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Synthesis and Partial Biological Evaluation of a Small Library of Differentially-Linked β-*C*-Disaccharides[1]

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The synthesis of a small library of differentially-linked β-*C*-disaccharides has been carried out through the use of a radical allylation-RCM strategy. Acids **6** were prepared by Keck allylation of a suitable carbohydrate-based radical precursor, followed by oxidative cleavage of the formed alkene. Dehydrative coupling of these acids with the known olefin alcohol **5** then gave the precursor esters **7** in excellent yield. Methylenation of the esters **7** was followed by RCM and in situ hydroboration−oxidation of the formed glycals to furnish the protected β-*C*-disaccharides **10** in good overall yield. Five examples were then deprotected and screened for their efficacy as enzyme inhibitors of β-glycosidase and against several solid-tumor cell lines for *in vitro* differential cytotoxicity.

Introduction

The preparation of *C*-glycoside-based derivatives is a fairly mature field[2] and has seen the use of interesting chemistry for the attachment of a variety of carbon-based groups to the anomeric carbon atom of carbohydrates. By definition, *C*-glycosides are compounds in which the interglycosidic oxygen atom has been replaced by a carbon atom to produce a stable glycoside derivative that will not be prone to enzymatic or chemical hydrolysis.[3] A wealth of approaches have been used for the synthesis of both alkyl and aryl *C*-glycosides.[4] The latter class of compounds is particularly important due to the existence of a number of naturally occurring aryl *C*-glycosides,[5,6] many of which possess interesting and potentially useful biological activity. *C*-Saccharide derivatives[7] are the carbon analogues of *O*-saccharides and the simplest class, *C*-disaccharides, can be divided into two categories. The (1→6)-linked derivatives such as **2** possess two carbohydrate rings connected by a two-atom linker, Figure 1. Any linkage, other than (1→6), generally consists of only a single carbon atom separating the two monosaccharide units and these include the (1→4)-, (1→3)-, and (1→2)-linked derivatives. The (1→4)-linked derivative **4**, is shown below.

It is generally easier to prepare (1→6)-*C*-disaccharides[8,9] such as **2**, since the two-carbon linker allows for more versatility in the type of coupling method used to join the two pyranosides. Although several approaches to the synthesis of a variety of differentially-linked *C*-disaccharides[10] have been described, few methods provide a unified and versatile strategy for a convergent

(1) This paper is dedicated to Professor Carl R. Johnson on the occasion of his retirement from Wayne State University.

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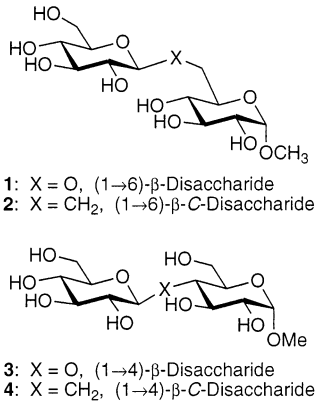


FIGURE 1. *O*-Disaccharides versus *C*-disaccharides.

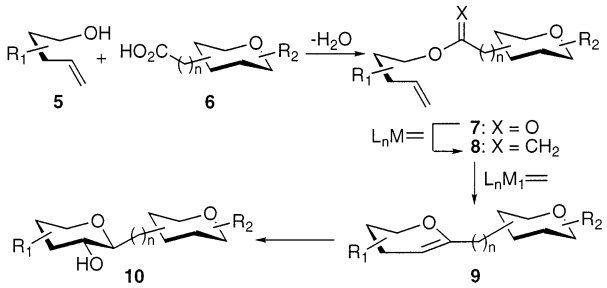
and efficient synthesis of (1→1)-, (1→2)-, (1→3)-, (1→4)-, and (1→6)-linked-*β*-*C*-disaccharides.

If they are to be suitable mimics, then *C*-saccharides should ideally possess conformations that are similar to those of the parent *O*-glycoside or conformations that still elicit a biological response or recognition event. The debate regarding the validity of *C*-saccharides as accurate conformational mimics of *O*-saccharides is ongoing and has yet to be resolved.[11] The K_i values for *O*- and *C*-lactose for the competitive inhibition of *β*-galactosidase are within 2 *μ*m of one another[12] and several groups[13] have convincingly shown that the substitution of the interglycosidic oxygen atom with a carbon atom does not greatly alter biological activity. Given the vast biological functions that carbohydrates possess,[14] it stands to reason that stable analogues of these derivatives could be useful as biological probes or enzyme inhibitors.

