A Unified Approach to Differentially Linked *β*-*C*-Disaccharides by Ring-Closing Metathesis

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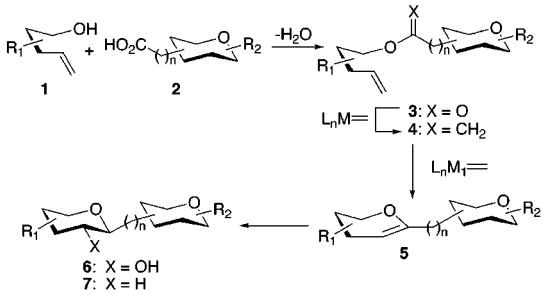
C-Glycosides, compounds in which the interglycosidic oxygen atom has been replaced by a carbon atom, are an important class of stable carbohydrate mimics.[1] These compounds have received considerable attention from both a synthetic[2] and biological[3] point of view, and the debate regarding their validity as conformational mimics of the parent *O*-glycosides is ongoing.[4]

The preparation of *C*-saccharides,[5] whether they are *C*-disaccharides or higher homologues, is considerably more challenging than the synthesis of simple *C*-glycosides. Any linkage, other than (1→6), consists of only one carbon atom separating the two monosaccharide units. Although there have been several approaches to the synthesis of a variety of differentially linked *C*-disaccharides,[6] no single method provides a unified and versatile strategy for a convergent and efficient synthesis of (1→1), (1→2), (1→3), (1→4), and (1→6) linked-*C*-disaccharides. In this communication, we report that a Keck allylation−ring-closing metathesis (RCM) approach delivers a variety of differentially linked *β*-*C*-disaccharides in an efficient manner and provides the first unified entry to this important class of carbohydrate mimics.[7]

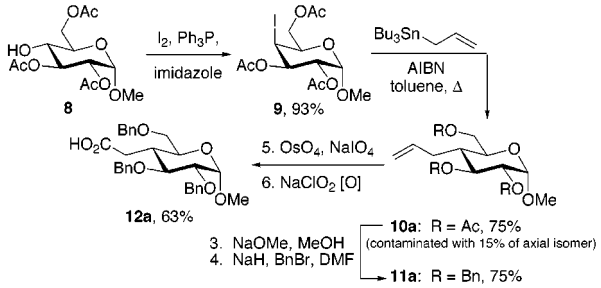
The general approach begins with dehydrative coupling of a suitable carbohydrate-based acid such as **2** with olefin alcohol **1** to give ester **3**, Scheme 1. Methylenation of **3** is followed by RCM to then give glycal **5**. Functionalization of the double bond then delivers the *β*-*C*-disaccharides **6** or **7**.

For the preparation of the various carbohydrate-based carboxylic acids, we relied upon a radical allylation−oxidative cleavage approach. The chemistry is illustrated with the preparation of the *C*-4 gluco acid **12a**, Scheme 2.

Scheme 1. Metathesis Approach to *C*-Saccharide Synthesis



Scheme 2. Preparation of *C*-4 Acid **12a**



Alcohol **8**[8] was converted to iodide **9** and exposure to allyltributyltin and AIBN[9] gave the equatorially allylated product **10a** in 75% yield. Some of the inseparable axial isomer (15%) was also formed. The acetates were exchanged for benzyl groups (75% over two steps), and oxidative cleavage of the mixture of olefins **11a** gave the corresponding aldehydes which were separated.[10] The major aldehyde was then oxidized to acid **12a**, Scheme 2.

DCC-mediated coupling of acid **12a** with alcohol **13** gave ester **14a** in good yield. Methylenation[11] of **14a** and subsequent ring-closing metathesis of acyclic enol ether **15a** mediated by catalyst **19**[12] furnished the (1→4)-*C*-disaccharide glycal **16a** (41%). This low yield was puzzling, since TLC analysis of the reaction showed clean conversion of **15a** to the cyclized material **16a**. We reasoned that the glycal was decomposing or hydrolyzing during purification, and this prompted us to explore a one-pot approach. Once the RCM reaction was deemed complete by TLC analysis, an excess of BH_3·THF[13] was added to the reaction mixture. Oxidative workup then furnished the (1→4)-*β*-*C*-disaccharide **17a** in 64% over two steps. Hydrogenolysis of the benzyl groups on **17a** and peracetylation then afforded the known[14] (1→4)-*β*-*C*-disaccharide **18a**, Scheme 3. This one-pot protocol not only improved the yield of the final product but also removed the need for purification of the sensitive *C*-disaccharide glycal **16a**.

