved in the enyne substrates to restrict conformational freedom,[10] thereby facilitating bidentate coordination of enyne substrates to metal center of the catalyst.[12] No product[13] or only very low yield[10] was observed in synthesizing monocyclic eight-membered ring bearing a single heteroatom. Therefore, the synthesis of eight-membered oxacyclic diene compounds, which was frequently found in natural products, remains undeveloped. Herein, we report the synthesis of five- to eight-membered oxacyclic diene compounds via ring-closing enyne metathesis using Grubbs ruthenium catalysts. In contrast to the construction of the five-membered rings, a completely opposite substrate selectivity that methyl substituted internal alkyne showed much higher reactivity than terminal alkyne was observed in building eight-membered ring derivatives.

Initially, synthesis of five-membered oxacyclic diene compounds via ring-closing enyne metathesis was systemically studied. The second-generation Grubbs catalyst **2**, which exhibits higher catalytic activity and stability than the first-generation Grubbs catalyst **1**, was used as catalyst in our experimental investigations. As shown in Table 1, a variety of allyl propargyl ether derivatives were used as substrates and their reactivities toward ring-closing enyne metathesis were tested.

It seems that propargylic substitution has little influence on the reactivity (Table 1, entries 2, 5, 6, 8, 10–12 and 14). Contrarily, the ring-closing enyne metathesis turned out to be sensitive to alkyne substitution. For the allyl ether substrates **3a–3d**, compared with terminal alkyne **3a**, methyl substituted alkyne **3b** gave slightly decreased yield (Table 1, entries 1 and 2), while *n*-octyl (**3c**) and phenyl (**3d**) substituted alkynes failed to yield the corresponding



1 2

Scheme 1. The first-generation (**1**) and second-generation (**2**) Grubbs catalyst.

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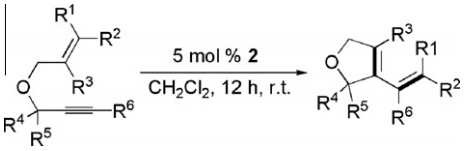
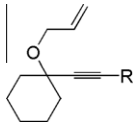
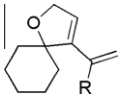
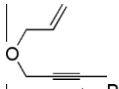
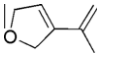
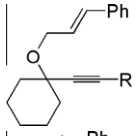
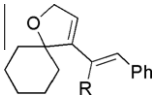
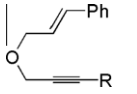
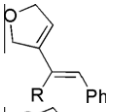
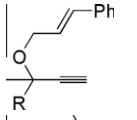
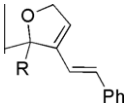
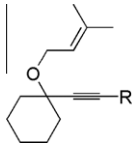
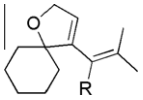
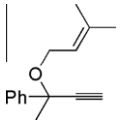
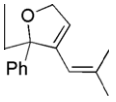
Table 1
Synthesis of five-membered oxacyclic diene compounds[a]



Entry	Substrates		R	Products		Yield[b] (%)
1		**3a**	H		**4a**	89
2		**3b**	Me		**4b**	84
3[c]		**3c**	C_8H_{17}		**4c**	<1
4[c]		**3d**	Ph		**4d**	<1
5[d]		**3e**			**4e**	99
6		**3f**	H		**4f**	80
7[d]		**3g**	Me		**4g**	21
8		**3h**	H		**4h**	81
9[c]		**3i**	Me		**4i**	<1
10		**3j**	Me		**4j**	80
11		**3k**	Ph		**4k**	92
12[e]		**3l**	H		**4l**	83
13[c,e]		**3m**	Me		**4m**	<1
14[e]		**3n**			**4n**	96

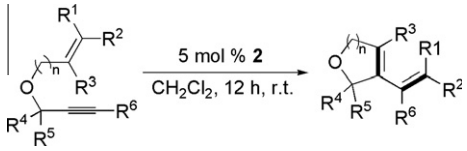
[a] Reaction conditions: **2** (5 mol %), substrates (0.2–0.4 mmol), CH_2Cl_2 (0.05 M), 12 h, room temperature.
[b] Isolated yields.
[c] Yields were determined by ^1H NMR, more than 90% substrates remained.
[d] Yields were determined by ^1H NMR.
[e] Reaction time: 36 h.

