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# Use of Cyclopropanols as Conformational Constraints in RCM

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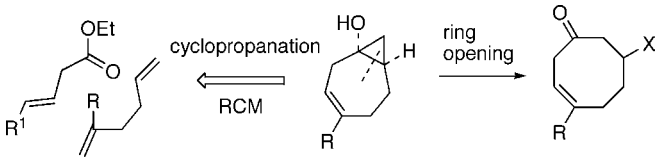
## ABSTRACT

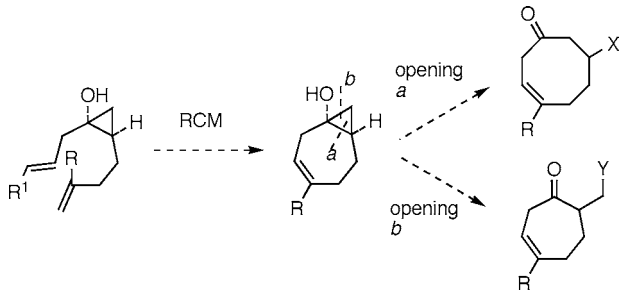



**Sequential application of the Kulinkovich cyclopropanation of carboxylic esters and RCM of the resulting *cis*-dialkenyl-tethered cyclopropanols provides an expedient route to functionalized medium-sized carbocycles. Subsequent elaboration of the cyclopropanol functionality, such as one-carbon ring expansion, to afford synthetically useful $\alpha,\beta$-enones is also worth noting.**

Transition-metal-catalyzed olefin metathesis has quickly become one of the most versatile and powerful tools in organic synthesis. Dazzling arrays of cyclic and acyclic unsaturated molecules are now available by this multi-faceted chemistry. In particular, ring-closing metathesis (RCM) has been frequently utilized in the syntheses of a variety of functionalized carbocycles and heterocycles: five-, six-, and seven-membered rings, along with macrocycles, are easily accessible by this unrivaled transformation.[1] Construction of eight-membered rings, however, has been shown to be less than satisfactory. The presence of conformational constraints has proven to be indispensable to circumventing this notable limitation.[1a,2] We report herein an effective use of a cyclopropanol moiety to provide expedient access to suitably functionalized eight-membered carbocycles.

Among essential attributes of an ideal conformational restraint are its ability to promote cyclization, ease of introduction, and straightforward removal or elaboration to a common functional group found in biologically relevant natural products. A cyclopropanol seemed well suited for satisfying these requisite characteristics. An additional advantage is subsequent ring opening of bicyclic cyclopropanols, both modes *a* and *b* of which are readily available; ring expansion by one carbon offers a new route to synthetically useful eight-membered ring ketones (Scheme 1).[3−5] Moreover, the Kulinkovich cyclopropanation of unhindered esters provides convenient access to requisite *cis*-dialkylcyclopropanols;[6−8] a pivotal element of this sequence underscores the well-documented stereochemical outcome of the Kulinkovich cyclopropanation.

**Scheme 1**




(1) For reviews on RCM, see: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (c) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592. (d) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900. (e) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. (f) Wallace, D. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 1912.

(2) Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108.

(3) See also: (a) Gibson, D. H.; DePuy, C. H. *Chem. Rev.* **1974**, *74*, 605. (b) Ryu, I.; Matsumoto, K.; Kameyama, Y.; Ando, M.; Kusumoto, N.; Ogawa, A.; Kambe, N.; Murai, S.; Sonoda, N. *J. Am. Chem. Soc.* **1993**, *115*, 12330 and references therein.

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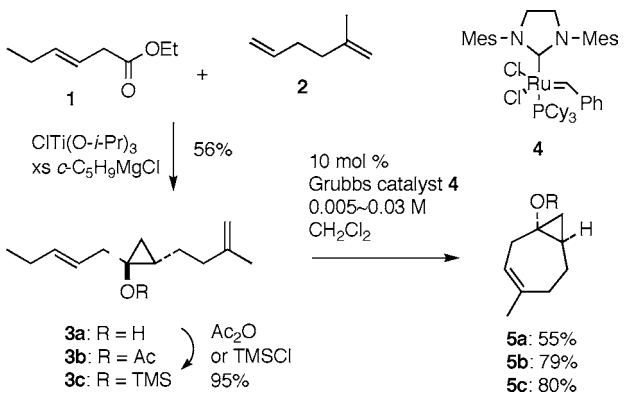
In the initial experiment, cyclopropanol **3a** was first prepared in 56% yield from **1** and **2** (Scheme 2). RCM of

