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Stereoselective Entry to β-Linked *C*-Disaccharides Using a Carbon-Ferrier Reaction

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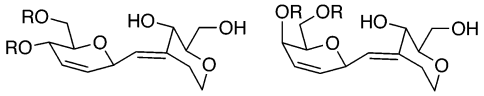
ABSTRACT



The synthesis of unsaturated β-linked *C*-disaccharides by the Lewis acid-mediated reaction of 3-*O*-acetylated glycals with monosaccharide-derived alkenes is described. Deprotection and selective hydrogenation of an exocyclic carbon–carbon double, in the presence of an endocyclic double bond, for representative targets is also illustrated.

The recognition that carbohydrates are involved in a whole range of biological processes has provoked both the desire to develop new methods for carbohydrate synthesis[1] and the investigation of carbohydrates as therapeutic agents.[2] For example, carbohydrates have received synthetic interest as disease-associated targets that may prove to be of use for vaccination programs.[3] Carbohydrate analogues have also been identified as useful glycosidase inhibitors, and as such have proved to be of use in therapeutic strategies for the treatment of cancer, AIDS, and diabetes.[4] Such studies have, however, identified a clear need for carbohydrate analogues that directly mimic natural *O*-linked carbohydrates and offer enhanced hydrolytic stability. In this respect, *C*-linked carbohydrates have been suggested as useful synthetic targets. A number of methods are available in the literature for synthesizing *C*-linked glycosides, with some reports detailing entry to *C*-linked disaccharides.[5] As part of a research program aimed at synthesizing functionalized *C*-linked disaccharides, we were interested in synthesizing unsaturated *C*-linked disaccharides that would offer a scope for further functionalization to allow introduction of hydroxyl or amine substituents, as well as hydrogenation to afford saturated *C*-linked disaccharides. Previous reports[6] had illustrated that cyclohexene derivatives could be used as nucleophilic components for carbon-Ferrier reactions[7] with C-3-*O*-acetylated glycals. We were therefore keen to ascertain whether this approach could be extended to incorporate carbohydrate-derived alkenes to potentially allow access to *C*-linked disaccharides.

At the start of this program, alkene **2** was selected as a suitable target that may allow entry to 1,3-*C*-linked disaccharides, upon reaction with a glycal, under Lewis acidic conditions. Ketone **1** served as a key precursor to alkene **2**, via reaction with an instant ylid reagent. The ketone was itself easily prepared from methyl-α-D-mannopyranoside via a two-step procedure (Scheme 1).[8]

It is interesting to note that there is no single universal approach for performing the Ferrier rearrangement.[7] A variety of promoters have been documented for effecting this rearrangement, and indeed a number were studied by us in this research program to potentially effect reaction between alkene **2** and glycal **3**. Use of $SnCl_4$, $SnBr_4$, TMSOTf, or $InCl_3$ as a promoter formed a complex mixture of products,

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(1) For examples of recent reviews, see: (a) Dwek, R. A.; Butters, T. D. *Chem. Rev.* **2002**, *102*, 283. (b) Bertozzi, C. R.; Kiessling, L. L. *Science* **2001**, *291*, 2357. (c) Seitz, O. *Chem. Biochem.* **2000**, *1*, 215.

(2) Koeller, K. M.; Wong, C.-H. *Nature Biotech.* **2000**, *18*, 835.

(3) Ragupathi, G.; Coltart, D. M.; Williams, L. J.; Kiude, F.; Kagan, E.; Allan, J.; Harris, C.; Glunz, P. W.; Livingstone, P. O.; Danishefsky, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 13699.

(4) For example, see: Lillelund, V. H.; Jensen, H. H.; Liang, X. F.; Bols, M. *Chem. Rev.* **2002**, *102*, 515.

(5) For some reviews, see: (a) Beau, J. M.; Gallagher, T. *Topics Curr. Chem.* **1997**, *187*, 1. (b) Nicotra, F. *Topics Curr. Chem.* **1998**, *187*, 55.

(6) (a) de Raadt, A.; Stütz, A. E. *Carbohydr. Res.* **1991**, *220*, 101. (b) Herscovici, J.; Muleka, K.; Boumaiza, L.; Antonakis, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1995.

(7) For a recent review of the Ferrier reaction, see: Ferrier, R. J. *Topics Curr. Chem.* **2001**, *215*, 153.

(8) Horton, D.; Werckle, W. *Carbohydr. Res.* **1975**, *44*, 227.

