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Carbohydrate-based oxepines: ring expanded glycals for the synthesis of septanose saccharides☆

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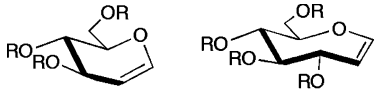
Abstract—A ring-closing metathesis (RCM) approach to a family of carbohydrate-based oxepines is described. A variety of readily accessible, protected monosaccharide derived dienes were used to demonstrate the utility of the synthetic sequence and to investigate how factors such as rigidification and deoxygenation mediate RCM using the Grubbs or Schrock catalyst. The seven-membered cyclic enol ethers are ring expanded glycals to be used in the synthesis of septanose carbohydrates.

Natural carbohydrates exist almost exclusively in the furanose or pyranose form. Larger ring saccharides, such as seven-membered ring septanoses, hold tremendous potential as probes of carbohydrate structure and function and as starting materials for the synthesis of natural products and designed structures. We have initiated a program to synthesize and characterize carbohydrates composed in whole or in part of septanose monomers. In this letter, we report a three-step sequence—Wittig olefination, vinyl ether formation, and ring-closing metathesis (RCM)—to synthesize carbohydrate based seven-membered cyclic enol ethers from protected pyranose lactols. The resulting enol ethers will serve as glycosyl donors in the synthesis of septanose-based carbohydrates.

Our inspiration for the investigation of septanose carbohydrates[1] is based on work that has focused on pyranose based nucleic acids[2] and peptides derived from β-amino acids.[3] These examples share a common feature in that the natural biopolymer monomer units are homologated by one carbon. We anticipate that the homologation of pyranose monosaccharides will lead to biologically interesting unnatural carbohydrates. The ability of a furanose or pyranose monosaccharide within an oligosaccharide to access more than one low energy conformation has an effect on a carbohydrate's biological activity.[4] We intend to mimic the conformationally dynamic nature of selected polysaccharide sequences by replacing the flexible monosaccharide with a septanose monosaccharide. The objective is to approximate natural structure and function with the unnatural carbohydrate in an effort to understand how conformational flexibility is used by nature in protein–carbohydrate interactions. Eventually we would like to incorporate conformationally dynamic monosaccharides to give unnatural oligosaccharides with a predictable function.



1 2

Drawing inspiration from glycal (**1**) chemistry,[5] the seven-membered ring cyclic enol ether **2** presented itself as a promising starting point toward the synthesis of septanose carbohydrates. The ring expanded glycal (septanal) should have a reactivity profile similar to that of glycals themselves. Glycals have proven to be formidable glycosyl donors and can also be used in the generation of other types of donors through simple transformations.[6] As such, we expect septanals to undergo glycosylations to form 2-oxo,[7] 2-amino,[8] and 2-deoxy[9] septanosides. Access to this family of cyclic enol ethers is a prerequisite to understanding the selectivity of subsequent glycosylation reactions.

Oxepines derived from carbohydrates have recently been described. One notable synthetic approach was the dihalocyclopropanation of a glycal followed by nucle-

Keywords: septanose carbohydrate; oxepine; ring-closing metathesis; glycal.

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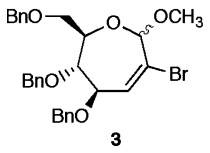
ophilic ring expansion to give the corresponding 2-halooxepine **3**.[10] A second example involved Wittig homologation of a protected furanose followed by formation of an allyl ether and ring-closing metathesis to give molecules such as **4**.[11] The key factor of these reported syntheses is that they are not directly amenable to subsequent glycosylation reactions. The strategy described here provides precursors that can directly utilize precedented procedures in the formation of glycosidic linkages.



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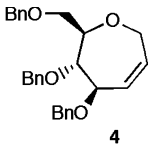

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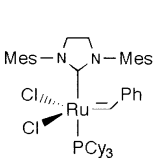
Demonstrations of synthetic routes to seven membered cyclic enol ethers have employed either a cyclization–elimination procedure of hydroxy acetals[12] or the ring-closing metathesis of olefin enol ethers.[13] Our approach was driven by the success of RCM for preparation of cyclic enol ethers in systems with similar functionality.[13a,b,14] No examples of the RCM of carbohydrate derived enol ethers in the formation of oxepines have yet been reported. We were mindful that formation of six-membered cyclic enol ethers by RCM of olefin enol ethers had shown various substituent effects.[15,16] We have established that the RCM strategy can be implemented in the presence of highly demanding functionality inherent in the carbohydrate systems described here to form oxepines.