In this paper, we present full details of our RCM methodology for the preparation of differentially-linked *β*-*C*-disaccharides.[15] Three additional examples have been prepared and the overall yield of the three-step protocol has been optimized. Biological data on several of the *C*-saccharide derivatives are also presented.

At the outset of this work, we wished to develop a general approach for the synthesis of *C*-glycosides[16] and a variety of *β*-*C*-saccharides.[17,18] Our generic synthetic approach to *C*-disaccharide synthesis is shown in Scheme 1 and begins with the dehydrative coupling of the generic

SCHEME 1. RCM Approach to *C*-Saccharides



olefin alcohol **5** with a suitable carbohydrate-based acid such as **6** to give ester **7**, Scheme 1. Methylenation[19] (**7**→**8**) is to be followed by RCM[20] to give glycal **9**. Hydroboration[21] of the formed double bond then affords the *gluco*-*β*-*C*-disaccharide **10**.

Our approach to (1→6)-linked-*β*-*C*-disaccharides[17,18] relied upon a similar strategy and the needed acids were readily prepared by Wittig-type chemistry.[22] For any linkage, other than (1→6), a suitable method for installing the acetyl pendant onto the pyranose ring with the correct regio- and stereochemistry would be needed. Keck allylation[23] seemed well-suited for this task since, in theory, the needed radical precursor could be generated at any position of a suitably protected glucopyranoside.

Preparation of the Carbohydrate-Based Acids

The equatorial *C*-4 acid was prepared first, since the 4-position of *gluco* derivatives is generally considered to be the most hindered one. Several radical precursors (**13**−**17**) were prepared from the known[24] tri-*O*-benzyl derivative **11** and separate exposure of all of these compounds to either thermal or photochemical allylation conditions gave only complex reaction mixtures, Scheme 2. The inordinately large number of products was attributed to 1,5-*H* radical abstraction of the *O*-6 benzylic hydrogens.[25] Deuteration studies to confirm this hypothesis were not carried out, but instead, the *O*-6 benzyl group was exchanged for a TIPS group. Attempted

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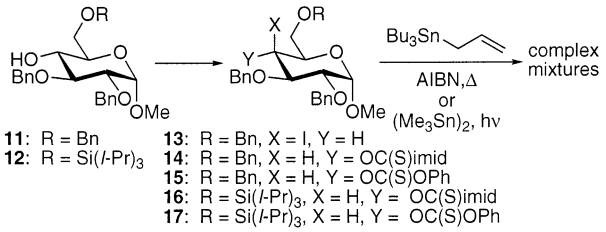
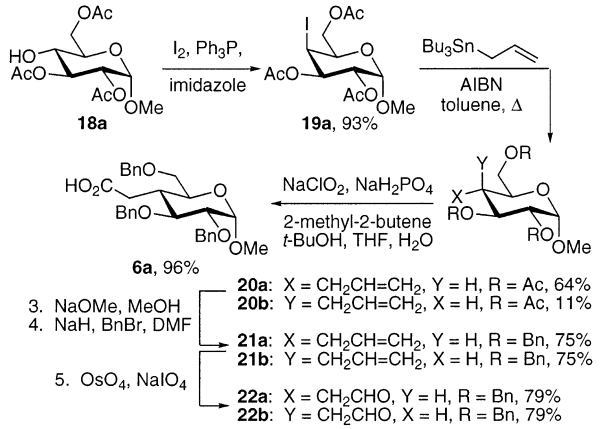
(25) Mootoo, D.; Wilson, P.; Jammalamadaka, V. *J. Carbohydr. Chem.* **1994**, *13*, 841−849.

SCHEME 2. Initial Allylation Attempts



SCHEME 3. Formation of the *C*-4 Acid 6a



radical allylation of **16** gave similar results as with the fully benzylated derivatives. Presumably, the formed radical exists in a conformation or conformations where other benzylic hydrogen atoms are accessible for radical abstraction. The ultimate solution was to remove the abstractable hydrogen atoms by replacing all of the benzyl groups with acetates. These would, however, eventually need to be exchanged for benzyl groups due to their incompatability with the methylenation step.

