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Tandem RCM–Isomerization Approach to Glycals of Desoxyheptoses from a Common Precursor

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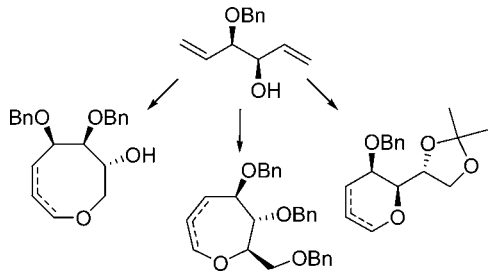
ABSTRACT



Ring closing metathesis and tandem RCM–isomerization have been applied to the synthesis of six- to eight-membered oxacycles, starting from a common precursor. The products of the tandem RCM–isomerization sequence are glycals of 3-deoxyheptoses of varying ring size.

Glycals,[1] cyclic enol ethers derived from or related to carbohydrates, have found numerous applications in the total synthesis of natural products[2] or in the construction of oligosaccharide chains.[3] While the reduction of glycosyl bromides, first introduced by Fischer and Zach,[4] remains a reliable, well-established and improved[5] synthesis for many derivatives, several other methods have been developed which are especially suited for non-natural derivatives or for glycals which are derived from less common sugars. Among these, the hetero-Diels−Alder reaction is particularly important,[6] but several transition-metal-mediated reactions have also attracted considerable attention recently. Examples are the catalyzed endo-cyclization of alkynols[7] or ring closing olefin metathesis[8] of enol ethers. Although a significant number of successful enol ether metathesis reactions have been reported,[9] the method is often associated with some drawbacks as high dilution and, in most cases, the more active but less conveniently available molybdenum[10] or second generation ruthenium catalysts[11] are required. Furthermore, undesired non-metathesis side reactions such as isomerization[12] may occur if a metathesis catalyst reacts with electron-rich olefins such as vinyl ethers.[13] These issues have recently been addressed by the development of a tandem[14] RCM−isomerization sequence by Snapper et al.[15] and by us,[16] where a metathesis catalyst is converted to a selective olefin isomerization catalyst after completion of the metathesis reaction.

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In this contribution, we describe the application of the tandem RCM−isomerization method to the synthesis of heptose glycals. Certain heptopyranoses are found as constituents in lipopolysaccharides,[17] and recently, a route to KDO starting from a heptopyranose glycal has been described.[18] The seven-membered ring sugars, septanoses,[19] are not found in Nature but have recently attracted considerable attention because they may serve as building blocks for non-carbohydrate natural products or non-natural homologues of hexoses, with significantly different conformational properties.[20,21]

The starting point of the current investigation was epoxide **2**. We have previously obtained **2** from **1**[22] by vanadium-catalyzed epoxidation; however, only a poor diastereoselectivity was observed.[23] Enantio- and diastereomerically pure **2** was obtained in good yield by subjecting **1** to the conditions of a Sharpless epoxidation using (+)-DET as a ligand.[24] With a view toward accessing 3-deoxyheptopyranoses, **2** was allylated to give **3**, which underwent ring closure to dihydropyran **4** in the presence of ruthenium catalyst [$Cl_2(PCy_3)_2$-Ru═CHPh] (**A**) in 94% yield. Under RCM−isomerization conditions, **3** was cleanly converted to enol ether **5** using the isopropanol/NaOH protocol.[16b,c] NMR spectroscopy of the crude reaction mixture revealed that **5** was the only product of the reaction, and that the presence of a base and a nucleophilic cosolvent did not affect the epoxide moiety. However, **5** was found to be rather sensitive toward chromatography on silica, resulting in a significantly reduced yield. This problem was overcome by cleaving the epoxide and protecting the resulting diol **6** as an acetonide **7** prior to RCM and RCM−isomerization. For both reactions, dihydropyrans **8** and **9**, respectively, were obtained in high yields and selectivities. An alternative route to a monoprotected *vic*-diol side chain was investigated by selectively cleaving the epoxide moiety in **3** with benzylic alcohol. The resulting precursor **10** undergoes RCM in a fair yield of 67% of **11**. A significantly reduced yield was obtained for **12** under the conditions mentioned above for the tandem RCM−isomerization. Thus, tandem RCM−isomerization of partially unprotected metathesis precursors is, in principle, possible but does not appear to be the method of choice (Scheme 1).