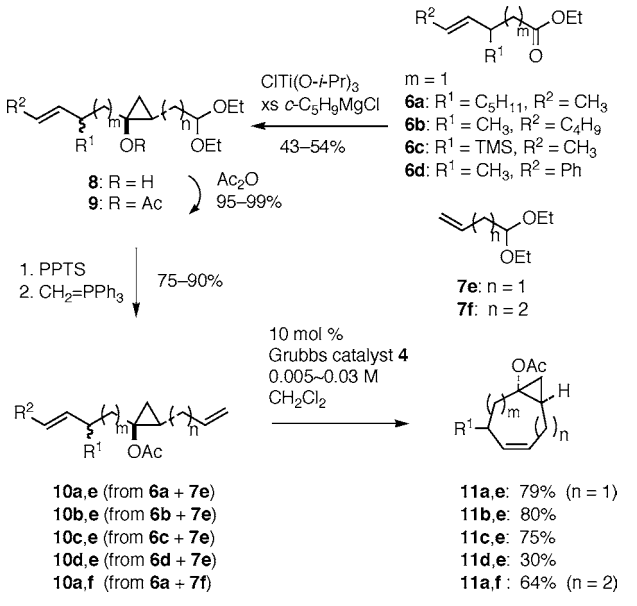
**Scheme 2**




**3a** was then accomplished by the action of **4** to afford **5a** in 55% yield in refluxing dichloromethane (5−30 mM). Lower yield could be attributed to competing, albeit slow, ring opening of cyclopropanol by the catalyst. Protection of the hydroxyl group as the acetate or the trimethylsilyl ether provided **5b** and **5c** in higher yields (79−80%).

The generality of this cyclopropanation−RCM sequence was next examined. For convenience and flexibility of preparing disubstituted olefins (as well as trisubstituted olefins), acetal-tethered terminal olefins were employed in the titanium-mediated cyclopropanation (Scheme 3). Cyclo-

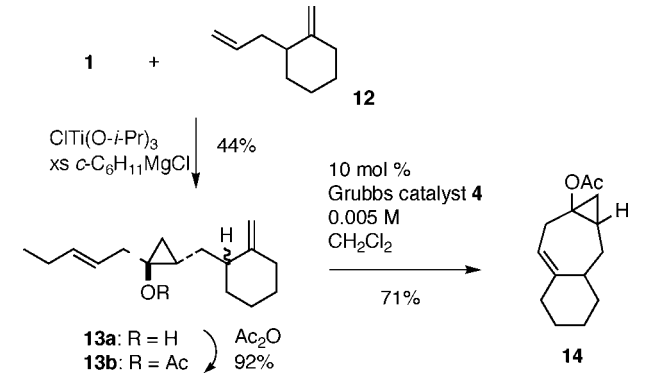
**Scheme 3**




propanols **8** were first prepared starting with **6a**−**d** and **7e**,**f**.[6−8] Following acetylation, the RCM substrates **10** were then secured by standard methods. RCM furnished **11a**,**e**, **11b**,**e**, and **11c**,**e** in 75−80% yield under typical conditions. In accord with the literature, RCM of a styrene derivative **10d**,**e** proved to be sluggish. It is noteworthy that direct eight-membered ring formation (**10e**,**f** to **11e**,**f**) was achieved in 64% (unoptimized) yield without resorting to high dilution.

A large number of bioactive, medium-sized (seven- and eight-membered) carbocyclic natural products is characterized by the presence of a fused bicyclic or tricyclic skeleton such as is found in 5,7-, 5,8-, 6,7-, and 6,8-fused ring compounds. Toward eventual applications in natural product synthesis, the identical sequence started with a cyclic diene. The Kulinkovich cyclopropanation of **1** and **12** delivered cyclopropanol **13a**, as an inseparable 1:1 diastereomeric mixture, in 44% (unoptimized) yield (Scheme 4). Following