The known tri-*O*-acetyl derivative **18a**[26] was converted[27] to iodide **19a** in good yield and in this case, radical allylation[23] of **19a** proceeded to deliver a mixture of equatorial and axial allylation products in a 6:1 ratio. The major isomer, **20a**, was formed in 64% yield, and resulted from radical addition from the bottom α-face of the molecule, opposite the adjacent OAc and CH_2OAc groups. The two isomers were inseparable under a variety of chromatographic conditions and the mixture was, therefore, carried on to the next step. The acetates were removed and replaced with benzyl groups and, once again, the formed compounds **21a** and **21b** were found to be inseparable. Only after oxidative cleavage of the double bond to give the corresponding aldehydes **22a** and **22b** was separation of the isomers possible. At this point, the aldehydes were separated and fully characterized.[28] Pinnick oxidation[29] of the major aldehyde **22a** then gave the needed *C*-4 equatorial acid **6a**, Scheme 3.

Table 1 outlines the preparation of all the intermediates en route to the required carboxylic acids **6**. Entry 1 outlines the 4-gluco case discussed above. The minor isomer **20b** from the allylation of **19a** was converted to acid **6b** in a similar fashion as that for **6a** (entry 2). The *C*-3 acid **6c** (entry 3, Table 1) was accessed from the known methyl 2-benzoyl-4,6-di-*O*-benzylidene-D-glucoside (**18c**).[30] Thionocarbonate formation on **18c** by the NHS method[31] gave **19c** and radical allylation furnished **20c** as a single isomer, presumably due to the bicyclic nature of the molecule. Exchange of the benzoate blocking group (**20c**→**21c**) was followed by oxidative cleavage of the alkene to furnish an intermediate aldehyde that was then oxidized to the corresponding acid **6c** (entry 3, Table 1).

The preparation of *C*-2 *gluco*-acid began with tri-*O*-acetyl-D-glucal (**18d**). Exposure of **18d** to iodine in methanol gave **19d** in 85% yield,[32] which was then allylated in the usual manner to give, in this case, a 1:1.5 ratio of *gluco* **20d** to *manno* **20e** isomers in 64% combined yield (entries 4 and 5, Table 1). Once again, the two formed olefins were inseparable. The acetates were exchanged for benzyl groups (on the mixture of allylated compounds) and the double bond cleaved to reveal two separable aldehydes that were then separately oxidized to the corresponding *C*-2 *gluco* and *manno* acids **6d** and **6e**, respectively. In this case, the adjacent groups exert an opposing stereochemical bias on the allylation reaction with the axial anomeric substituent dominating over the equatorial *C*-3 substituent.

The needed β- and α-*C*-1 acids **6f** and **6g** (entries 6 and 7, Table 1) were readily accessible since the corresponding allyl derivatives are known compounds and are both easily prepared. Compound **21f**, previously prepared by Kishi,[33] was converted to the β-derivative **6f** in two steps (53%) and the known α-allyl derivative **21g**[34] was converted to the α-acid derivative **6g** in 62% yield.

The equatorial *C*-3 acid of methyl α-D-galactoside **6h** was also prepared (entry 8, Table 1). The known derivative **18h**[35] was converted to **19h** and, as expected, the axial group directed the radical allylation reaction to give the equatorial isomer **20h** as the minor compound. It was formed in a 1:1.7 ratio as shown by ^{1}H NMR analysis of the crude reaction mixture. The acetylated products were not separable, but in this case the corresponding benzyl derivatives were separable. Accordingly, compound **21h** was oxidized to acid **6h** in 60% yield over the two steps.

For all of the entries in Table 1 (save for compounds **21f** and **21g**), the stereochemistry of the allylation step was confirmed by H−H decoupling experiments and NOE studies.[28]

Ester Formation, Methylenation, and Ring-Closing Metathesis

With all the acids in hand, the RCM sequence was then examined. DCC-mediated coupling of alcohol **5a**[36] and acid **6a** proceeded uneventfully to afford ester **7a** in good

