

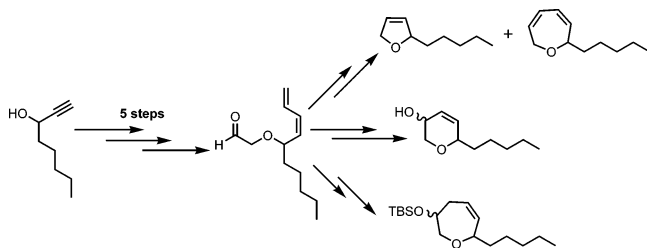
## Regioselectivity in the Formation of Small- and Medium-Sized Cyclic Ethers by Diene-Ene Ring-Closing Metathesis

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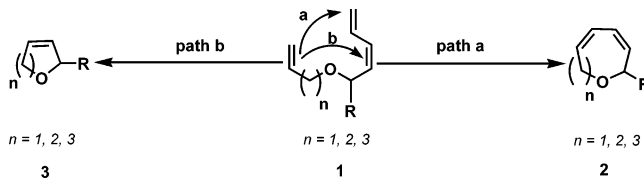
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In the formation of medium-sized ethers by diene-ene ring-closing metathesis, the formation of cyclic allyl ethers with a smaller ring size and of pentadienyl ethers with a larger ring size compete with each other. In the competition between six- and eight-membered and seven- and nine-membered ring formation, the smaller rings are formed exclusively, whereas in the competition between the five- and seven-membered rings, both products are formed in comparable amounts.

Seven-, eight-, and nine-membered oxygen heterocycles with one or two double bonds embedded into the heterocyclic ring systems are characteristic structural frameworks of various natural products.<sup>1</sup> In the course of a project aimed at the synthesis of such natural product frameworks, we became interested in their synthesis, employing the ring-closing metathesis (RCM) reaction as the key transformation.<sup>2</sup> In particular, the diene-ene RCM reaction employing pentadienyl ethers **1** as substrates (Scheme 1) attracted our interest because it would give rise to seven- to nine-membered cyclic dienes that would be amenable to substantial structural variation by means of various transformations. The diene-ene RCM has been used several times in natural-product synthesis<sup>3</sup> but not for the synthesis of small- and medium-sized cyclic ethers. In this context, the regioselectivity of the reaction giving rise to either

## SCHEME 1. Strategy for the Synthesis of Medium-Sized Cyclic Ethers by Means of Diene-ene RCM, Employing Differently Substituted Pentadienyl Ethers as Substrates



the larger dienyl ethers **2** or the smaller monounsaturated ethers **3** was of particular interest.

## Results and Discussion

The substrates for the decisive ring-closing reaction were synthesized via aldehyde **6** as the central intermediate, as shown in Scheme 2. Commercially available oct-1-yne-3-ol **4** was converted nearly quantitatively to the alkynyl iodide by treatment with NIS in the presence of  $\text{AgNO}_3$ ,<sup>4</sup> and the alcohol was then alkylated by treatment with bromoacetic acid ethyl ester after deprotonation with  $\text{NaH}$ .<sup>5</sup>

Stereoselective reduction of the alkyne to the *Z* olefin with diimide prepared in situ gave vinyl iodide **5** in high yield.<sup>4,6</sup> After a Stille reaction with vinyltributyl tin, the resulting dienyl ether was converted into aldehyde **6** in 75% yield by means of reduction of the ester to the aldehyde with DIBAL-H in diethyl ether for 20 min at  $-78^\circ\text{C}$ . Aldehyde **6** was then converted into pentadienyl ethers **7**, **10**, and **13** by means of established methods (Scheme 2).<sup>4,7</sup> Compounds **10** and **13** embody a free or a protected alcohol to determine a possible influence of a coordinating group on the course of the ring-closing reaction.

When subjected to RCM with either 10 mol % of first-generation Grubbs catalyst **16** or 5 mol % of second-generation catalyst **17** in refluxing dichloromethane (DCM), dienyl allyl ether **7** yielded the five- and seven-membered cyclic ethers **8** and **9** in a ratio of 2:3. However, under similar conditions, dienyl homoallyl ether **10** yielded exclusively the six-membered ether **11**, and the formation of the eight-membered ring cyclic ether **12** was not observed at all. While the latter result was not unexpected, the formation of the seven-membered ring in a nearly equal amount as the five-membered cyclic ether was surprising. To investigate whether a seven-membered ring was also formed predominantly in competition to ring closure to a