Our three-step synthetic strategy is demonstrated in Scheme 1 using tetra-*O*-benzyl glucose (**5**). The sequence is initiated by known Wittig olefination[17] of **5** with concomitant release of the C5 (glucose numbering) hydroxyl group. Recently reported conditions for vinyl ether formation, using Pd(II) in the presence of phenanthroline,[18] provided enol ether **7**[19] in modest yield. Compound **7** was heated in an appropriate solvent in the presence of each of the commercially available RCM catalysts **9** and **10**. No product formation was observed using Grubbs catalyst **9** under a range of reaction conditions.[20] Schrock catalyst **10**[21] cleanly converted the diene **7** to the tetra-benzyl oxepine **8**[22] in 92% yield.

Encouraged by the successful formation of oxepine **8**, a series of diene precursors with varying protecting groups or sites of deoxygenation were synthesized (i) to probe the generality of the approach and (ii) to identify protecting groups that would allow for cyclization using the less expensive and more easily handled Grubbs catalyst **9** (Table 1).

Dienes **11**–**14** were synthesized from known lactols[23] via olefination and vinyl ether formation as described for tetra-*O*-benzyl glucose. These RCM precursors were used to address different properties of the diene that we thought might contribute to successful cyclization using **9**. For example, dienes **11** and **12** were derived from

Table 1. RCM of monosaccharide derived dienes



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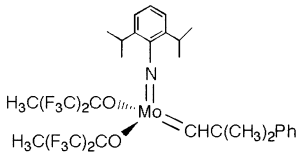
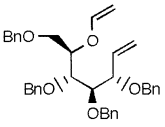
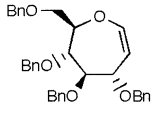
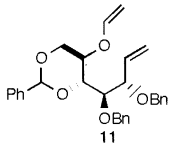
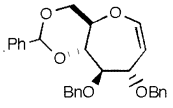
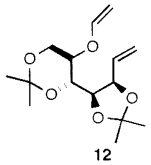
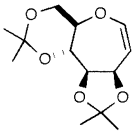
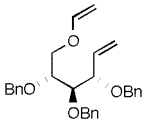
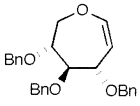
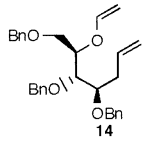
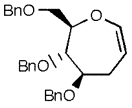
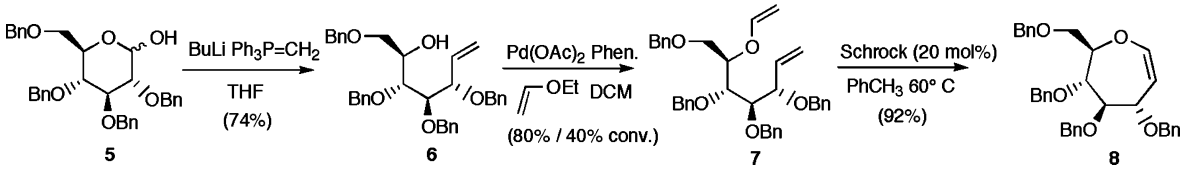


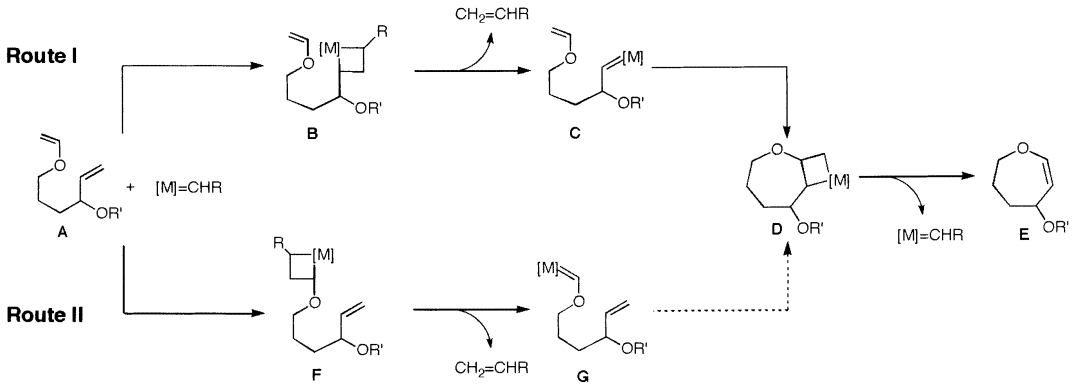
10

Diene	Cyclic enol ether	% Yield	
		9§	**10**†
 **7**	 **8**	NR	92
 **11**	 **15**	10	71
 **12**	 **16**	25	89
 **13**	 **17**	NR	82
 **14**	 **18**	27	86

