

A ring closing metathesis–osmylation approach to oxygenated oxepanes as carbohydrate surrogates

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Abstract

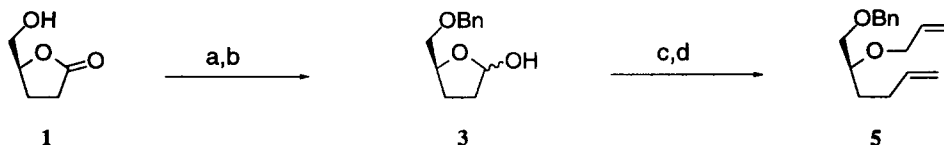
A ring closing metathesis (RCM)–osmylation sequence has been developed for the formation of highly oxygenated cyclic ethers from the corresponding acyclic dienes. A systematic examination of various substrates in this reaction revealed that the process is general in scope and is insensitive to the number of alkoxy substituents present. Subsequent osmylation of the metathesis product proceeds with excellent diastereoselectivity to furnish highly oxygenated oxepanes. These oxepanes represent one-carbon homologated carbohydrates. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Carbohydrates play a central role in many biological processes¹ and, accordingly, they have elicited numerous investigations into their synthesis as well as the synthesis of carbohydrate analogs.² We have recently reported on the use of ruthenium carbenes to induce the ring closing metathesis (RCM) of vinyl ethers to generate dihydropyrans.³ The aim of this study was to identify a general strategy for the synthesis of both natural and non-natural glycals. These glycals would then serve as entry points for the preparation of various carbohydrates. As a continuation of this work, we became interested in the possibility of using oxepanes as carbohydrate homologs. The oxepane unit is of interest in its own right as it is present in a number of important and structurally interesting natural products. As a consequence, considerable attention has been directed towards developing methods for the synthesis of these structural units.⁴ A recent report by van Boom's group has detailed their work in the RCM reaction of glycofuranose derivatives to generate oxepanes.⁵ In our previous vinyl ether study, a pronounced substitution effect on the efficiency of the RCM reaction was observed, with some substrates failing to provide any of the dihydropyran. In light of this observation, we decided to examine the influence of alkoxy substituents on the metathesis process leading to seven-membered ring ethers. We wish to report herein our work on the use of the RCM reaction for the synthesis of oxepanes and the subsequent stereoselective osmylation generating highly oxygenated systems as potential carbohydrate surrogates.

Part of the motivation in the present study was to systematically examine the influence of oxygen substitution on the ensuing metathesis reaction. Thus, we required a general route to synthesize a

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broad range of acyclic dienes. To accomplish this, we made use of commercially available hydroxy gamma-lactones as many are available in chiral, non-racemic form and thus would provide access to enantiomerically pure cyclic ethers. Scheme 1 is illustrative of the approach taken to convert the starting lactones to the metathesis precursors. Hydroxy lactone **1**⁶ was treated with benzyl 2,2,2-trichloroacetimidate in the presence of catalytic quantities of triflic acid to provide benzyl ether **2** in 75% yield.⁷ This lactone was then reacted with DIBAL in toluene at -78°C to cleanly furnish the corresponding lactol **3** in 91% yield.⁸ Exposure of lactol **3** to standard Wittig conditions provided hydroxy alkene **4** in 70% yield.⁹ Finally, alkylation of the hydroxyl group with allyl bromide and $\text{KN}(\text{TMS})_2$ gave the desired diene in 77% yield.

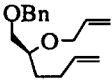
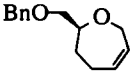
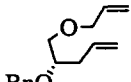
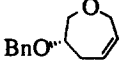


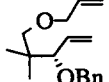

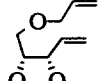
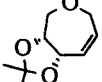
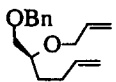
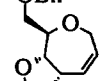


Scheme 1. (a) $\text{BnOC}(\text{-NH})\text{CCl}_3$, $\text{Cy}/\text{CH}_2\text{Cl}_2$, 0°C (75%); (b) DIBAL, toluene, -78°C (91%); (c) $\text{Ph}_3\text{P}=\text{CH}_2$, THF (70%); (d) $\text{KN}(\text{TMS})_2$, THF, allyl bromide, 0°C (77%)