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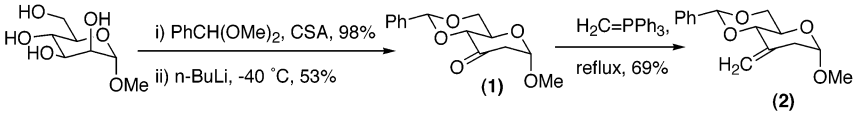
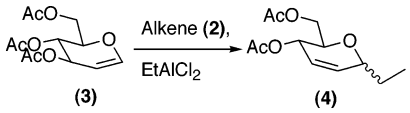
Scheme 1



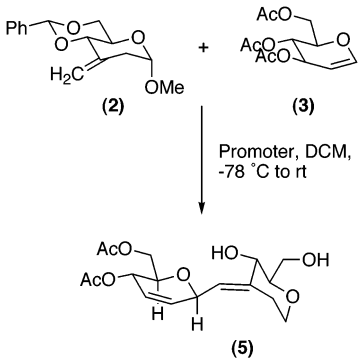
and use of $EtAlCl_2$ only succeeded in forming 2,3-dideoxy *C*-glycoside **4** in 30% yield (Scheme 2).

Scheme 2



More useful results, however, were obtained when $BF_3 \cdot OEt_2$ or I_2 was used to effect reaction. In these cases, the desired carbon-Ferrier reaction occurred between alkene **2** and glycal **3** to afford one predominant *C*-linked disaccharide (**5**) (Scheme 3, Table 1). Careful characterization of this

Scheme 3



target illustrated that the reaction conditions had also served to effect one-pot deprotection of the 4,6-*O*-benzylidene acetal and in situ reduction of the anomeric acetal. NOE studies confirmed that the newly formed *C*-linkage adopted the β-configuration, since a positive interaction was evident between H-1 and H-5 of the 2,3-dideoxy-4,6-di-*O*-acetyl component of the target.

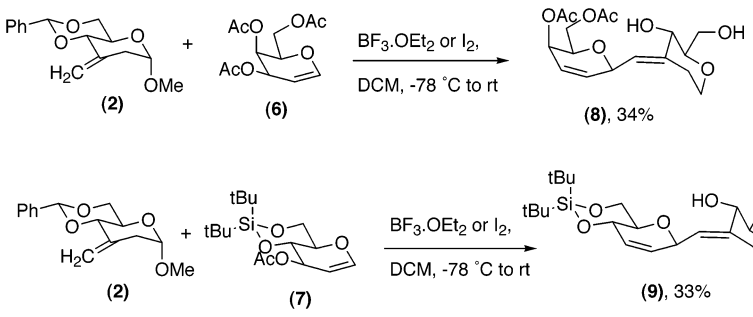
Table 1.

equiv of **2**	equiv of **3**	lewis acid	yield of **5** (%)
1	1	$BF_3 \cdot OEt_2$	22
1	2	$BF_3 \cdot OEt_2$	45
1	1	I_2	25
1	2	I_2	55

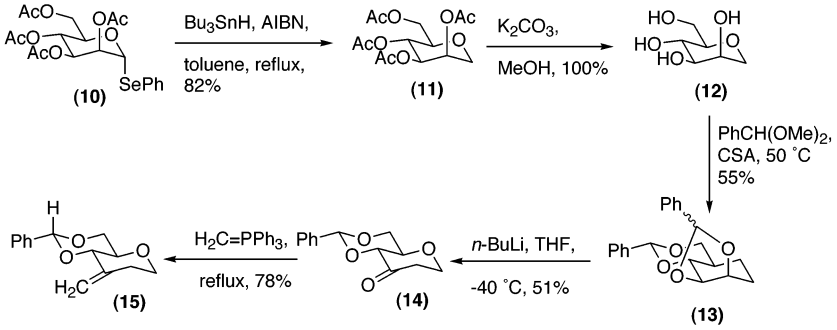
Optimum conversion yields were obtained when alkene **2** and glycal **3** were used in a ratio of 1:2. Cleavage of the anomeric acetal affords 1 equiv of methoxide, which subsequently undergoes Ferrier reaction with 1 equiv of glycal. Therefore, to ensure that sufficient glycal remains for the desired carbon-Ferrier reaction, it is essential that 2 equiv is introduced at the onset of the reaction. Use of more equivalents of glycal only served to promote self-condensation of the glycal, affording more complex mixtures of products. The oxonium ion formed by cleavage of the acetal is quenched by addition of hydride to form the C-1 deoxy *C*-linked disaccharide. It is postulated that hydride is generated by transfer from the benzylidene acetal protecting group, in a process analogous to that reported previously for hydride transfer from benzyl ethers.[9] This then destabilizes the benzylidene acetal, leading to its subsequent removal.

Two additional glycal donors **6** and **7**[10] were also utilized for the carbon-Ferrier reaction with alkene **2**. Pleasingly, both glycals allowed entry to the 1-deoxy *C*-linked disaccharides **8** and **9**, respectively, in moderate synthetic yield (Scheme 4).

