Preparation of *C*-1 Glycals via Olefin Metathesis. A Convergent and Flexible Approach to *C*-Glycoside Synthesis[1]

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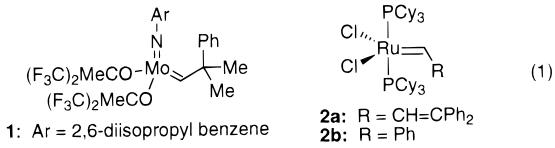
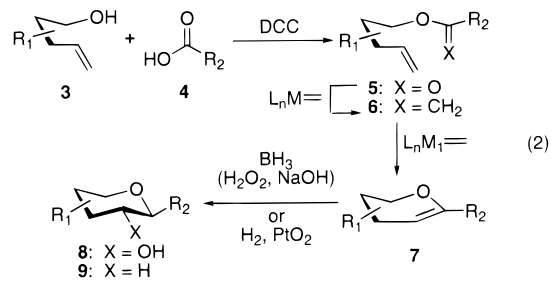
The recent interest in olefin metathesis is attested by the abundance of work that has appeared dealing with this new[2] and exciting approach to carbon−carbon bond formation.[3] This is largely due to the availability of effective catalyst systems such as **1**[4] and **2**[5] used to carry out this mild[6] and selective transformation.



(1)

Metathesis chemistry has been applied to many types of systems,[3] and its use has started to find application in the carbohydrate field.[7] *C*-Glycosides,[8] compounds in which the glycosidic oxygen atom has been replaced by a carbon-based group,[9] are biologically relevant compounds that have potential as enzyme inhibitors and stable sugar mimics. Conceptually, we felt that olefin metathesis and *C*-glycoside chemistry would mesh together quite well to provide a convergent and flexible route to a wide variety of *C*-1 glycals (eq 2). The sequence begins with a dehydrative coupling of

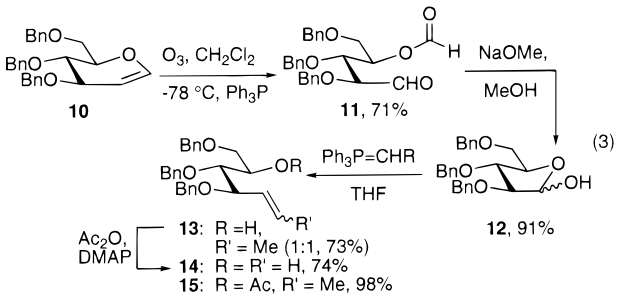


(2)

an appropriate olefin alcohol **3** with the requisite acid **4** to give ester **5**. Ring-closing metathesis, either via a one- or two-pot method, is then expected to give the *C*-1 glycal **7**. Compound **7** will then serve as an intermediate to both the *β*-*C*-glycosides with the general structures **8** and **9** available from **7** by hydroboration (followed by oxidative workup) or stereoselective reduction, respectively.

Initial work by Grubbs[10] established the viability of this ring closure with simple substrates. Later work by Nicolaou[11] focused on the one-pot preparation of cyclic enol ethers directly from esters using stoichiometric titanium reagents.[12] More recently, the preparation of cyclic enol ethers from olefinic acyclic enol ethers using a two-step protocol was reported.[13,14] While this work was underway, Rainier[15] reported an olefin−enolether metathesis-based method of fusing glycals onto existing carbohydrates. In addition, scientists at Merck Frosst[16] found that some carbohydrate-derived unsubstituted (on the enol ether olefin) enol ethers can undergo ring-closing metathesis with the use of **2b** to give glycals.

