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Ring-Closing Metathesis/Fragmentation Route to Geometrically Defined Medium-Ring Cycloalkenes: Total Synthesis of (±)-Periplanone C

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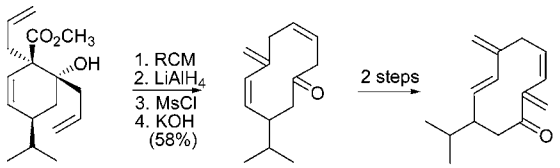
ABSTRACT



Periplanone C

The combination of alkene metathesis and β-fragmentation offers an efficient entry into (*Z*)-configured medium-ring cycloalkenes. The versatility of this method is demonstrated by the total synthesis of Periplanone C, a semiochemical of *Periplaneta americana*.

Ring-closing metathesis (RCM) has rapidly evolved into one of the most versatile approaches for the synthesis of cyclic systems of various sizes and has found widespread application in the synthesis of complex organic compounds.[1] Continuous efforts in the field have resulted in a steady improvement of the catalyst performance in terms of functional group tolerance, increased reactivity and stability toward oxygen and moisture, and in the development of polymer-supported reagents. Recently, enantioselective variants of RCM have also been reported.[2]

However, the control of alkene geometry in the medium- and large-ring cycloalkene products remains an unsolved problem.[3] The (*E*/*Z*) outcome is difficult to predict and almost impossible to modify. Most often it appears to be substrate controlled, profoundly influenced by the ring size and substituents. Thus, even cyclooctene ring closure, normally expected to occur with (*Z*)-selectivity, under certain conditions can afford an (*E*)-derivative exclusively.[4] Numerous examples are known where metathetic closures of medium-sized rings proceed with (*E*)-selectivity, both in the carbo- and heterocyclic series.[5] In larger rings, (*E*)-products are usually favored, where the degree of selectivity may depend on the reaction temperature[6] and solvent.[7] While the ap-

(1) For review articles on RCM, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141.

(2) For some recent reviews on the developments in RCM and the use of the last-generation catalysts, see: (a) Schrock, R. R., Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592. (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (c) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (d) See also: Blechert, S.; Connon, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900.

(3) For a short review on the application of RCM in the synthesis of medium-sized rings, see: Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073.

(4) Bourgeois, D.; Pancrazi, A.; Ricard, L.; Prunet, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 726.

(5) For some examples of (*E*)-selective RCM of 10-membered rings, see the following. (a) Cycloalkene: Nevalainen, M.; Koskinen, A. M. P. *J. Org. Chem.* **2002**, *67*, 1554. (b) Lactam: Fink, B. E.; Kym, P. R.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 4334. (c) Ester: Furstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061. (d) For examples of both (*E*)- and (*Z*)-selective 11-membered ring formation, see: Nicolaou, K. C.; Vassilikogiannakis, G.; Montagnon, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3276.

(6) Furstner, A.; Langemann, K. *Synthesis* **1997**, 792.

(7) Nakashima, K.; Ito, R.; Sono, M.; Tori, M. *Heterocycles* **2000**, *53*, 301.

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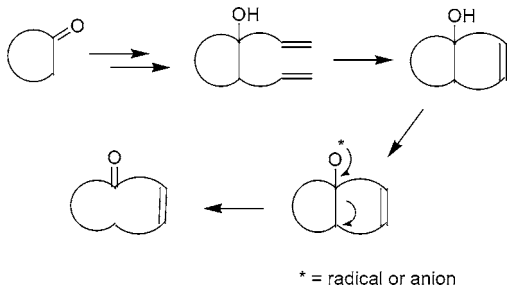
Scheme 1. Metathesis/Fragmentation Approach to Medium-Ring (*Z*)-Cycloalkenes



plication of RCM in the synthesis of (*E*)-alkene units in cyclic natural products has been recently reviewed,[8] (*Z*)-selective RCM remains elusive.[9]