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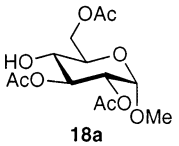
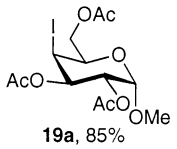
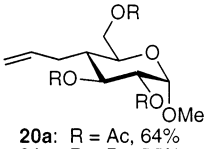
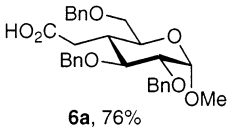
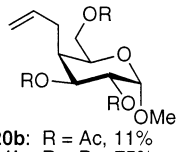
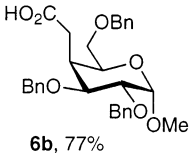
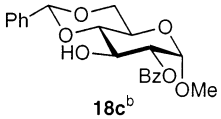
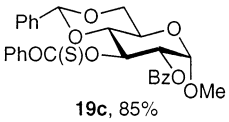
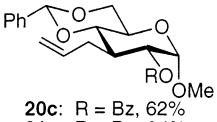
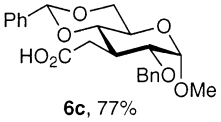
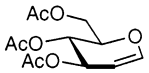
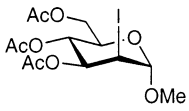
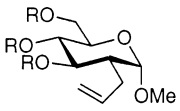
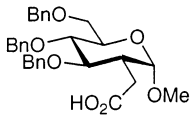
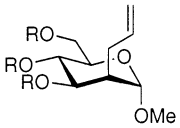
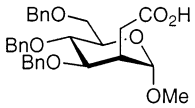
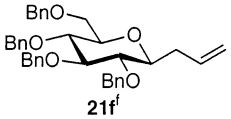
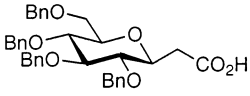
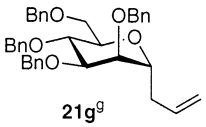
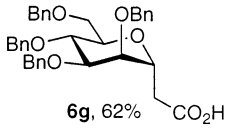
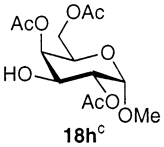
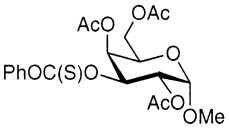
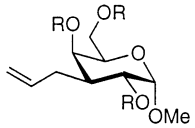
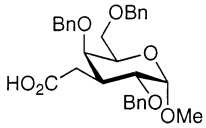
TABLE 1. Synthesis of Carbohydrate-Based Acids 6[a]

entry	alcohol **18**	radical precursor **19**	allyl derivatives **20**[d]/**21**[e]	acid **6**[i,j]
1	 **18a**	 **19a**, 85%	 **20a**: R = Ac, 64% **21a**: R = Bn, 75%	 **6a**, 76%
2			 **20b**: R = Ac, 11% **21b**: R = Bn, 75%	 **6b**, 77%
3	 **18c**[b]	 **19c**, 85%	 **20c**: R = Bz, 62% **21c**: R = Bn, 94%	 **6c**, 77%
4	 **18d**	 **19d**, 85%	 **20d**: R = Ac, 26% **21d**: R = Bn, 92%	 **6d**, 78%
5			 **20e**: R = Ac, 38% **21e**: R = Bn, 92%	 **6e**, 84%
6			 **21f**[f]	 **6f**, 53%
7			 **21g**[g]	 **6g**, 62%
8	 **18h**[c]	 **19h**, 94%	 **20h**: R = Ac, 24%[h] **21h**: R = Bn, 98%	 **6h**, 60%

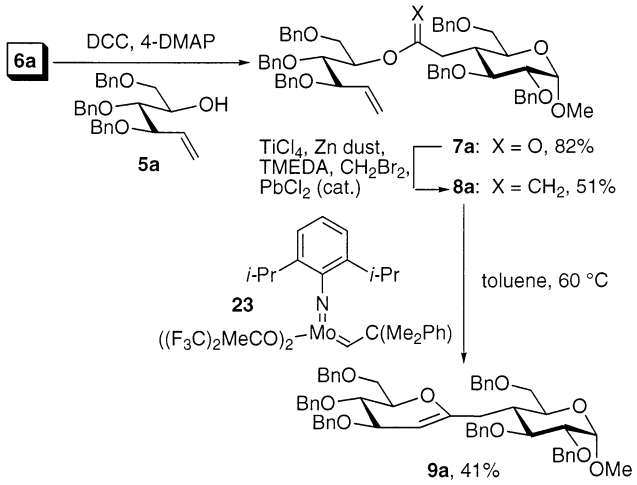
[a] Yields refer to chromatographically and spectroscopically homogeneous materials. [b] Prepared by the method of Szeja.[30] [c] Prepared by the method of Hashimoto.[35] [d] Any epimeric allylated derivatives **20** were separated after benzylation and oxidative cleavage to the corresponding aldehydes. [e] Reaction carried out with NaOMe in MeOH/THF followed by benzylation (BnBr/NaH/DMF). [f] Prepared by the method of Kishi.[33] [g] Prepared by the method of Hosomi.[34] [h] The corresponding axial isomer was formed in 40% yield. [i] Oxidative cleavage of the olefin carried out in two steps. [j] Yields are for two steps.

yield. Methylenation[19] of **7a** gave **8a** and exposure to catalyst **23**[37] in the glovebox gave a 41% yield of the *C*-disaccharide glycal **9a**. This was surprising, since TLC analysis showed clean conversion of the starting material to the product. We reasoned that the glycal was decomposing or hydrolyzing during purification and this prompted us to explore a one-pot approach in which the glycal was not isolated.