Acids **12c**−**12e** (not shown) were prepared using the same general approach outlined in Scheme 2.[15] The stereochemistry of the allylation step was ascertained by Noe and ^{1}H NMR decoupling experiments on the corresponding aldehydes and was

(1) (a) Postema, M. H. D. *C-Glycoside Synthesis,* 1st ed.; CRC Press: Boca Raton, 1995; p 379. (b) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides,* 1st ed.; Elsevier Science: Oxford, 1995; Vol. 13, p 291.

(2) For reviews on *C*-glycoside synthesis, see: (a) Postema, M. H. D.; Calimonte, D. In *Glycochemistry Principles, Synthesis and Applications*; Bertozzi, C., Wang, P. G., Eds.; Marcel Dekker: New York, 2000; pp 77−131. (b) Du, Y.; Lindhart, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913−9959. (c) Beau, J.-M.; Gallagher, T. *Top. Curr. Chem.* **1997**, *187*, 1−54. (d) Nicotra, F. *Top. Curr. Chem.* **1997**, *187*, 55−83.

(3) Bertozzi, C.; Bednarski, M. In *Modern Methods in Carbohydrate Synthesis*; Khan, S. H., O'Neil, R. A. O., Eds.; Harwood Academic Publishers: Amsterdam, 1996; pp 316−351.

(4) (a) Wei, A.; Haudrechy, A.; Audin, C.; Jun, H.-S.; Haudrechy-Bretel, N.; Kishi, Y. *J. Org. Chem.* **1995**, *60*, 2160−2169 (b) Asensio, J. L.; Espinosa, J. F.; Dietrich, H.; Cañada, F. J.; Schmidt, R. R.; Martín-Lomas, M.; André, S.; Gabius, H.-J.; Jiménez-Barbero, J. *J. Am. Chem. Soc.* **1999**, *121*, 8995−9000. (c) Rubinstenn, G.; Sinaÿ, P.; Berthault, P. *J. Chem. Phys. A* **1997**, *101*, 2536−2540 and references therein.

(5) For a review of *C*-saccharide synthesis, see: McKee, M., Liu, L. Postema, M. H. D. *Curr. Org. Chem.* **2001**, *5*, in press.

(6) For some synthetic approaches to *C*-disaccharides, see: (a) Postema, M. H. D.; D. Calimente, D.; Liu, L.; Behrmann, T. L. *J. Org. Chem.* **2000**, *65*, 6061−6068. (b) Griffin, F. K.; Paterson, D. E.; Taylor, R. J. K. *Angew Chem. Int. Ed.* **1999**, *38*, 2939−2942. (c) Khan, N.; Cheng, X.; Mootoo, D. R. *J. Am. Chem. Soc.* **1999**, *121*, 4918−4919. (d) Leeuwenburgh, M. A.; Timmers, C. M.; van der Marel, G.; van Boom, J. H.; Mallet, J. M.; Sinaÿ, P. *Tetrahedron Lett.* **1997**, *38*, 6251−6254. (e) Dondoni, A.; Zuurmond, H.; Boscarato, A. *J. Org. Chem.* **1997**, *62*, 8114−8124. (f) Mallet, A.; Mallet, J.-M.; Sinaÿ, P. *Tetrahedron Asymmetry* **1994**, *5*, 2593−2608. (g) Sutherlin, D. P.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 5267−5283. (h) Martin, O. R.; Lai, W. *J. Org. Chem.* **1993**, *58*, 176−185.