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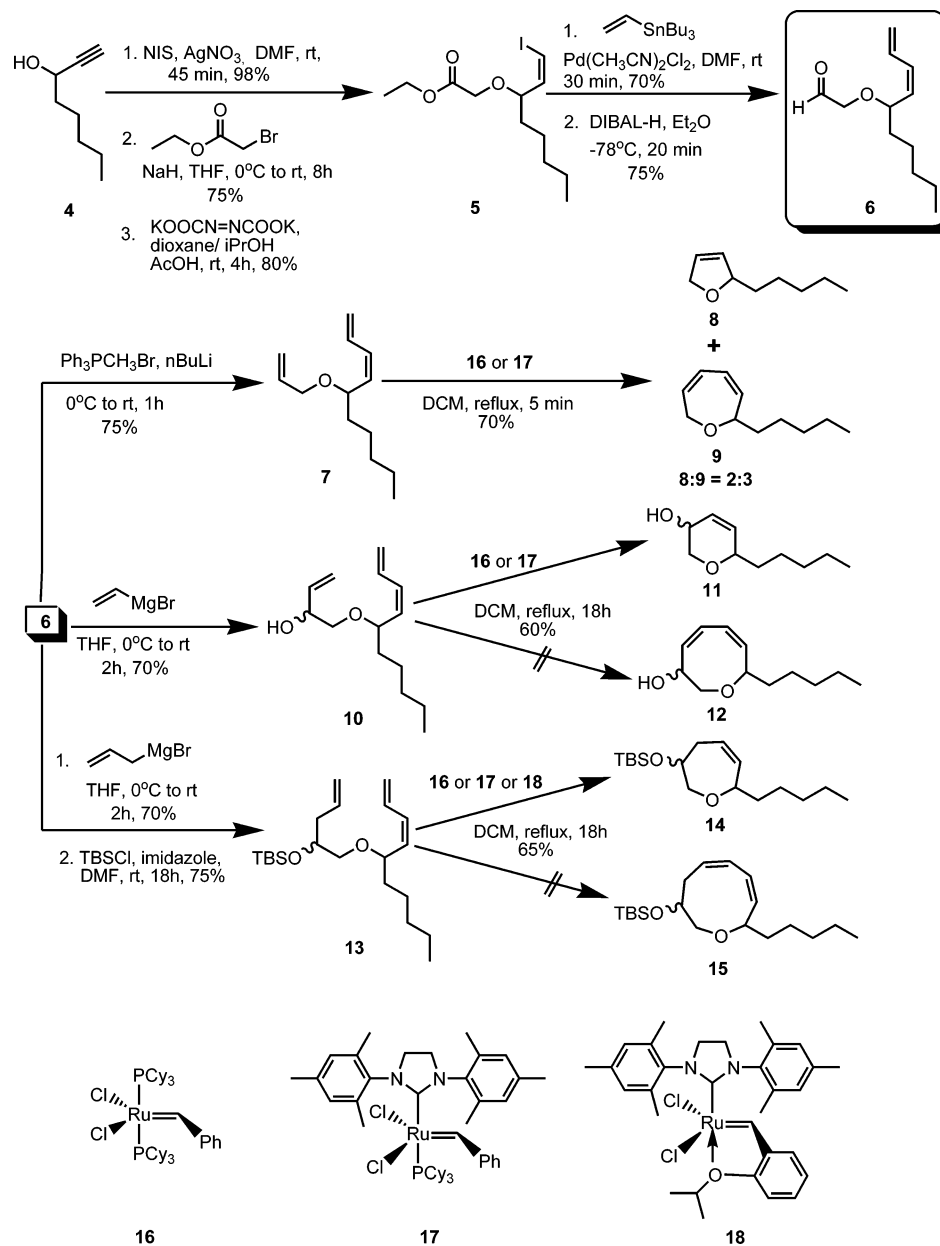
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## SCHEME 2. Synthesis of the Substrates and Attempted RCM Reactions



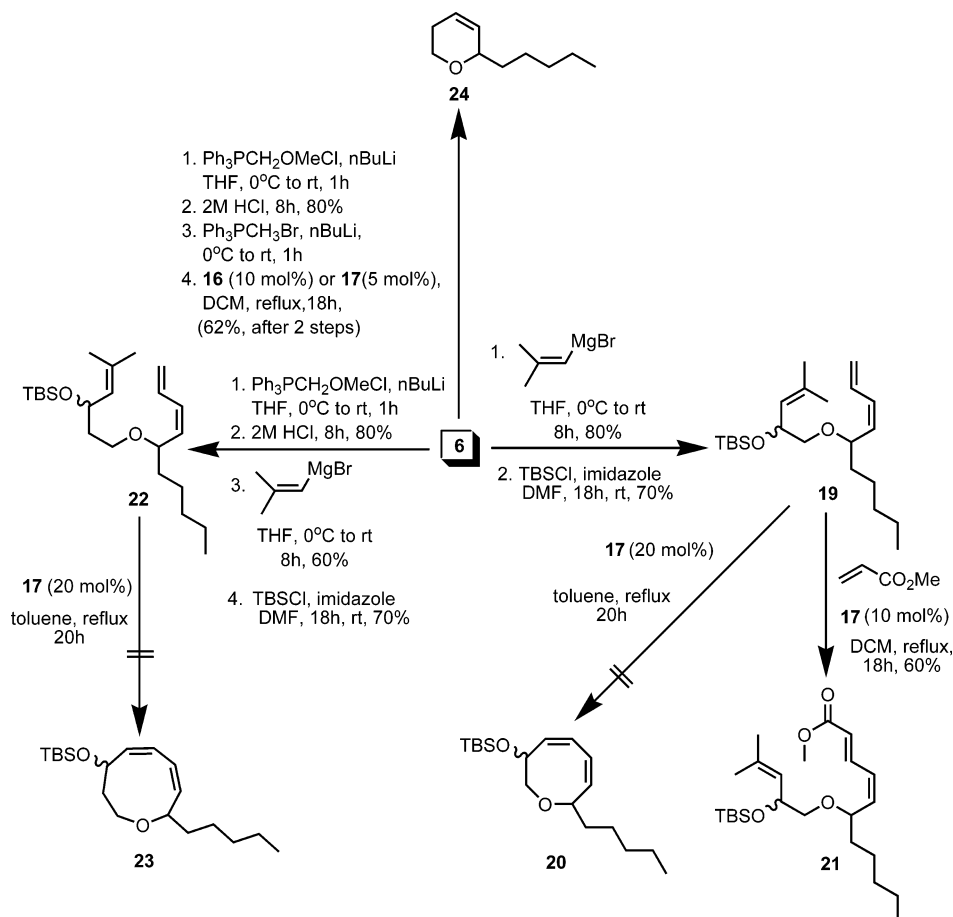
nine-membered ring, pentadienyl ether **13** was treated with either one of the Grubbs catalysts and also with 5 mol % of the phosphine-free second-generation Hoveyda–Grubbs catalyst **18** in refluxing DCM, and indeed, exclusive formation of the seven-membered cyclic ether **14** in 65% yield was observed.