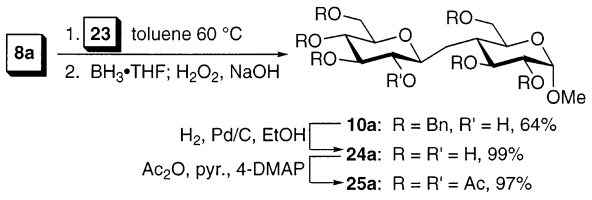
The RCM was carried out as before, but before removal of the reaction from the drybox, an excess of BH_3·THF

(37) (a) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875−3886. (b) Feldman, J.; Murdzek, J. S.; Davis, W. M.; Schrock, R. R. *Organometallics* **1989**, *8*, 2260−2265.

SCHEME 4. Synthesis of the (1→4)-*β*-*C*-Glycal 9a



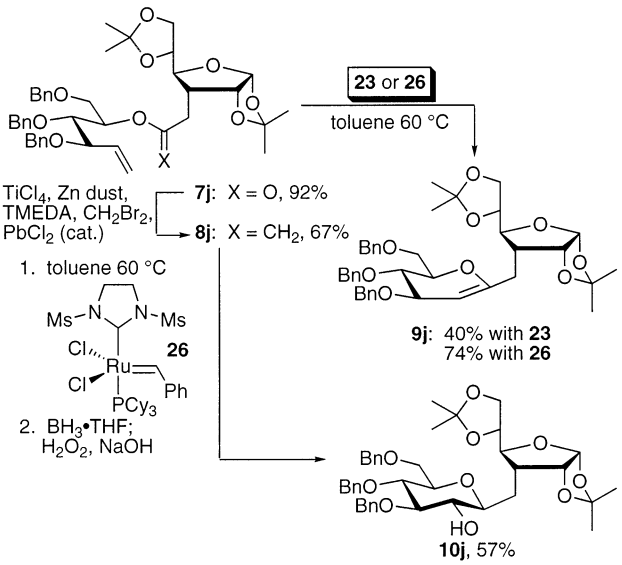
SCHEME 5. One-Pot Protocol for the RCM Sequence



was added and the reaction was then quenched with basic hydrogen peroxide and stirred overnight. After the usual workup and purification by flash chromatography, a 64% yield of the *β*-*C*-disaccharide **10a** was obtained, Scheme 5. Presumably, the cyclized material **9a** was hydrolyzing on the column, even in the presence of 1−3% of triethylamine. The benzyl groups were removed (**10a**→**24a**) and global acetylation gave the peracetylated (1→4)-*β*-*C*-disaccharide **25a** in good overall yield.

We examined a case where acetonide protecting groups were present in the starting ester. Accordingly, compound **8j** was exposed to catalyst **23**[37] and RCM ensued giving the product glycal **9j** in 40% yield while reaction with the second generation Grubbs catalyst **26**[38] gave **9j** in 74% yield, Scheme 6. When **9j** was heated to 60 °C for 4 h in the presence of 20 mol % of $(CF_3)_2CH_3COH$, TLC analysis indicated that the glycal had undergone partial decomposition under the reaction conditions. It would seem that some of the alcohol ligand is lost from **23** during the RCM and this may be the cause of glycal decomposition. This direct comparison (between **23** and **26**) shows that if the glycal is the desired product, then **26** is the catalyst of choice. Application of the one-pot protocol, this time with the second generation Grubbs catalyst **26**,[38] was explored and RCM of **8j** mediated by **26** was followed by hydroboration and oxidative quench to furnish the *C*-disaccharide **10j** in 57% overall yield, Scheme 6. The yield for the two steps was still very acceptable, especially since the RCM chemistry could now be carried out on the benchtop with use of conventional inert gas line techniques.

SCHEME 6. RCM with the Grubbs Catalyst 26



SCHEME 7. RCM with No Linking Atom

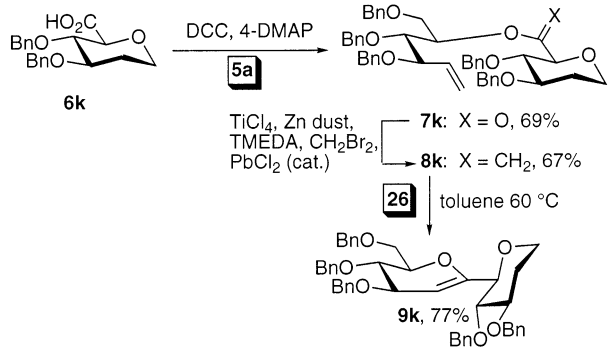


Table 2 shows the examples that were examined. The esters **7** were all formed in good yield while methylenation proceeded consistently in ∼50% yield, even with a large excess of the methylenating reagent. RCM for entries 1, 7, and 9 were carried out with catalyst **23** and proceeded in good yield over the two steps, while entries 2−6, 8, and 10 were carried out with catalyst **26** in comparable yield. In two cases (entries 1 and 7), both catalysts **23** and **26** were employed for a side-by-side comparison and yielded similar results.

