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Triple Ring Closing Metathesis Reaction: Synthesis of Adjacent Cyclic Ethers

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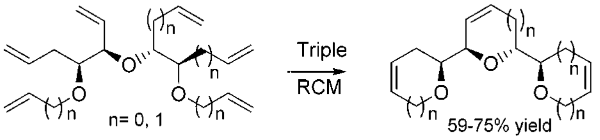
ABSTRACT



Adjacent tris(cyclic ethers) and enol ethers have been synthesized in good yields for the first time via a triple olefin metathesis reaction using Grubbs' catalyst RuCl$_2$(=C(H)Ph)(PCy$_3$)$_2$ (Cy = cyclohexyl), and the 1,3-dimesitylimidazol-2-ylidene ruthenium benzylidene catalyst RuCl$_2$(=C(H)Ph)(PCy$_3$)(IMes) ((IMes) = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene). The latter proved to be the most efficient catalyst in these transformations.

Although there are many methods for preparing cyclic structures in organic chemistry,[1] the ring closing metathesis (RCM)[2] of α,ω-dienes has emerged as a powerful synthetic tool for the construction of various ring systems. This is mainly due to the discovery of highly reactive (molybdenum alkylidene) and more stable (ruthenium alkylidene) catalysts.[3]

Recent reports from our laboratory and others have shown a catalytic tetraene double ring closing metathesis reaction to be a useful protocol for the formation of bicyclic ethers.[4] To extend the scope of these studies, we explored the possible formation of triadjacent cyclic ethers by a ring closing metathesis reaction involving an acyclic hexaene system as outlined in Scheme 1. Acyclic hexaenes can formally undergo ring closing metathesis through two different modes, leading to two different types of products: contiguous tris(cyclic ethers) stemming from selective triple metathesis through mode **a** or/and bicyclic carbocycles resulting from a double cyclization through mode **b**. In our previous studies on the cyclization of tetraene by RCM,[4a] we found that the formation of five- and six-membered ring cyclic ethers was favored over the formation of carbocycles.

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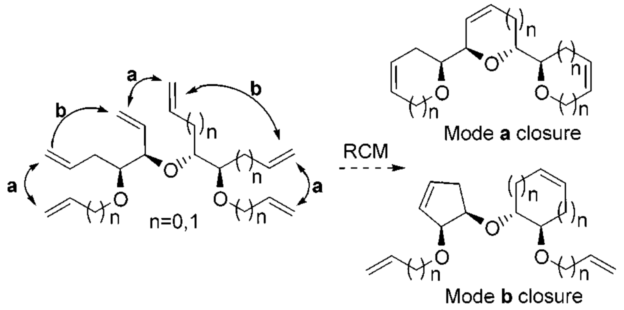
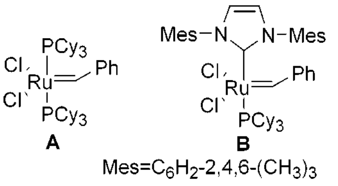
Scheme 1. RCM Reactions of Acyclic Hexaene



We now extend this study to the reactivity of acyclic hexaenes and find similar results indicating that mode **a** (Scheme 1), leading only to adjacent tris(cyclic ethers), is the preferred reaction pathway. Interestingly, we observe that formation of these three contiguous ring systems proceeds either through simultaneous or consecutive triple RCM reactions. Using Grubbs' catalyst **A**, $\mathrm{RuCl_2({=}C(H)Ph)(PCy_3)_2}$ (Cy = cyclohexyl), or the ruthenium-based imidazolinylidene complex **B**, $\mathrm{RuCl_2({=}C(H)Ph)(PCy_3)(IMes)}$ (IMes = 1,3-bis-(2,4,6-trimethylphenyl)imidazol-2-ylidene), adjacent tris-(cyclic ethers) were prepared in good yields and generated as single products (Scheme 2).

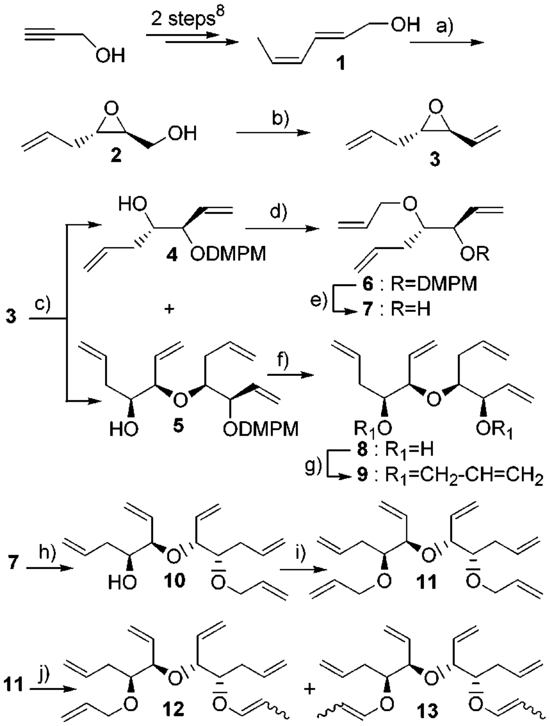
Scheme 2. RCM Catalysts



Cyclic polyethers are interesting structures due to their ability to chelate metallic cations, conferring them ionophore properties.[5] Moreover, the three contiguous tetrahydrofuranic motive ($n = 0$) constitute the core structure of natural type D acetogenin which reveals a wide variety of biological activities.[6]