Scheme 4



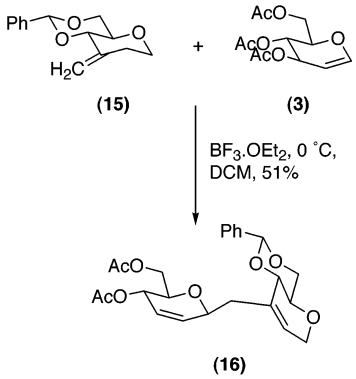
Scheme 5



In an effort to probe the proposed mechanism for the removal of the 4,6-*O*-benzylidene and anomeric acetal functionalities and also improve the efficiency of the reaction, 1-deoxy alkene **15** was selected as an alternative alkene acceptor. Since this alkene did not contain an anomeric acetal functionality, there was no opportunity for the competing *O*-Ferrier reaction to occur with glycal **3**. It was therefore anticipated that only stoichiometric equivalents of the glycal donor would be needed for efficient reaction. Entry to the desired alkene **15** proved to be possible from phenyl selenide **10**[11] as outlined in Scheme 5.

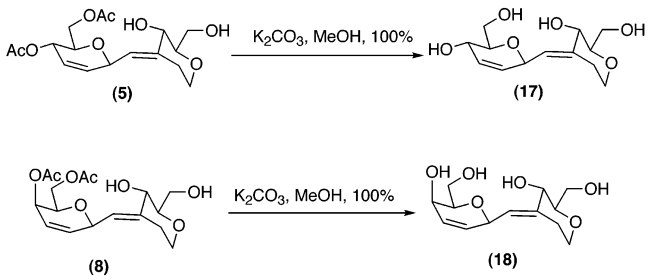
Removal of the phenyl selenide functionality was easily achieved in excellent yield under homolytic conditions to afford 1-deoxy derivative **11**.[12] Deprotection of the acetate esters and reprotection of tetrol **12** thus formed with benzaldehyde dimethyl acetal under acidic conditions then furnished dibenzylidene acetal **13** as a mixture of diastereoisomers in 55% yield over two steps. Treatment of the diastereomeric mixture with *n*-BuLi at low temperatures then afforded C-3 ketone **14** in 51% yield. Conversion to the desired 1-deoxy C-3 alkene **11**, via reaction with a phosphorus ylid, proceeded smoothly in 78% yield. Incorporation of this alkene within the carbon-Ferrier reaction, with 1 equiv of glucal **3** allowed entry to the desired *C*-linked disaccharide **16** in 51% yield (Scheme 6). In this case, and in contrast to the reaction with alkene **2**, the benzylidene group proved to be stable to the reaction conditions, the alkene functionality within disaccharide **16** was endocyclic, and rotamers existed for the *C*-linked disaccharide. The two latter observations are presumably due to extra steric constraints presented by incorporation of the benzylidene acetal within disaccharide **16**.

Scheme 6



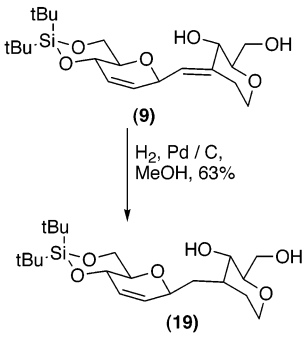
Having established that this approach was feasible for entry to *C*-linked disaccharides, we next turned our attention to performing further synthetic manipulations on some representative *C*-linked disaccharide targets. Pleasingly, it proved to be possible to effect total deprotection of the acetylated targets **5** and **8** to afford disaccharides **17** and **18**, respectively, in quantitative yield, upon exposure to potassium carbonate in methanol (Scheme 7).

Scheme 7



Interestingly, it also proved to be possible to effect hydrogenation of the exocyclic alkene of disaccharide **9**, in

Scheme 8



the presence of the endocyclic double bond, to afford *C*-linked disaccharide **19** in 63% yield (Scheme 8).

Further elaboration of the *C*-linked targets is currently being investigated within our laboratories. Further work is also in progress to synthesize and incorporate a wider range of carbohydrate-derived alkenes within the above protocol to potentially allow access to a greater variety of *C*-linked disaccharides.

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(10) Hoberg, J. O. *Carbohydr. Res.* **1997**, *300*, 365.
(11) Randall, K. P.; Johnston, B. D.; Brown, P. N.; Pinto, B. M. *Carbohydr. Res.* **2000**, *325*, 253.
(12) Yamazaki, O.; Togo, H.; Yokoyama, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2891.

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Supporting Information Available: Experimental procedures for compounds **5**, **8**, **9**, and **16**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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