An example in which there was no linking atom between the two sugar units was also examined. Ester **7k**, formed by DCC-mediated coupling of acid **6k**[41] with olefin alcohol **5a**, was methylenated to provide **8k** in 67% yield and exposure to catalyst **26**[38] furnished glycal **9k**, which in this case was isolable, in 77% yield, Scheme 7.

Optimization of the Three-Step Protocol

Once the results in Table 2 were compiled, it became clear that the overall yield of the *C*-disaccharide **10** from ester **7** needed optimization. This is especially true if the chemistry was to be used in an iterative sense or for two

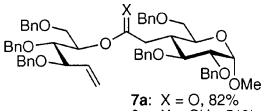
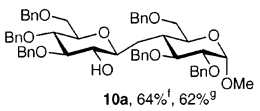
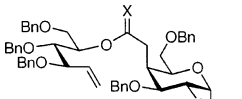
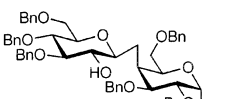
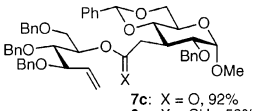
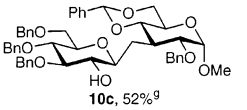
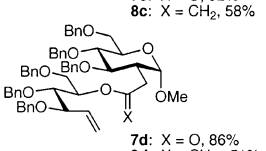
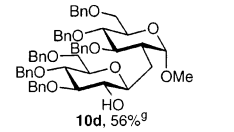
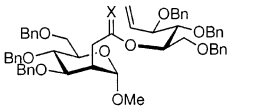
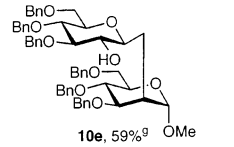
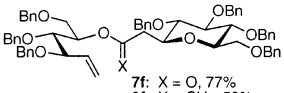
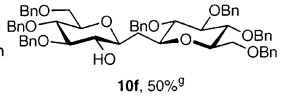
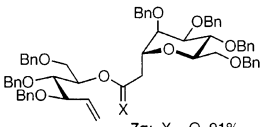
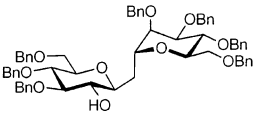
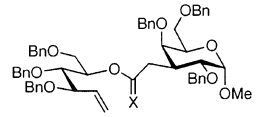
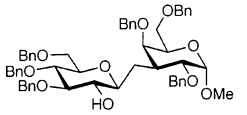
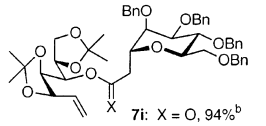
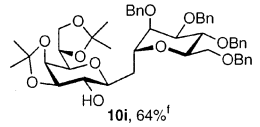
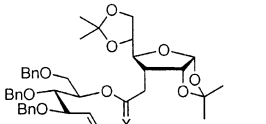
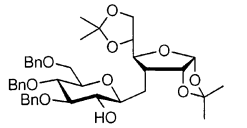
(38) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(39) Haudrechy, A.; Sinaÿ, P. *J. Org. Chem.* **1992**, *57*, 4142−4151.

(40) Lourens, G. J.; Koekemoer, J. M. *Tetrahedron Lett.* **1975**, 3719−3722.

(41) Nicolaou, K. C.; Postema, M. H. D.; Yue, E. W.; Nadin, A. *J. Am. Chem. Soc.* **1996**, *118*, 10335−10336.