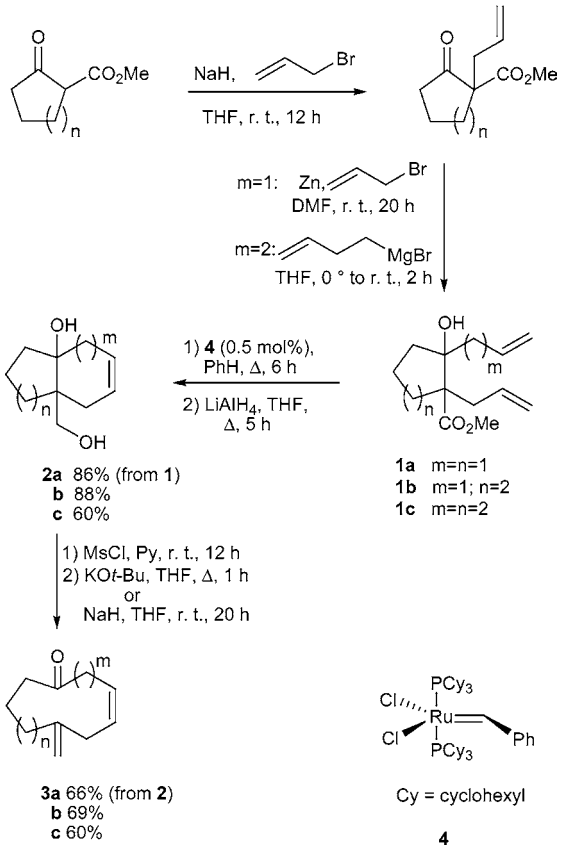
An indirect method, which circumvents the selectivity problem, relies on ring-closing alkyne metathesis; the macrocyclic alkynes thus obtained can often be further reduced selectively to (*Z*)-cycloalkenes.[10] The catalysts for this type of transformation are, however, less developed than those for the alkene RCM.

We set out to devise a method that would allow for a general, stereoselective synthesis of medium-ring (*Z*)-cycloalkenes, based on RCM. Our approach, delineated in Scheme 1, involves RCM of a cyclic substrate followed by fragmentation of a central bond in a condensed bicyclic intermediate. Several features of this indirect procedure should contribute to its efficiency: (a) the stereochemical constraints associated with small-ring closure could secure the (*Z*)-configuration of the new alkene bond; (b) a RCM reaction that led to a five-, six-, or seven-membered ring could be expected to proceed in a better yield, as compared to a direct medium-sized ring closure; (c) given the vast number of methods for small-ring formation, as well as for nucleophilic and electrophilic introduction of alkenyl units, the RCM precursors should be readily available; (d) the fragmentation step could be performed under various conditions (anionic, radical), which adds to the versatility of the overall sequence.

The annulation/fragmentation principle is well precedented and has been used in the synthesis of many complex natural products. However, we are aware of only two, relatively specific, examples of the RCM-based stereoselective ring expansion approach to medium-sized rings.[11]

To test the feasibility of the envisaged protocol, several model compounds were prepared according to Scheme 2.

Scheme 2



Upon submission to the cyclization/fragmentation cascade, compounds **1a**−**c** were expected to yield 9−11-membered cycloalkenones with an additional *exo*-methylene double bond. On exposure to Ru catalyst **4**, all the substrates afforded bicyclic products in almost quantitative yields. Reduction of the esters, followed by selective mesylation of the primary hydroxyl groups in **2**, set the stage for the Grob fragmentation, which proceeded without event to give the expected cycloalkenones **3**. The overall yield from **1** was 35−59%, which we found to be acceptable for an unoptimized four-step procedure. Notably, regio- and stereochemical integrity of the endocyclic double bond in the final products **3** was not affected under the basic conditions of the latter reaction.

These preliminary results encouraged us to apply the RCM/fragmentation method in the synthesis of more complex systems. We turned our attention toward a group of cyclic sesquiterpenes known as periplanones, sex pheromones of the American cockroach, *Periplaneta americana*, which have proven to be of considerable interest of synthetic chemists.[12] Periplanone C **5** appeared to us as a challenging target for the application of our method, as this germacrene derivative possesses four alkene units of both (*Z*)- and (*E*)-configuration, as well as a highly activated, conjugated *exo*-

(8) Prunet, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 2826.

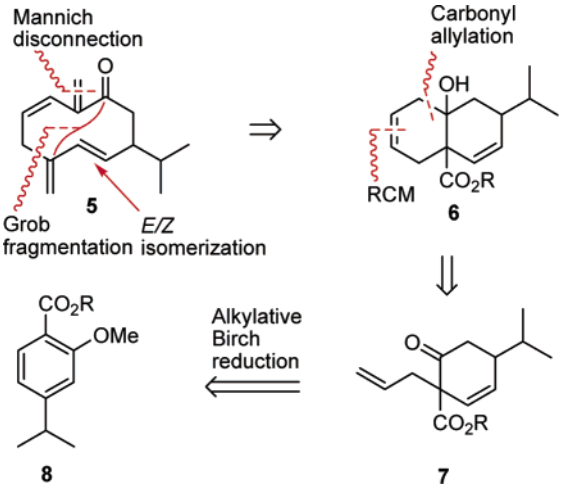
(9) Examples from the epothilone syntheses: (a) Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073. (b) Yang, Z.; He, Y.; Vourloumis, D.; Vallberg, H.; Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 166. (c) Schinzer, D.; Limberg, A.; Bauer, A.; Bohm, O. M.; Cordes, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 523.