These results indicate that the reaction starts via ruthenium carbene complex formation at the site of the isolated double bond, and then the ring closes with a preference for formation of the smaller ring except in the competition between the five- and seven-membered rings. Consequently, formation of the larger rings should occur if the ruthenium carbene would initially be formed at the diene unit. To investigate this possibility, aldehyde **6** was converted into pentadienyl ethers **19** and **22** by means of established methods (Scheme 3). Ethers **19** and **22** carry additional methyl groups at the terminal olefin carbon to direct the attack of the ruthenium catalyst to the less-substituted terminal olefin of the diene unit. Treatment of the pentadienyl ethers **19** and **22** with 20 mol % of second-generation Grubbs

catalyst in refluxing toluene did not lead to the formation of the desired eight- or nine-membered cyclic ethers **20** and **23**. Instead, in both cases, the unreacted starting material was reisolated. To ascertain that the initial formation of the ruthenium carbene had occurred, diene **19** was subjected to cross metathesis with methyl acrylate. Cross metathesis reactions with this electron-poor olefin proceed via initial carbene formation with the more electron-rich olefin.<sup>8</sup> When **19** was treated with methyl acrylate and 10 mol % of second-generation Grubbs catalyst in refluxing DCM, cross metathesis product **21** was isolated in 60% yield. To investigate whether the hydroxyl group in the substrates **10** or **13** has a determinant role directing the RCM reaction toward the formation of an alkene rather than a diene, we synthesized a deoxygenated analogue to **10** by means of established Wittig homologation and Wittig olefination from

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SCHEME 3. Synthesis of Dienyl Ethers 19 and 22 and Attempted RCM To Yield Eight- and Nine-Membered Cyclic Ethers 20 and 23



aldehyde **6** and subjected it to the RCM conditions using both **16** (10 mol %) or **17** (5 mol %). In these experiments, compound **24** was obtained as the sole product in 62% yield after two steps, indicating that the hydroxyl does not direct the RCM reaction.

Finally, to investigate whether the ring-closing reaction was kinetically or thermodynamically controlled, two further experiments were carried out. On one hand, the formation of five- and seven-membered ethers **8** and **9** was followed by means of GC-MS. The treatment of dienyl ether **7** with first-generation Grubbs catalyst **16** in refluxing DCM within 5 min led to complete consumption of the starting material, and the initially determined product ratio did not change if the refluxing was continued for 1 h. At room temperature, the reaction required 2 h to proceed to completion with the product ratio showing the same distribution. If the seven-membered cyclic dienyl ether **9** was subjected to the conditions of the RCM, that is, reflux in DCM in the presence of 10 mol % of first-generation Grubbs catalyst and in the mixture of ethylene for 3 h, formation of the five-membered cyclic ether **8** was observed by GC-MS. Assuming that the five-membered ring ether is more stable than the seven-membered ring ether, these results indicate that this RCM reaction is thermodynamically controlled. We note that this may be different for the analogous formation of **11** or **12** from **10** and of **14** or **15** from intermediate **13**.

In conclusion, we have shown that in the attempted formation of medium-sized cyclic ethers by means of the diene-ene RCM, with the exception of the competition between five- and seven-membered rings, the smaller ring sizes are formed.

## Experimental Section

**General Procedure for the Ring-Closing Metathesis:** The triene was dissolved in dry degassed DCM (0.002M) in a two-neck round-bottom flask under argon. The Grubbs catalyst was added, and the solution was stirred at reflux until the starting material was totally consumed (monitored by TLC). The solvent was evaporated, and the crude product was subjected to column chromatography.

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**Supporting Information Available:** Full experimental details and spectral characterization of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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