TABLE 2. Preparation of Differentially-Linked *β*-*C*-Disaccharides[a]

entry	ester **7**/ enol ether **8**	β-*C*-disaccharide **10**[d, e]
1	 **7a**: X = O, 82% **8a**: X = CH_2, 51%	 **10a**, 64%[f], 62%[g]
2	 **7b**: X = O, 82% **8b**: X = CH_2, 52%	 **10b**, 53%[g]
3	 **7c**: X = O, 92% **8c**: X = CH_2, 58%	 **10c**, 52%[g]
4	 **7d**: X = O, 86% **8d**: X = CH_2, 51%	 **10d**, 56%[g]
5	 **7e**: X = O, 88% **8e**: X = CH_2, 50%	 **10e**, 59%[g]
6	 **7f**: X = O, 77% **8f**: X = CH_2, 52%	 **10f**, 50%[g]
7	 **7g**: X = O, 91% **8g**: X = CH_2, 54%	 **10g**, 63%[f], 50%[g]
8	 **7h**: X = O, 77% **8h**: X = CH_2, 50%	 **10h**, 50%[g]
9	 **7i**: X = O, 94%[b] **8i**: X = CH_2, 51%	 **10i**, 64%[f]
10	 **7j**: X = O, 92%[c] **8j**: X = CH_2, 67%	 **10j**, 57%[g]

[a] Yields refer to chromatographically and spectroscopically homogeneous materials. [b] The corresponding olefin alcohol is known.[39] [c] The corresponding ethyl ester is known.[40] [d] Yields are for two steps; RCM and hydroboration−oxidative workup. [e] Stereochemistry at *C*-1 and *C*-2 determined by acetylation and analysis of the *H*-2 coupling constant in ^{1}H NMR.[28] [f] Reaction carried out with 20−30 mol % of **23** in a glovebox followed by hydroboration. [g] Reaction carried out with 20−30 mol % of **26** on an argon manifold followed by hydroboration.

SCHEME 8. Overall Yield Optimization with Ester 7l

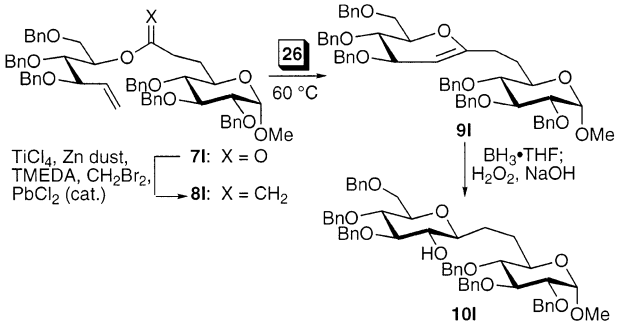


TABLE 3. Optimization Yields (%) for Scheme 8

yield of **8*l***	yield of **9*l***	yield of **10*l***	overall yield of **10*l***
76[a]	68	90	47
76[a]	not purified[b]	65	49
not purified[d]	58[c]	90	52
not purified[d]	**not purified**[e]	**55**[f]	**55**

[a] The acyclic enol ether was purified by flash chromatography. [b] The product glycal was not isolated, but rather the one-pot protocol was employed. [c] Yield is over two steps. [d] The acyclic enol ether was not purified by flash chromatography, but the crude reaction mixture was filtered through a pad of basic alumina. [e] Then glycal was not isolated, but carried on crude to the next step. [f] Yield is over three steps.

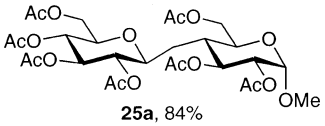
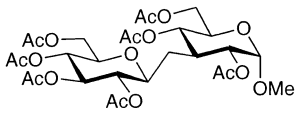
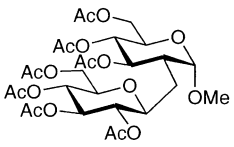
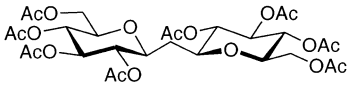
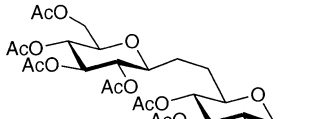
more simultaneous cyclizations. Since we had gram amounts of ester **7*l*** in hand, a few different methods for the conversion of **7*l*** to the target *β*-C-disaccharide **10*l*** were examined.

We therefore carried out the three-step sequence in a few different ways as shown in Scheme 8 and Table 3. The first entry shows that the overall yield of the sequence is 47% if the acyclic enol ether **8*l***, the product of RCM **9*l***, and the product of hydroboration **10*l*** are all purified by flash chromatography. The second entry 2 shows the overall yield of **10*l*** is 49% if the glycal is not purified. If the product of methylenation is not purified, but merely filtered through a short plug of basic alumina, then a 52% overall yield of **10*l*** is obtained. If the sequence is carried out with both crude acyclic enol ether and crude glycal, and only the final product is purified, the target *β*-*C*-disaccharide **10*l*** is now obtained in 55% overall yield for the three steps. In our initial work,[16] the Schrock catalyst **23**[37] was used to effect the cyclization and we found that it was not tolerant of any impurities in the acyclic enol ether, so it had to be purified prior to the RCM step.