(10) (a) Furstner, A.; Mathes, C.; Grela, K. *Chem. Commun.* **2001**, 1057. (b) Furstner, A.; Grela, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 1234.

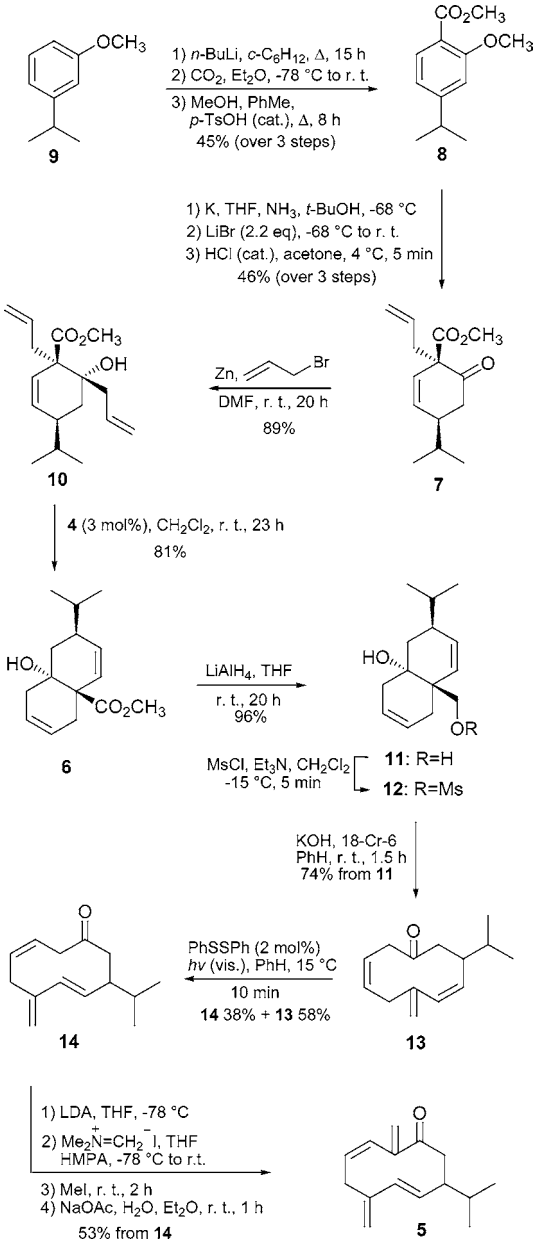
(11) (a) Mehta, G.; Kumaran, R. S. *Chem. Commun.* **2002**, 1456. (b) Rodriguez, J. R.; Castedo, L.; Mascarenas, J. L. *Chem. Eur. J.* **2002**, *8*, 2923.

(12) (a) Persoons, C. J.; Ritter, F. J.; Verwiel, P. E.; Hauptmenn, H.; Mori, K. *Tetrahedron Lett.* **1990**, *31*, 1747, and the references therein. (b) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, 1996; Chapters 13 and 21.

Scheme 3. Retrosynthetic Analysis of Periplanone C



Scheme 4. Synthesis of Periplanone C



methylene group.[13] In addition, the total synthesis of periplanone C would also constitute formal syntheses of periplanones A[14] and D.[15]

Our retrosynthetic analysis of periplanone C is outlined in Scheme 3. Mannich disconnection and selective alkene isomerization in **5** pave the way for application of the fragmentation transform, which converts the 10-membered ring into the unsaturated condensed bicycle **6**, itself potentially obtainable by RCM. Our precursor for the metathesis reaction could possibly be prepared by C-allylation of the unsaturated β-ketoester **7**. The latter compound could be assembled from the aromatic ester **8** by an alkylative Birch reduction.