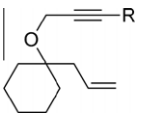
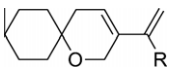
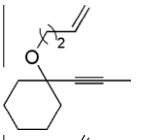
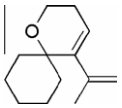
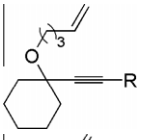
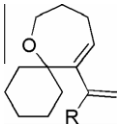
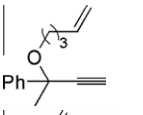
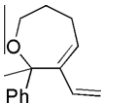
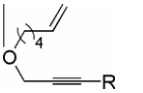
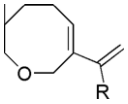
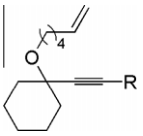
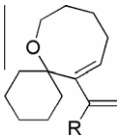
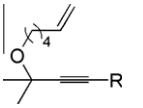
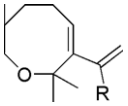
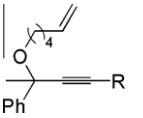
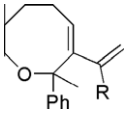
five-membered oxacyclic diene products at the same conditions (Table 1, entries 3 and 4).

When cinnamyl ethers were used as substrates, 80% yield of 6,5-spirocyclic diene product was obtained for terminal alkynes **3f**, while a dramatic decrease in yield was observed for methyl substituted alkynes **3g** (Table 1, entries 6 and 7). Cinnamyl propargyl ether **3h** conducted ring-closing enyne metathesis reaction smoothly, however, cinnamyl 2-butynyl ether **3i** failed to undergo this reaction (Table 1, entries 8 and 9). The ring-closing enyne metathesis reaction of substrates **3l** and **3n** containing trisubstituted alkene and terminal alkyne groups could be successfully carried out although the reactions were completed in a prolonged time (Table 1, entries 12 and 14). Methyl substituted alkyne (**3m**) with a prenyl group gave no ring-closing enyne metathesis product (Table 1, entry 13).

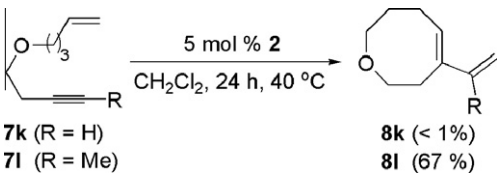
Subsequently, synthesis of six-, seven-, and eight-membered oxacyclic diene compounds via ring-closing enyne metathesis was performed at the same conditions as previously (Table 2). The substrates bearing terminal alkene group were transferred into six- and seven-membered oxacyclic diene compounds in moderate

Table 2
Synthesis of six-, seven-, and eight-membered oxacyclic diene compounds[a]



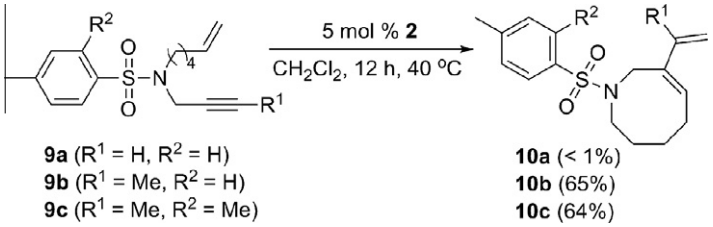
Entry	Substrates		R	Products		Yield[b] (%)
1[c,d]		**5a**	H		**6a**	45
2[c,d]		**5b**	Me		**6b**	42
3		**5c**			**6c**	98
4		**5d**	H		**6d**	98
5		**5e**	Me		**6e**	96
6		**5f**			**6f**	95
7[e]		**7a**	H		**8a**	<1
8[e,f]		**7a**	H		**8a**	<1
9		**7b**	Me		**8b**	82
10		**7c**	Et		**8c**	81
11[e]		**7d**	CH_2OH		**8d**	<1
12[e]		**7e**	H		**8e**	8
13		**7f**	Me		**8f**	93
14[e]		**7g**	H		**8g**	<1
15		**7h**	Me		**8h**	89
16[e,g]		**7i**	H		**8i**	<1
17[d,e,g]		**7i**	H		**8i**	<1
18[g]		**7j**	Me		**8j**	96