The syntheses of the acyclic hexaenes are outlined in Scheme 3. The strategy involves the preparation of vinyl epoxide **3**, followed by its ring opening with various alcohols. The precursor 2,5-hexadien-1-ol **1** was synthesized in two steps from propargylic alcohol following a described procedure.[7] Asymmetric epoxidation of **1** using the Sharpless process[8] gave epoxy alcohol **2**[9] which was oxidized and submitted to Wittig olefination to afford vinyl epoxide **3**. Treatment of **3** with 3,4-dimethoxybenzyl alcohol (DMPMOH)[10] yielded the easily separable mixture of alcohols **4** and **5**. Alkylation of compound **4** with allyl bromide gave **6** which was deprotected with DDQ to afford vinyl alcohol **7**. Stereo-and regiospecific ring opening of epoxide **3** with **7** gave **10** which was alkylated to the corresponding hexaene **11**. Isomerization of **11** using Wilkinson's catalyst afforded hexaenes **12** and **13**. Hexaene **9** was prepared by deprotection of alcohol **5** with DDQ, followed by dialkylation with allyl bromide.

Scheme 3. Preparation of the Acyclic Hexaenes



The four acyclic hexaenes **9**, **11**, **12**, and **13** were then submitted to our typical metathesis reaction conditions.[11] The results obtained are summarized in Table 1 and constitute the first examples of a triple RCM reaction.

First, we investigated the reactivity of hexaene **9** with Grubbs' catalyst **A** (entry 1). After 2 h, a single product was isolated and identified as a compound bearing three contiguous cyclic ethers **14** resulting from a triple RCM (65% yield). Then substrate **11** was subjected to Grubbs' catalyst **A** under identical conditions (entry 2). Surprisingly, only the bicyclic ether **15** (69% yield) resulting from a double metathesis reaction was obtained. In this case, the central diallyl ether

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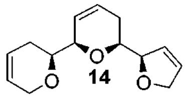
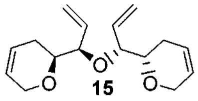
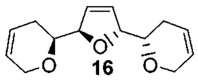
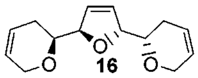
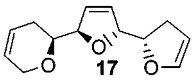
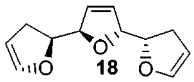
(11) **Representative procedure**: A solution of acyclic hexaene in dry solvent (typical concentration 0.02 M in $\mathrm{CH_2Cl_2}$ or toluene) with a catalytic amount of ruthenium benzylidene **A** or **B** (5 mol %) was stirred at room temperature or 80 °C (see Table 1). After disappearance of the starting material, the reaction mixture was concentrated and purified on silica gel to yield the tricyclic compound.

Table 1. Results of the RCM of Hexaenes

entry	substrates	products	conditions	yields*
1	**9**	 **14**	**A**, C_6H_6, RT, 2h	65%
2	**10**	 **15**	**A**, C_6H_6, RT, 3h	69%
3	**15**	 **16**	**A**, C_6H_6, RT, 8 days	59%
4	**10**	 **16**	**B**, toluene, 70°C, 4h	75%
5	**12**	 **17**	**B**, toluene, 70°C, 4h	55%
6	**13**	 **18**	**B**, toluene, 70°C, 6h	62%

* isolated yields

did not undergo cyclization to form the expected 2,5-dihydrofuran. Under prolonged reaction time and by further catalyst additions, no tris-(cyclic) compound was observed in situ. However, when bicyclic compound **15** was isolated and resubmitted to RCM conditions with successive additions of catalyst **A** (30% mol), compound **16** resulting from a triple RCM was isolated in 59% yield after 8 days (entry 3).

In view of the increased thermal stability and higher reactivity displayed by olefin metathesis catalyst **B**, the RCM reaction was performed on substrate **11** using the imidazol-2-ylidene-modified ruthenium catalyst. This RCM reaction afforded directly the triadjacent cyclic ether **16** in 75% yield after only 4 h in toluene at 70 °C (entry 4). Catalyst **B** was found to be a more effective RCM catalyst for cyclizing the central five-membered ring. Using Grubbs' catalyst **A**, we have shown that the RCM of the two lateral cycles 6−5-membered rings (entry 1) or 6−6-membered rings (entry 2) were rapidly completed. Nonetheless, the cyclization of the central five-membered ring system (entry 2) was rather sluggish compared to the formation of the central six-membered ring (entry 1). In this case, catalyst **B** was required to achieve useful dihydrofuran cyclization (entry 4).

We completed our studies by subjecting hexaenes **12** and **13** to RCM reaction with catalyst **B**. In both cases tricontiguous cyclic ethers **17** and enol ether **18** were isolated as single products in 55% and 62% yields, respectively (entries 5 and 6). The use of Grubbs' catalyst **A** with these substrates leads to incomplete cyclizations. It is noteworthy that compound **18** possesses three adjacent five-membered ring ethers which are present in several natural type D acetogenins.

In conclusion, the first selective triple RCM reaction of acyclic hexaenes leading to triadjacent cyclic ethers in good yields (55−75%) is reported. The 1,3-dimesitylimidazol-2-ylidene-modified ruthenium benzylidene catalyst proved to be more efficient for tricyclization reactions of various hexaenes than Grubbs' catalyst.

Further studies aimed at probing the general use of this triple RCM reaction for the synthesis of poly-THF products and for the use of the very efficient ruthenium-based imidazolylidene complex catalyst in a variety of metathesis reactions are ongoing.

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Supporting Information Available: Experimental procedure and ^{1}H NMR, ^{13}C NMR, MS, and IR for compounds **2**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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