(7) For a review on the use of olefin metathesis in carbohydrate chemistry, see: Jorgensen, M.; Hadwiger, P.; Madsen, R.; Stutz, A. E.; Wrodnigg, T. M. *Curr. Org. Chem.* **2000**, *4*, 565−588.

(8) Koch, K.; Chambers, R. J. *Carbohydr. Res.* **1993**, *241*, 295−299.

(9) Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley: M. R. *Tetrahedron* **1985**, *41*, 4079−4094.

(10) All new compounds were fully characterized by extensive 1-D and 2-D NMR techniques, IR, and high-resolution mass spectrometry.

(11) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668−2670.

(12) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875−3886.

(13) (a) Hanessian, S.; Martin, M.; Desai, R. C. *J. Chem. Soc., Chem. Commun.* **1986**, 926−927. (b) Schmidt, R. R.; Preuss, R.; Betz, R. *Tetrahedron Lett.* **1987**, *28*, 6591−6594.

(14) Khan, A. T.; Sharma, P.; Schmidt, R. R. *J. Carbohydr. Chem.* **1995**, *14*, 1353−1367.

(15) See Supporting Information.

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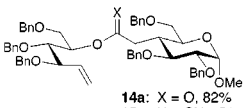
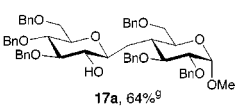
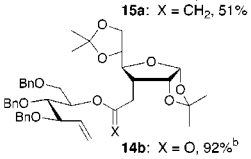
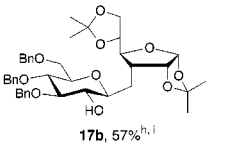
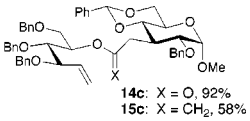
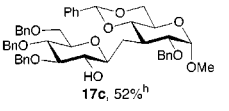
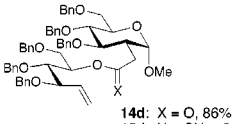
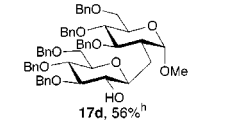
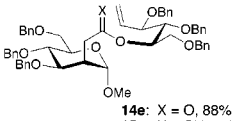
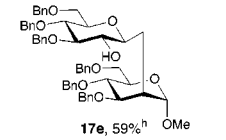
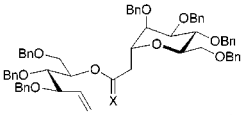
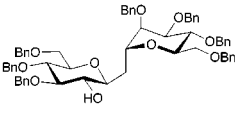
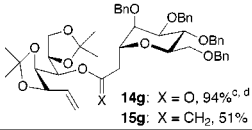
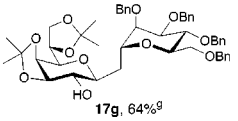
Table 1. Synthesis of β-*C*-Disaccharides by RCM[a]

Entry	Ester **14**/Enol Ether **15**	β-*C*-Disaccharide **17**[e, f]
1	 **14a**: X = O, 82% **15a**: X = CH_2, 51%	 **17a**, 64%[g]
2	 **14b**: X = O, 92%[b] **15b**: X = CH_2, 67%	 **17b**, 57%[h, i]
3	 **14c**: X = O, 92% **15c**: X = CH_2, 58%	 **17c**, 52%[h]
4	 **14d**: X = O, 86% **15d**: X = CH_2, 51%	 **17d**, 56%[h]
5	 **14e**: X = O, 88% **15e**: X = CH_2, 50%	 **17e**, 59%[h]
6	 **14f**: X = O, 91%[c] **15f**: X = CH_2, 54%	 **17f**, 63%[g]
7	 **14g**: X = O, 94%[c, d] **15g**: X = CH_2, 51%	 **17g**, 64%[g]

[a] Yields refer to chromatographically homogeneous material. [b] Acid **12b** was prepared from the corresponding known[20] ethyl ester.[15] [c] Acid **12f** was prepared from the known[21] allyl derivative.[15] [d] The corresponding olefin alcohol is known.[22] [e] Yields are for two steps; RCM and hydroboration-oxidative workup. [f] Stereochemistry at *C*-1 and *C*-2 determined by acetylation and analysis of *H*-2 coupling constant in ^{1}H NMR.[15] [g] Reaction carried out with 20−30 mol % of **19** in a glovebox followed by hydroboration. [h] Reaction carried out with 20−30 mol % of **20** on an argon manifold followed by hydroboration. [i] RCM with 20−30 mol % of **19** gave a 34% yield of the corresponding glycal.