[a] Reaction conditions: **2** (5 mol %), substrates (0.2–0.4 mmol), CH_2Cl_2 (0.05 M), 12 h, room temperature.
[b] Isolated yields.
[c] Yields were determined by ^1H NMR.
[d] Reaction temperature: 40 °C.
[e] Yields were determined by ^1H NMR, more than 90% substrates remained.
[f] The reaction was conducted in the presence of 1 atm ethylene gas.
[g] Reaction time: 36 h.



Scheme 2. Synthesis of eight-membered oxacyclic diene compounds via enyne metathesis of 3-butynyl ether.

to excellent yield (Table 2, entries 1–6). Undheim and coworker reported that 6,6-spirocycles were accessible while 6,7-spirocyclic products were not achieved in their synthesis of unnatural amino



Scheme 3. Synthesis of eight-membered nitrogen-containing heterocyclic diene compounds via enyne metathesis.

acids via ring-closing enyne metathesis using catalyst **1**.[14] In our reaction system, both 6,6- and 6,7-spirofused oxacycles were obtained (Table 2, entries 3–5). Likewise, terminal alkynes **5a** and **5d** provided slightly higher yields than corresponding methyl substituted alkynes **5b** and **5e** (Table 2, entries 1, 2, 4 and 5).

In striking contrast to the construction of the smaller sized rings, when eight-membered oxacyclic dienes were targeted, terminal alkyne substrates showed no or very low reactivity toward ring-closing enyne metathesis (Table 2, entries 7, 12, 14 and 16), even at enhanced temperatures (Table 2, entry 17).[15] Mori et al. reported that ethylene gas could accelerate the ring-closing enyne metathesis of terminal alkyne.[16] However, in the presence of ethylene gas, no observable improvement was found in the ring-closing enyne metathesis regarding those terminal alkynes suitable substrates in our system (Table 2, entry 8). Methyl substituted alkynes **7b**, **7f**, **7h**, **7j** proceeded ring-closing enyne metathesis smoothly affording corresponding eight-membered oxacyclic diene in good yield (Table 2, entries 9, 13, 15 and 18). It is noteworthy that 6,8-spirofused oxacycles can also be achieved (Table 2, entry 13). Interestingly, with hydroxymethyl substituted alkynes **7d** as substrate, no ring-closing product was detected, probably due to the deactivation the ruthenium catalyst (Table 2, entry 11).

Similarly, when 3-butynyl ethers were used as substrates to construct eight-membered oxacyclic diene compounds, terminal alkyne **7k** was also proven to be unreactive in ring-closing enyne metathesis, while methyl substituted alkyne **7l** gave a moderate yield (Scheme 2).

Likewise, when the heteroatom in the enyne substrate was changed from oxygen to nitrogen, terminal alkyne **9a** gave no diene product in ring-closing enyne metathesis, while methyl substituted alkyne **9b** and **9c** produced corresponding eight-membered nitrogen-containing heterocyclic diene **10b** and **10c** in moderate yields (Scheme 3).

In conclusion, a variety of oxacyclic diene compounds, especially eight-membered products bearing a single oxygen atom, were successfully synthesized via ring-closing enyne metathesis using the second-generation Grubbs catalyst. In striking contrast to the synthesis of the smaller sized rings, completely opposite substrate selectivity that methyl substituted internal alkyne showed much higher reactivity than terminal alkyne was observed in the construction of eight-membered rings. Mechanistic exploration and further application study are in progress in our laboratory.