Our synthesis, displayed in Scheme 4, commenced with a regioselective ortho-lithiation of the anisole derivative **9**, which, after carboxylation and esterification, gave ester **8**.[16] The Birch reduction of **8** with potassium gave the required cyclic β-ketoester **7** as a mixture of diastereoisomers in a 7:1 ratio, after quenching of the corresponding lithium enolate with allyl bromide[17] and in situ hydrolysis. Allylation of the carbonyl group in **7** was best performed with the allylzinc reagent, prepared in situ in DMF, and gave the RCM precursor **10** as a single stereoisomer.[18] Upon exposure to 3 mol % of the first-generation Ru-catalyst **4**, diene **10** was smoothly converted into the bicyclic intermediate **6**. Scission of the central bond in the condensed bicycle **6** was envisioned to occur via Grob fragmentation. To this end, ester **6** was reduced to **11** with lithium aluminum hydride and its primary hydroxyl group was O-mesylated. Mesylate **12** was not purified but was submitted directly to the action of powdered potassium hydroxide in benzene, in the presence of 18-crown-6. The required cyclodecadienone intermediate **13** was obtained as a single geometrical isomer.

The sensitive nature of **13** severely restricted the choice of methods available for effecting the penultimate synthetic step, namely, regioselective isomerization of the (*Z*)-double bond of the conjugated diene moiety. Clearly, both basic and acidic reagents had to be avoided, as the nonconjugated (*Z*)-olefinic bond would most probably suffer positional isomerization into the thermodynamically more stable conjugated enone. Not unexpectedly, under conditions of photochemical isomerization, **13** underwent transannular [2 + 2] photocy-

(13) Total syntheses of Periplanone C: (a) Shizuri, Y.; Matsunaga, K.; Tamaki, K.; Yamaguchi, S.; Yamamura, S. *Tetrahedron Lett.* **1988**, *29*, 1971. (b) McMurry, J. E.; Siemers, N. O. *Tetrahedron Lett.* **1994**, *35*, 4505. (c) Nishii, Y.; Watanabe, K.; Yoshida, T.; Okayama, T.; Takahashi, S.; Tanabe, Y. *Tetrahedron* **1997**, *53*, 7209.

(14) Hofmeister, P.; Krieg, W.; Neudert, R.; Hauptmann, H. U.S. Patent 4939275.

(15) Biendl, M.; Hauptmann, H.; Sass, H. *Tetrahedron Lett.* **1989**, *30*, 2367.

(16) Shirley, D. A.; Harmon, T. E.; Cheng, C. F. *J. Organomet. Chem.* **1974**, *69*, 323.

(17) Hook, J. M.; Mander, L. N.; Woolias, M. *Tetrahedron Lett.* **1982**, *23*, 1095.

(18) The stereochemical outcome of the allylation reaction can be predicted according to the model proposed by Molander: Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.* **1995**, *117*, 3705.

cloaddition to yield 8-*exo*-methylene tricyclo[4.4.0.0^{7,10}]-decan-3-one. Therefore, we envisaged accomplishing the necessary transformation through use of reversible thiyl radical addition. Although extensively studied theoretically, such radical isomerizations have seldom been employed in synthesis.[19] Much to our pleasure, the irradiation of **13** with visible light in the presence of a catalytic amount of diphenyl disulfide brought about a smooth conversion into **14**. Although a 1:1 ratio of isomers **13** and **14** was established at equilibrium, these were easily separated by column chromatography on silver nitrate-impregnated silica gel (SNIS).[20] Compound **14** was isolated in 38% yield, and **13** was recovered in 58% yield.

The final step in the synthesis, the regioselective Mannich methylenation of the nonsymmetrical ketone **14**, was accomplished via the preformed metal enolate.[21] When the lithium enolate of **14** was treated with an excess of Eschenmoser's reagent at −78 °C, aminomethylation proceeded, followed by spontaneous elimination of dimethylamine to give periplanone C.[22] Its transformation into periplanones A and D has been reported previously.[14,15]

In summary, we have shown that the RCM/fragmentation sequence offers an expedient, stereoselective entry into unsaturated medium-sized ring compounds.

Acknowledgment. We dedicate this work to Professor Pierre Potier. This research was partially supported by the Ministry of Science, Technology and Development of the Republic of Serbia (Project No. 1719).

Supporting Information Available: Experimental procedures and spectral data for compounds **6**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Review article on the alkene (*E*)−(*Z*) isomerization: Dugave, C.; Demange, L. *Chem. Rev.* **2003**, *103*, 2475.

(20) Review article on SNIS: Williams, C. M.; Mander, L. N. *Tetrahedron* **2001**, *57*, 425.

(21) Roberts, J. L.; Borromeo, P. S.; Poulter, C. D. *Tetrahedron Lett.* **1977**, 1621.

(22) ^{1}H NMR and IR spectra identical to those reported for the naturally occurring compound in ref 15; ^{13}C NMR spectrum identical to the spectrum previously reported in ref 13c.