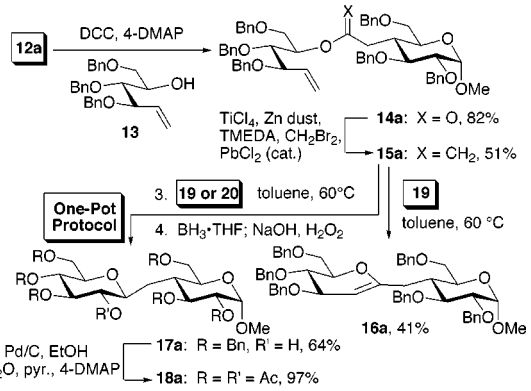
found to favor equatorial allylation at *C*-3 and *C*-4, but not at *C*-2 (entries 4 and 5).[15] In this case, the adjacent OBn and OMe groups exert opposing steric effects on the course of the allylation to give a mixture (α:β, 2:3) of allylated products.

Olefin alcohol **13** was prepared by Wittig reaction[16] of 3,4,6-tri-*O*-benzyl-D-arabinofuranose[17] with $Ph_3P{=}CH_2$.

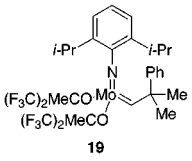
Ester formation (**12**+**13**→**14**), mediated by DCC and 4-DMAP, proved to be routine. Methylenation of the resulting esters

(16) Freeman, F.; Robarge, K. D. *Carbohydr. Res.* **1986**, *154*, 270−274.
(17) Commercially available from Sigma.

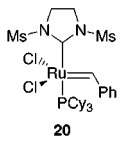
Scheme 3. RCM-Based Synthesis of β-*C*-Disaccharides



(**14**→**15**) proceeded in reasonable yield, although a large excess of the methylenating reagent was required for reactions to be driven to completion. The one-pot RCM−hydroboration protocol works well, and the results in Table 1 (entries 1 and 2) contrast the difference between the one-pot procedure and simple isolation of the glycal. The *C*-disaccharide **17** was consistently isolated in ∼60% yield over two steps. Significantly, the one-pot protocol works efficiently with the easily handled catalyst **20**[18] (entries 2−5). It was necessary to add 20−30 mol % of metathesis catalyst portion-wise over the course of the reaction (toluene, 60 °C) to drive the cyclization to completion.[19]



19



20

The above results show that the RCM approach to *C*-saccharide synthesis is a viable route to a variety of differentially linked β-*C*-disaccharides in good overall yield starting from readily available starting materials. This approach should allow access to a host of other biologically relevant glycosidic linkages.

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Supporting Information Available: Experimental procedures for the preparation of compounds **9**, **10a**−**12a**, and **14a**−**18a**, spectral data listing for **14a**−**g**, **15a**−**g**, **17a**−**g**, **18a** and copies of ^{1}H NMR spectra for **9**, **10a**, **14a**, **15a**, **17a**, **16b**, **18a**, and Schemes showing the preparation of acids **12b**−**f** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA010641+

(18) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.
(19) Upon completion of this work, the RCM of an enol ether−olefin mediated by **20** appeared: Rainier, J. D.; Cox, J. M.; Allwein, S. P. *Tetrahedron Lett.* **2001**, *42*, 179−181.
(20) Lourens, G. J.; Koekemoer, J. M. *Tetrahedron Lett.* **1975**, 3719−3722.
(21) Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett.* **1984**, *25*, 2383−2386.
(22) Haudrechy, A.; Sinaÿ, P. *J. Org. Chem.* **1992**, *57*, 4142−4151.