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Supplementary data

Supplementary data (experimental procedure, characterization of products and copies of NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.107.

References and notes

1. (a) Trnak, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18; (b) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117; (c) Astruc, D. *New J. Chem.* **2005**, *29*, 42.
2. (a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100; (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953; (c) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543; (d) Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T.-L.; Ding, S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 2546.
3. (a) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317; (b) Hansen, E. C.; Lee, D. *Acc. Chem. Res.* **2006**, *39*, 509; (c) Mori, M. *Adv. Synth. Catal.* **2007**, *349*, 121; (d) Diver, S. T. *Coord. Chem. Rev.* **2007**, *251*, 671; (e) Mori, M. *Materials* **2010**, *3*, 2087; (f) Fischmeister, C.; Bruneau, C. Beilstein *J. Org. Chem.* **2011**, *7*, 156.
4. (a) Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 12388; (b) Stragies, R.; Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed.* **1997**, *36*, 2518; (c) Smulik, J. A.; Diver, S. T. *J. Org. Chem.* **2000**, *65*, 1788; (d) Kulkarni, A. A.; Diver, S. T. *Org. Lett.* **2003**, *5*, 3463; (e) Kulkarni, A. A.; Diver, S. T. *J. Am. Chem. Soc.* **2004**, *126*, 8110; (f) Park, S.; Kim, M.; Lee, D. *J. Am. Chem. Soc.* **2005**, *127*, 9410.
5. (a) Maifeld, S. V.; Lee, D. *Chem. Eur. J.* **2005**, *11*, 6118; (b) Villar, H.; Frings, M.; Bolm, C. *Chem. Soc. Rev.* **2007**, *36*, 55; (c) Yang, X.; Zhang, Y.; Shao, Z. *Chinese J. Org. Chem.* **2010**, *30*, 968; (d) Majumdar, K. C. *RSC Advances* **2011**, *1*, 1152.
6. (a) Kinoshita, A.; Mori, M. *Synlett* **1994**, 1020; (b) Kim, S.-H.; Zuercher, W. J.; Bowden, N. B.; Grubbs, R. H. *J. Org. Chem.* **1996**, *61*, 1073; (c) Furstner, A.; Ackermann, L.; Gabor, B.; Goddard, R.; Lehmann, C. W.; Mynott, R.; Stelzer, F.; Thiel, O. R. *Chem. Eur. J.* **2001**, *7*, 3236; (d) Kitamura, T.; Sato, Y.; Mori, M. *Adv. Synth. Catal.* **2002**, *344*, 678; (e) Guo, H.; Madhushaw, R. J.; Shen, F.-M.; Liu, R.-S. *Tetrahedron* **2002**, *58*, 5627; (f) Castarlenas, R.; Eckert, M.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 2576; (g) Kim, B. G.; Snapper, M. L. *J. Am. Chem. Soc.* **2006**, *128*, 52; (h) Wakamatsu, H.; Sato, Y.; Fujita, R.; Mori, M. *Adv. Synth. Catal.* **2007**, *349*, 1231.
7. Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490.