§ 0.005 M diene, 20 mol% **9** in DCM under N_2, reflux overnight.
† 0.002 M diene, 20 mol% **10** in toluene 60°C, 4 h. Diene **11** was reacted for 12 h for complete conversion.



Scheme 1.



Scheme 2.

4,6-*O*-benzylidene glucose and mannose diacetonide, respectively. They incorporated acetal protecting groups that rigidified the diene in comparison to **7**. Deoxygenated derivatives **13** and **14** allowed for greater accessibility to nearby olefins (based on the site of deoxygenation). The 2-deoxyglucose derived diene **14** was especially interesting because it tested the influence of the alkoxy substituent in the allylic position of the diene for cyclization.[24]

Cyclization using the 4,6-benzylidene protected precursor **11** (glucose numbering) showed limited formation of product using **9** (Table 1). The mannose derived precursor **12** showed slightly greater yields of the cyclic enol ether **16** and indicated that RCM efficiency using **9** could be affected by changing the nature of the protecting groups. Diene **13**, synthesized from tri-*O*-benzyl xylose, showed no reaction in the presence of **9**. Deoxygenated precursor **14** gave a modest yield using **9** and formation of a side product was also observed (**18**:side product ratio 3:1). After column chromatography, this side product was identified by ^{1}H and ^{13}C NMR as tri-*O*-benzyl glucal **1** (where R = Bn). The formation of this product could occur via a ruthenium mediated 1,3-hydrogen shift or through reductive elimination of a ruthenium hydrido species followed by RCM of the truncated diene.[25] High yields of oxepines **15**–**18** were observed using Schrock catalyst **10** (Table 1).

The reactivity profile of the RCM substrates can be rationalized by considering the proposed reaction mechanism (Scheme 2). A few examples of RCM reactions involving enol ethers using Grubbs catalyst have been reported.[13a,b,d] Of critical importance is the formation of Fisher-type carbenes such as **G** (Scheme 2, Route II). Recent reports have shown that this carbene species, generated from electron-rich olefins, can be reactive in specific metathesis reactions, but is otherwise unreactive.[20,26] Our findings suggest that the features critical to RCM using **9** are: (i) the preorganization or rigidity of the diene, (ii) the steric accessibility of the vinyl ether or the alkene, and (iii) the alkoxy substituent allylic to the alkene. In comparing diene **7** to **11** and **12**, there is a progression toward fewer allowed bond rotations by virtue of the acetal protecting groups. Access to preferred conformations by internal cyclic constraint[13a,b,c] and acyclic steric effects[27] are well documented. Deoxygenation allows greater accessibility to the vinyl ether **13** or to the alkene **14** relative to **7**. The results show that increased access to the vinyl ether disfavors cyclization (presumably by favoring formation of **G**), while access to the alkene favors reactivity (via **B**) at the cost of formation of glucal as a side product. The use of diene **14**, which is deoxygenated at the allylic position of the olefin was motivated by reports that alkoxy substituents at this position slow the rate of metathesis or completely inhibit reaction.[24] Removal of the inductive effect from the alkoxy substituent also contributes to the increased reactivity of **14**. The more reactive Schrock catalyst gave consistently good yields with all diene precursors. The insensitivity of Schrock catalyst **10** to diene electronics observed here mirrors results from other systems.[13a,b,c,14]

In summary, we have introduced a convenient and concise route to ring expanded glycals from protected pyranose sugars. The method allows for the synthesis of a range of carbohydrate derived oxepines via a three step sequence from the protected reducing sugar. The approach provides a better understanding of substituent contributions in the RCM reaction of enol ethers using Grubbs catalyst. Current work is aimed at demonstrating that the carbohydrate-derived cyclic enol ethers are functional analogs of glycals and can serve as glycosyl donors in the synthesis of septanose carbohydrates.