These results were then applied to esters **7a**, **7c**, **7d**, **7f**, and **7l** and Table 4 shows the results. The product *β*-*C*-disaccharides **10** were formed in 53−59% overall yield over the three steps and were then converted to the fully acetylated *β*-*C*-disaccharides **25** in good yield.

The deacetylated C-disaccharides **24a**, **24c 24d 24f**, and **24*l*** were tested against various glycosidase enzymes. The results were unimpressive and only the deacetylated variant **24f**, the (1,1)-linked derivative, showed modest inhibitory activity with a K_i of 126 μM against *β*-glucosidase from almonds.[28]

TABLE 4. Optimized Conditions for RCM and Deprotection[a]

entry	ester **7**	β-*C*-disaccharide **10**[b, c]	β-*C*-disaccharide **25**[e]
1	**7a**	**10a**, 56%	 **25a**, 84%
2	**7c**	**10c**, 59%[d]	 **25c**, 90%
3	**7d**	**10d**, 53%	 **25d**, 71%
4	**7f**	**10f**, 59%	 **25f**, 94%
5	**7l**	**10l**, 55%	 **25l**, 93%

[a] Yields refer to chromatographically and spectroscopically homogeneous materials. [b] Yield is for three steps: methylenation, RCM, and hydroboration−oxidative workup. [c] 20−25 mol % of **26** used for the RCM reaction. [d] In this case, 40−45 mol % of **26** was needed to push the RCM to completion. [e] Reaction carried out in MeOH with 5% Pd/C under 50 psi of H_2 followed by acetylation (Ac_2O/pyridine/4-DMAP).

C-Disaccharide **24a** and **24*l*** were screened[42] for differential cytotoxicity[43] against both murine solid tumor colon cells (C38) and murine leukemia cells and showed no cytotoxicity whatsoever.

(42) We thank Dr. Frederick Valeriote of the Josephine Ford Cancer Center for carrying out these assays.

Conclusion

The synthesis of β-*C*-disaccharides by RCM has proven to be an effective means of gaining access to an array of β-*C*-disaccharides. The use of the new Grubbs catalyst **26** allows for the cyclization chemistry to be readily carried out with benchtop techniques, and coupled with our one-pot approach has made the synthesis of these compounds quite practical. Inhibition assays against β-glucosidase from almonds showed that only the *C*-1 derivative displayed modest to weak inhibitory behavior. Structural modification of the *C*-disaccharides to try and improve the inhibitory activity is a possible next step in the project. Application of the methodology in an iterative sense and to multiple simultaneous cyclizations is underway and will be reported in due course.

Acknowledgment. We are grateful to Professor Chuck Winter (WSU) for unlimited use of his glovebox. We thank Professor P. G. Wang for allowing us to carry out the inhibition assays in his laboratory and Professor Frederick Valeriote (Josephine Ford Health Center) for carrying out the *in vitro* differential cytotoxicity assays. We thank Professor Christopher Hadad (Ohio State University) for HRMS spectra and Dr. M. K. Ksebati (WSU) and Dr. L. Hryhorczuk (WSU) for assistance with NMR and mass spectral work, respectively. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society (#33075-G1) and the NSF (CHE-0132770), for partial support of this research.

Supporting Information Available: Experimental and spectral data listings for the major compounds, ^{1}H NMR spectra of **7a**−**k**, **8a**, **9a**, **9j**, **10a**−**k**, **19a**, **20a**, **22a**, **25a**, **25c**, **25d**, and **25f**, as well as details of the biological testing. This material is available free of charge via the Internet at http://pubs.acs.org.

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(43) Corbett, T. H.; Valeriote, F. A.; Polin, L.; Panchapor, C.; Pugh, S.; White, K.; Lowichick, N.; Knight, J.; Bissery, M.-C.; Wozniak, A.; LoRusso, P.; Biernat, L.; Polin, D.; Knight, L.; Biggar, S.; Looney, D.; Demchick, L.; Jones, J.; Jones, L.; Blair, S.; Palmewr, K.; Essenmacher, S.; Lisow, L.; Mattes, L. C.; Cavenaugh, P.; Rake, J.; Baker, L. In *Cytotoxic Anticancer Drugs: Models and Concepts for Drug Discovery and Development*; Kluwer Academic Publishers: Boston, MA, 1992; pp 35−87.