With the required dienes in hand, we set out to investigate the reaction conditions necessary to effect optimal ring closing metathesis of these compounds. Initially, diene **5** was treated with 10 mol% of Grubbs' catalyst in benzene at 80°C . Under these conditions, the starting material was consumed in approximately 5 min to provide the cyclic alkene **6** in 86% yield. Given the efficiency of this reaction both the temperature and catalyst loading were reduced. In doing so, it was found that 0.5 mol% of catalyst was sufficient to provide an 89% isolated yield of **6** at room temperature. The results of the RCM of the other substrates examined are summarized in Table 1.¹⁰ These reactions were carried out with 5 mol% of Grubbs' catalyst at the indicated concentrations in benzene at room temperature. In general, the RCM was found to provide the cyclic ether in good yields irrespective of the substitution pattern present in the substrates. This finding is in contrast to our earlier observation that, in structurally related vinyl ethers, the alkoxy substituent played a pivotal role in the success of the RCM reaction. We were particularly gratified to observe that even highly oxygenated diene **15** was an equally effective substrate in the metathesis reaction (Table 1, entry 6). We noted during our investigation that concentration was an important parameter with some of the RCM reactions. In particular, substrate **11** required dilution to 0.002 M before good yields of the cyclic product could be achieved. It is interesting to compare our findings with the metathesis results of highly oxygenated allyl ethers as reported by van Boom in which all the reported substrates gave good yields of the cyclic adduct.⁵ Also, we found that all attempts at generating the corresponding eight-membered ring analog of **6** from the homoallyl ether failed. This is in contrast to several successful RCM examples leading to medium-sized cyclic ethers.¹¹ This suggests that substitution patterns of the initial substrate play a role in the outcome of the RCM reaction for both allyl and homoallyl ethers.

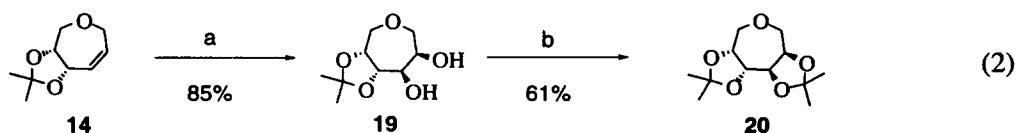
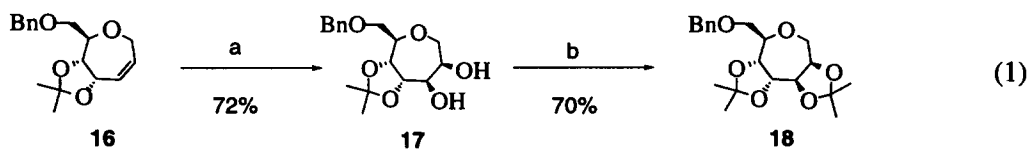
The above metathesis products are well suited for further manipulations. To demonstrate this point, ether **16** was subjected to a dihydroxylation reaction as shown in Eq. 1. Diol **17** was isolated in 72% yield as a single diastereomer. Exposure of this diol to acetone and *p*-TsOH provided the corresponding dimethylacetal **18** and inspection of its 400 MHz ^1H NMR spectrum verified the high level of stereoinduction in the osmylation process. Osmylation presumably occurs on the less sterically hindered β -face *anti* to the dimethylketal substituent.¹² It is worth noting that diol **17** is a highly oxygenated oxepane that possesses five contiguous stereogenic centers. Also, it represents an interesting one-carbon homolog of the rare sugar D-altrose with the 'extra' carbon in-between the anomeric center and the ring oxygen. Two additional metathesis adducts were also subjected to the osmylation protocol. Alkenes **14** and **12** (see Eqs. 2 and 3) provided the expected diols in both excellent yields and facial selectivity (>20:1).

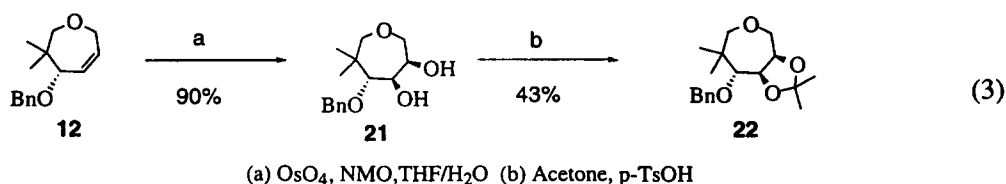
Table 1
Metathesis of functionalized dienes^a

Entry	Substrate	Product	Concentration	Yield
1			0.03 M	92%
			0.03 M ^b	86%
			0.03 M ^c	89%
2			0.03 M	49%
			0.02 M	69%
3			0.03 M 0.02 M	48% 68%
4			0.02 M	26%
			0.008 M ^d	52%
			0.002 M ^d	72%
5			0.02 M	64%
6			0.02 M	97%

(a) Reactions were conducted at room temperature in benzene with 5 mol% (Cy₃P)₂Ru(Cl)₂=CHPh at the indicated concentration. Yields refer to isolated chromatographically homogeneous material. (b) 10 mol% catalyst at 80 °C. (c) 0.5 mol% catalyst at room temperature. (d) 15 mol% catalyst at room temperature.

As before, the diols were converted into their dimethyl acetals to confirm the level of stereoinduction. Finally, oxepane **19** can also be considered a homolog of xylose.





In summary, we have outlined an efficient procedure for the preparation of oxygenated oxepanes by use of a ring closing metathesis–osmylation sequence. The metathesis reaction was found to tolerate a high degree of oxygen substitution in the substrate. These oxygenated oxepanes are interesting carbohydrate homologs and their use as sugar surrogates is currently being investigated in our laboratory.

Acknowledgements

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