8. (a) Kinoshita, A.; Mori, M. *J. Org. Chem.* **1996**, *61*, 8356; (b) Clark, J. S.; Townsend, R. J.; Blake, A. J.; Teat, S. J.; Johns, A. *Tetrahedron Lett.* **2001**, *42*, 3235; (c) Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773; (d) Cesati, R. R., III; de Armas, J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 96; (e) Kitamura, T.; Sato, Y.; Mori, M. *Tetrahedron* **2004**, *60*, 9649; (f) Brenneman, J. B.; Machauer, R.; Martin, S. F. *Tetrahedron* **2004**, *60*, 7301; (g) Tomita, T.; Kita, Y.; Kitamura, T.; Sato, Y.; Mori, M. *Tetrahedron* **2006**, *62*, 10518; (h) Kummer, D. A.; Brenneman, J. B.; Martin, S. F. *Tetrahedron* **2006**, *62*, 11437; (i) Zhang, Y. D.; Tang, Y. F.; Luo, T. P.; Shen, J.; Chen, J. H.; Yang, Z. *Org. Lett.* **2006**, *8*, 107; (j) Evanno, L.; Deville, A.; Bodo, B.; Nay, B. *Tetrahedron Lett.* **2007**, *48*, 4331; (k) Boyer, F. D.; Hanna, I. *Org. Lett.* **2007**, *9*, 715; (l) Krishna, P. R.; Narsingam, M. *Tetrahedron Lett.* **2007**, *48*, 8721; (m) Movassaghi, M.; Piizzi, G.; Siegel, D. S.; Piersanti, G. *Tetrahedron Lett.* **2009**, *50*, 5489; (n) Siegel, D. S.; Piizzi, G.; Piersanti, G.; Movassaghi, M. *J. Org. Chem.* **2009**, *74*, 9292; (o) Vuong, S.; Rodriguez-Fernandez, M. M.; Renoux, B.; Len, C. *Carbohydr. Res.* **2010**, *345*, 324.
9. (a) Codesido, E. M.; Castedo, L.; Granja, J. R. *Org. Lett.* **2001**, *3*, 1483; (b) Boyer, F.-D.; Hanna, I.; Ricard, L. *Org. Lett.* **2001**, *3*, 3095.
10. (a) Mori, M.; Kitamura, T.; Sakakibara, N.; Sato, Y. *Org. Lett.* **2000**, *2*, 543; (b) Mori, M.; Kitamura, T.; Sato, Y. *Synthesis* **2001**, 654; (c) Yang, Y.-K.; Tae, J. *Synlett* **2003**, 2017; (d) Tae, J.; Hahn, D.-W. *Tetrahedron Lett.* **2004**, *45*, 3757; (e) Peppers, B. P.; Diver, S. T. *J. Am. Chem. Soc.* **2004**, *126*, 9524; (f) Groaz, E.; Banti, D.; North, M. *Adv. Synth. Catal.* **2007**, *349*, 142; (g) Boyer, F.-D.; Hanna, I. *Eur. J. Org. Chem.* **2008**, 4938; (h) Wakamatsu, H.; Sakagami, M.; Hanata, M.; Takeshita, M.; Mori, M. *Macromol. Symp.* **2010**, *293*, 5; (i) Turlington, M.; Du, Y.; Ostrum, S. G.; Santosh, V.; Wren, K.; Lin, T.; Sabat, M.; Pu, L. *J. Am. Chem. Soc.* **2011**, *133*, 11780.
11. For the synthesis of macrocyclic compounds via ring-closing enyne metathesis, see: Ref. 3b, 8c and (a) Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2003**, *125*, 9582; (b) Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2004**, *126*, 15074; (c) Grimwood, M. E.; Hansen, H. C. *Tetrahedron* **2009**, *65*, 8132.
12. Lippstreu, J. J.; Straub, B. F. *J. Am. Chem. Soc.* **2005**, *127*, 7444.
13. Teichert, J. F.; Zhang, S.; van Zijl, A. W.; Slaa, J. W.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2010**, *12*, 4658.
14. Hammer, K.; Undheim, K. *Tetrahedron* **1997**, *53*, 10603.

15. Terminal alkynes were not suitable substrates also see: Ref. 6a, 13 and (a) Barrett, A. G. M.; Baugh, S. P. D.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Giles, M. R.; Marshall, E. L.; Procopiou, P. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1998**, *63*, 7893; (b) Gracias, V.; Gasiecki, A. F.; Djuric, S. W. *Tetrahedron Lett.* **2005**, *46*, 9049.

16. (a) Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082; (b) Lloyd-Jones, G. C.; Margue, R. G.; de Vries, J. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 7442; (c) Grotevendt, A. G. D.; Lummiss, J. A. M.; Mastronardi, M. L.; Fogg, D. E. *J. Am. Chem. Soc.* **2011**, *133*, 15918.