Next, an approach to septanose structures starting from epoxide **2** was investigated. To this end, the alcohol functionality in **2** was protected as a benzyl ether **13**, which was subsequently cleaved with benzylic alcohol to give **14**.[25] Allylation of **14** yields allyl ether **15**, which undergoes RCM smoothly to give the oxepine **16**.[26] Under tandem RCM−isomerization conditions, the glycal **17** is obtained in comparable yield (Scheme 2).[27]

Finally, application of the concept to the synthesis of eight-membered heptose derivatives was investigated (Scheme 3). The sequence started with epoxide **13**, which undergoes chemo- and regioselective ring opening with allyl alcohol in the presence of substoichiometric amounts of sodium methoxide to give **18**.[28] Lewis acid catalysis using BF_3OEt_2 results only in poor yields of impure epoxide cleavage product. In light of previous reports in the literature where the first generation catalyst **A** was used for the synthesis of medium-ring heterocycles,[29] we first tested **A** for the RCM of **18**, however, only the dimer **19** was isolated in low yield as a single isomer, which is presumably *E*-configured, along with unreacted starting material **18**. Attempts to convert **19** into the desired oxocene **20** via a backbite mechanism were unsuccessful with the first generation catalyst **A**. However, with **B** (5 mol %), **20** was quantitatively obtained from **19**. Compound **20** was of course more conveniently obtained from **18** by treatment with **B** at elevated temperature. There have been reports that **B**, in contrast to **A**, undergoes a defined thermal decomposition to a Ru−hydride complex which does not require any additives.[30] Although it has been