In this paper, we outline our preliminary results for the synthesis of *C*-1 glycals by an olefin−enol ether metathetical coupling approach. To have the structural diversity needed to prepare a variety of *C*-glycoside compounds, we needed a general approach to the sugar-based coupling partner **3**. Accordingly, treatment of 3,4,6-tri-*O*-benzyl-D-glucal (**10**) with ozone in dichloromethane at low temperature followed by reductive workup and deprotection of the formyl group gave lactol **12** as a mixture of inseparable anomers (91%). Wittig reaction, along ample literature precedent,[8] furnished olefins **13** as a 1:1 mixture (73%, ^{1}H NMR, 500 MHz) of partially separable isomers. Acetylation then provided **15** in quantitative yield demonstrating that diversity in the sugar portion is possible.[17] We employ commercially available 2,3,5-tri-*O*-benzyl-*β*-D-arabinofuranoside (**12***β*)[18] as our starting material for the Wittig olefination[19] reaction to prepare hydroxy-olefin **14**.



The ester precursors, except for **16a** (Ac_2O, 4-DMAP), were prepared by DCC-mediated coupling of **14** with the ap-

(1) Dedicated to the memory of Professor Michael G. Hogben, Concordia University, Montreal.

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(7) For some recent examples of the application of the olefin metathesis reaction to carbohydrates, see: (a) Sturino, C. F.; Wong, J. C. Y. *Tetrahedron Lett.* **1998** *39*, 9623−9626. (b) El Sukkari, H.; Gesson, J. P.; Renoux, B. *Tetrahedron Lett.* **1998**, *39*, 4043−4046. (c) O'Leary, D. J.; Blackwell, H. E.; Washenfelder, R. A.; Grubbs, R. H. *Tetrahedron Lett.* **1998**, *39*, 7427−7430.

(8) For reviews on *C*-glycoside synthesis, see: (a) Du, Y.; Lindhart, R. J. *Tetrahedron* **1998**, *54*, 9913−9959. (b) Togo, H.; He, W.; Waki, Y.; Yokoyama, M. *Synlett* **1998**, 700−717. (c) Postema, M. H. D.*C-Glycoside Synthesis*, 1st ed.; CRC Press: Boca Raton, 1995. (d) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*, 1st ed.; Elsevier Science: Oxford, 1995; Vol. 13.

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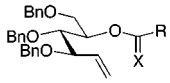
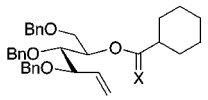
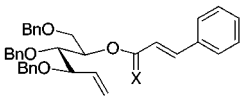
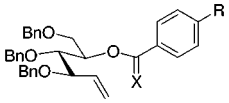
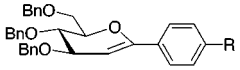
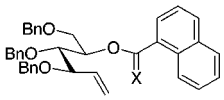
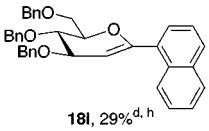
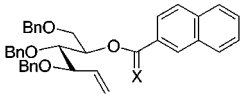
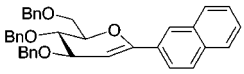
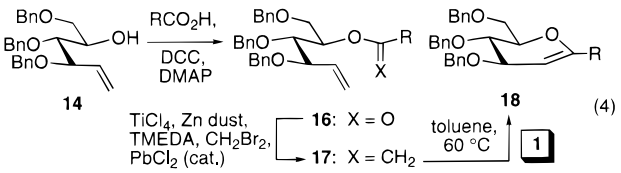
Table 1. Preparation of C-1 Glycals from Olefin Esters

Entry	Ester,**16**/Acyclic Enol Ether,**17**	*C*-1 Glycal, **18** (% Yield)[a, b, i]
1	 **16a**: X = O, R = Me, 98%[c] **17a**: X = CH_2, R = Me, 58%	 **18a**: R = Me, 72%[d]
2	**16b**: X = O, R = *n*-Bu, 67% **17b**: X = CH_2, R = *n*-Bu, 67%	**18b**: R = *n*-Bu, 58%[e]
3	**16c**: X = O, R = *t*-Bu, 42% **17c**: X = CH_2, R = *t*-Bu, 0%	[f]
4	 **16d**: X = O, 68% **17d**: X = CH_2, 61%	 **18d**, 73%[d]
5	 **16e**: X = O, 79% **17e**: X = CH_2, 62%	[g]
6	 **16f**: X = O, R = H, 68% **17f**: X = CH_2, R = H, 58%	 **18f**: R = H, 57%[d]
7	**16g**: X = O, R = Br, 72% **17g**: X = CH_2, R =Br, 64%	**18g**: R =Br, 60%[d]
8	**16h**: X = O, R = OMe, 92% **17h**: X = CH_2, R = OMe, 67%	**18h**: R = OMe, 55%[d]
9	 **16i**: X = O, 79% **17i**: X = CH_2, 64%	 **18l**, 29%[d, h]
10	 **16j**: X = O, 79% **17j**: X = CH_2, 54%	 **18j**, 68%