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19. **7**: Into a roundbottom flask under N_2 atmosphere were sequentially added 6 mL dry DCM and 20 mL ethylvinyl ether followed by 1,10-phenanthroline (6 mg, 0.03 mmol) and $Pd(OAc)_2$ (7 mg, 0.03 mmol). This was allowed to stir at room temperature for 10–15 min and a yellow suspension was observed. To this solution was added **6** (111 mg, 0.205 mmol) in 2 mL dry DCM. The flask was fitted with a reflux condensor, maintained under N_2 atmosphere and heated to reflux for 72 h. The reaction mixture slowly turned black, indicating formation of palladium black. The reaction was cooled to room temperature and the solvent removed under reduced pressure. The resulting oil was purified by column chromatography (silica, 15 mm×100 mm) eluting with 20% EtOAc/Pet. Ether to give 37 mg of **7** (32%, 80% based on recovered starting material) as a clear colorless oil. Starting material eluted second and was also recovered (66 mg). Yields up to 49% could be obtained with longer reaction times. R_f (25% EtOAc/pet. ether) = 0.92 ^{1}H NMR 400 MHz ($CDCl_3$) δ 7.31–7.23 (m, 20H), 6.23 (dd, J = 14.0, 6.5 Hz, 1H), 5.86 (ddd, J = 17.5, 10.3, 7.4 Hz, 1H), 5.28 (dd, J = 10.3, 1.2 Hz, 1H), 5.20 (d, J = 17.5, 1H), 4.78 (d, J = 11.2 Hz, 1H), 4.70–4.58 (m, 3H), 4.48 (s, 2H), 4.36 (dd, J = 14.3, 1.6 Hz, 1H), 4.15 (ddd, J = 5.3, 5.3, 3.4 Hz, 1H) 4.10 (dd, J = 6.8, 6.8 Hz, 1H), 3.99 (dd, J = 6.5, 1.6 Hz, 1H), 3.97 (dd, J = 5.0, 5.0 Hz, 1H), 3.84 (dd, J = 10.7, 3.3 Hz, 1H), 3.69 (dd, J = 6.3, 5.0 Hz, 1H), 3.66 (dd, J = 10.7, 5.8 Hz, 1H); ^{13}C NMR 100 MHz ($CDCl_3$) δ 151.3, 138.9, 138.4, 138.3, 135.5, 128.5 (2), 128.4 (2), 128.3, 128.2, 127.9 (2), 127.7, 127.6 (2), 119.4, 89.4, 81.7, 81.5, 79.3, 79.0, 76.9, 75.3, 74.3, 73.5, 70.8, 69.1. FAB MS m/z (M^++H) calcd 565.2954, found 565.2944.
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22. **8**: (In a glovebox) To a solution of **7** (94 mg, 0.166 mmol) in 15 mL dry toluene was added catalyst **10** (32 mg, 0.042 mmol) in 2 mL toluene. The reaction was sealed in a airfree screw-top roundbottom and removed from the glovebox. The reaction mixture was put on an oil bath and heated at 60°C for 4 h. The reaction was then allowed to cool to room temperature and exposed to air. The solvent was removed under reduced pressure and the resulting dark brown oil was purified by column chromatography (silica, 15 mm×85 mm) using 25% EtOAc/pet. ether as eluent to give a clear colorless oil (82 mg, 92%). R_f (25% EtOAc/pet. ether) = 0.63; $[\alpha]_D$ = +68.8° (c 1.7, $CHCl_3$); ^{1}H NMR 400 MHz ($CDCl_3$) δ 7.56–7.06 (m, 20H), 6.51 (d, J = 6.9 Hz, 1H), 4.80 (dd, J = 6.8, 6.8 Hz,

1H), 4.67–4.55 (m, 8H), 4.50 (d, $J=11.2$ Hz, 1H), 4.09 (dd, $J=5.9$, 5.9 Hz, 1H), 3.96 (dd, $J=4.5$, 4.5 Hz, 1 Hz), 3.87 (dd, $J=9.4$, 3.8 Hz, 1H), 3.78 (d, $J=3.2$ Hz, 2H); ^{13}C NMR 100 MHz ($CDCl_3$) δ 149.4, 138.6, 138.4(2), 128.6, 128.5, 128.0(2), 127.9(2), 127.8, 127.7(2), 123.0, 103.8, 82.8, 81.2, 80.3, 73.6(2), 73.5, 72.8, 70.9, 70.4; FAB MS m/z (M^+-H) calcd 535.2484, found 535.2455.

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