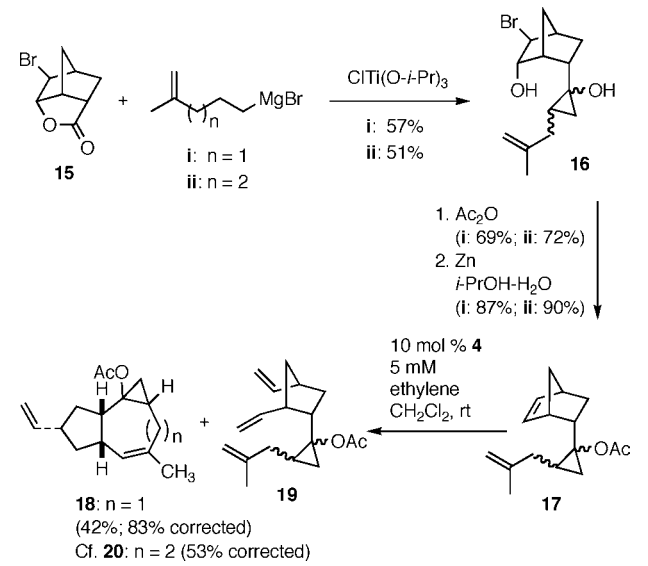
**Scheme 4**




acetylation, RCM of the resulting acetate **13b** afforded **14** in 71% yield as a single diastereomer; it is interesting to note that only one isomer underwent selective RCM, whereas the other diastereomeric acetate was isolated unreacted.

The cyclopropanation−RCM sequence was also extended to an *endo*-5-norbornene-2-carboxylate (Scheme 5). Since

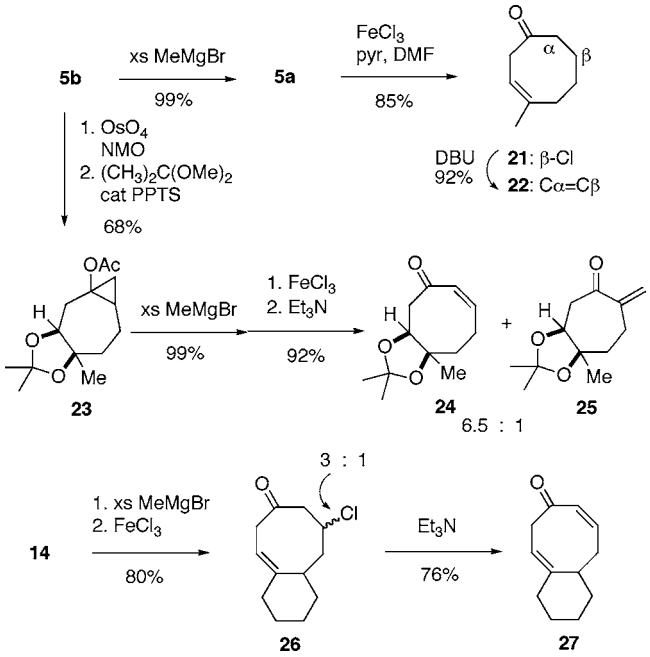
**Scheme 5**



the double bond of norbornenes also undergoes the Kulinkovich reaction due to strain,[8b] bromolactone **15** was employed as starting material for the cyclopropanation to provide **16** as an inseparable mixture (57%) of essentially three (two *cis*-dialkyl + one *trans*-alkyl) isomers in a ca. 1:0.7:0.3 ratio (GC/MS analysis). Bisacetylation of **16** and subsequent reduction with Zn then gave **17** to set the stage of ring-opening metathesis. The key olefin metathesis of **17** produced **18** as a single isomer (42%; ~83% based on consumed starting material), along with triene **19** (38%) and unreacted **17** (10%); it is apparent that only one of the two *cis*-alkyl cyclopropanols selectively underwent RCM. Similarly, the next homologue **20** was obtained as a single isomer in comparable yield. Since starting *endo*-5-norbornene-2-carboxylates are readily available in enantiopure form, this methodology lends itself to enantioselective synthesis of medium-sized carbocycles.[1,9]

By means of oxidation with $FeCl_3$,[4,10] the cyclopropanol functionality can be readily converted to the respective α,*β*-unsaturated enone. Thus, treatment of **5a** with $FeCl_3$ resulted in facile ring opening to afford **21** in 85% yield (Scheme 6). Subsequent elimination of the chloride of **21** proceeded cleanly (92%) by the action of DBU to give enone **22**. Similarly, a 6.5:1 mixture of **24** and **25** was obtained in good yield via **23** by initial dihydroxylation of **5b**. Comparable results were also obtained for the preparation of **27** from **14**.

**Scheme 6**




In conclusion, sequential application of the Kulinkovich cyclopropanation of carboxylic esters and RCM of the resulting *cis*-dialkenyl-tethered cyclopropanols provides an expedient route to functionalized medium-sized carbocycles. The cyclopropanol functionality permits not only direct formation of eight-membered rings but also subsequent elaboration, such as one-carbon ring expansion, to afford synthetically useful α,*β*-enones. This work also takes advantage of intrinsic *cis*-dialkyl diastereoselectivity of the Kulinkovich reaction of carboxylic esters. Applications in natural product synthesis will be reported in due course.

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**Supporting Information Available:** Experimental details and spectroscopic data for key intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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