[a] Yields refer to chromatographically homogeneous (^{1}H NMR, 400 MHz) material. [b] Reaction was carried out on 40−70 mg scale at 0.01−0.02 M in substrate using 25 mol % **1** for entries 1−4 and 50 mol % **1** for entries 6−10. [c] Reaction was carried out using Ac_2O, 4-DMAP. [d] Reaction was carried out in the glove box. [e] Reaction was carried out under argon (rubber septum) on the benchtop. [f] Reaction was not carried out. [g] Only starting material was recovered (∼95%). [h] 28% recovered starting material was isolated along with an unidentified second product (∼30%). [i] Product contained a small amount of catalyst-derived impurity (2,6-diisopropylaniline) following chromatography.

propriate acids. These couplings proceeded in 67−92% yield (Table 1) with unreacted starting material accounting for the remainder of the mass balance. The preparations of the labile acyclic enol ethers **17** were carried out using the modified Takai procedures[20,21] and were purified to about 95% purity by flash chromatography. Exposure of the formed acyclic enol ether (derived from **15**) to the Schrock catalyst **1**[4] under the prescribed conditions for this type of ring closure failed to produce any of the desired cyclized material. We then employed the monosubstituted olefin **17a** (Table 1, entry 1) as the substrate for metathesis and exposure to **1** produced cyclized product **18a** in 53% yield along with recovered starting material **17a** (∼20%) as well as some of alcohol **14** (∼15%), the latter product arising from hydrolysis of the acyclic enol ether **17a**.



(4)

Operationally, the reagents were weighed out in a glovebox, and the reaction was then heated under argon on the bench. If the reagents and substrate were weighed in the box and the reaction then *heated in the box* the yield of the ring closure (**17a** → **18a**) increased to 72%. Similar observations, with regard to catalyst handling,[22] have been reported.[23] Table 1 shows some of the substrates that were examined.

Both alkyl (entries 1−2) and cycloalkyl (entry 4) substituents posed no problem for the ring-closing metathesis (RCM) reaction when 25 mol % of **1** was employed. The presence of the benzyloxy substituent adjacent to the olefin did not seem to impede the metathesis reaction. No acyclic enol ether was formed when **16c** (entry 3) was subjected to an excess of the the standard reagent. The cinnamyl derivative **16e** (entry 5) was readily methylenated (62%) to **17e**, but in our hands, attempted ring-closing metathesis with **1** gave only recovered **17e** (95%). Several aromatic substrates were also examined (**16f**−**h**) and gave acceptable yields of products, but required the use of 50 mol % of **1** in order to obtain the results shown. Naphthyl ester **16i** (entry 9) gave a good yield of the methylenation product **17i**, but we have not yet been able to improve the yield for the RCM step. This is due to competitive formation[24] of a second as of yet unidentified product. The less sterically encumbered β-naphthyl derivative **17j** (entry 10) underwent smooth RCM to give **18j** (68%).

In summary, we have demonstrated that a variety of *C*-1 glycals can be prepared via a highly convergent and efficient esterification−metathesis protocol.

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Supporting Information Available: Copies of experimental procedures for the preparation of **11**−**13** and **16**−**18** and spectral data listings for **11**−**13**, **16a,b,d**, **16f-j**, **17a,b,d**,**f**−**j** and **18a,b,d**,**f**−**j**.

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(17) For example, application of this sequence to 3,4,5-tri-*O*-benzyl-D-galactal should allow access to the corresponding *C*-1-galactals, although we have not yet carried this out.

(18) Commercially available from Sigma.

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(24) This second product is not the expected dimer.