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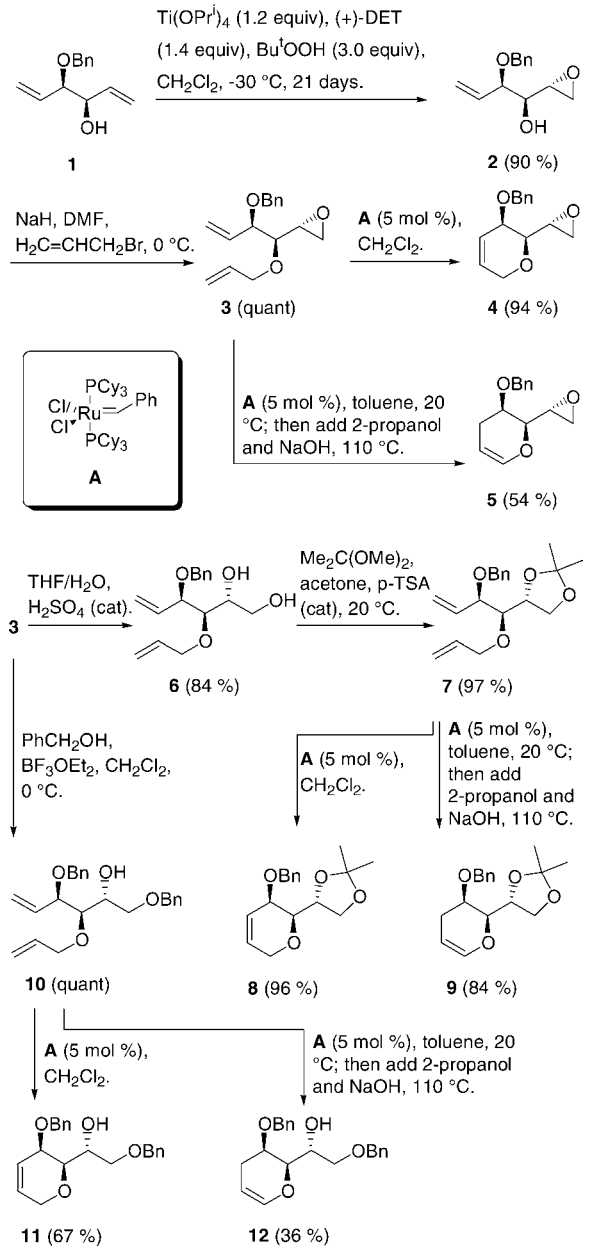
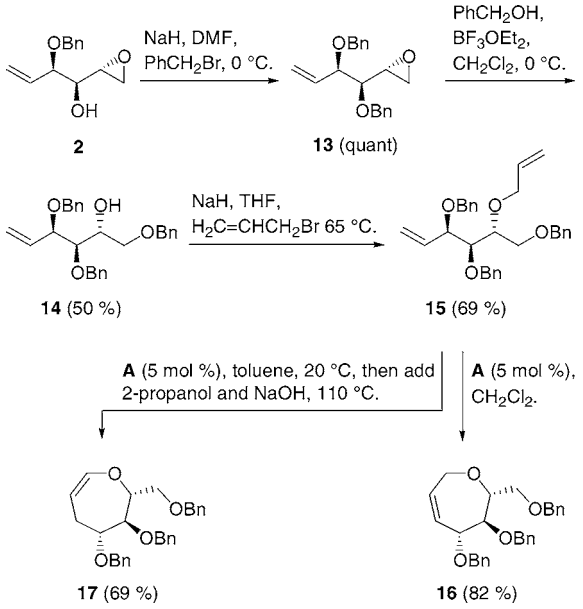
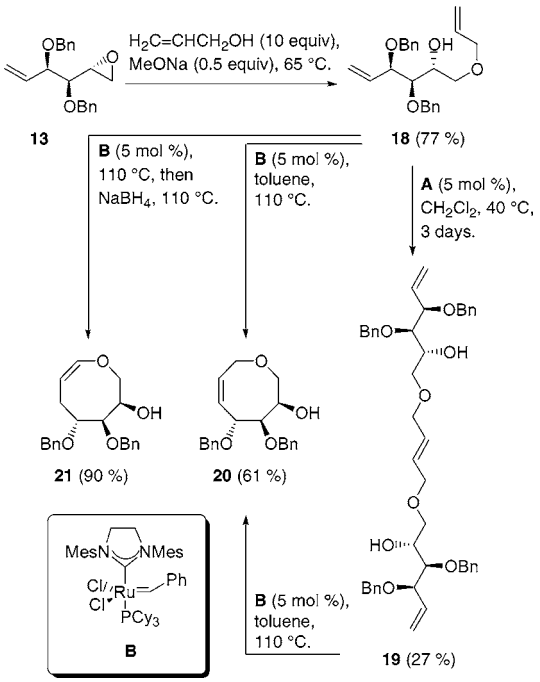
Scheme 1. 3-Desoxyheptopyranose Glycals



Scheme 2. Septanose Glycal



Scheme 3. Extension to Eight-Membered Oxacycles



reported that the use of **B** at elevated temperatures might result in the formation of isomerized products,[31] we only observed the initial metathesis product **20** under our conditions. A possible explanation might be that the formation of a Ru−hydride upon thermolysis of **B** is a bimolecular process[30] which will most likely proceed efficiently only at catalyst loadings significantly higher than those used in our experiments.[31] In order to access the cyclic enol ether **21** via our tandem process, the standard protocol was tested. However, 2-propanol and NaOH as additive combination did not give any isomerized product. Gratifyingly, the use of $NaBH_4$[16a,c] was successful, and **21** was obtained in good yield as a single isomer. The conversion of **18** to **21** represents the first application of the tandem RCM−isomerization concept to an eight-membered ring.

In conclusion, we have shown that the combination of RCM and tandem RCM−isomerization opens up promising opportunities for the synthesis of unsaturated six- to eight-membered oxacycles related to heptoses. Remarkably, just one precursor is required to access a considerable number of structurally diverse carbohydrate-related products.

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Supporting Information Available: Experimental procedures, analytical data, and copies of ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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