

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

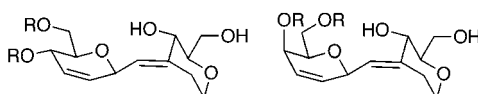
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ABSTRACT



The synthesis of unsaturated β -linked C-disaccharides by the Lewis acid-mediated reaction of 3-O-acetylated glycols 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 synthesis¹ 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 reports⁶ had illustrated that cyclohexene derivatives could be used as nucleophilic components for carbon-Ferrier reactions⁷ with C-3-O-acetylated glycols. 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 glycol, 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 glycol **3**. Use of SnCl₄, SnBr₄, TMSOTf, or InCl₃ 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.

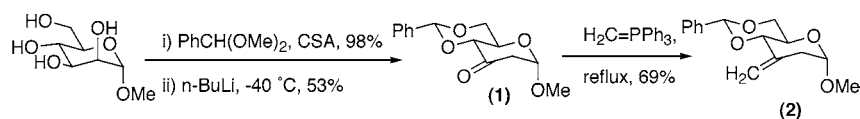
(5) For some reviews, see: (a) Beau, J. M.; Gallagher, T. *Topics Curr. Chem.* **1997**, *187*, 1. (b) Nicotra, F. *Topics Curr. Chem.* **1998**, *187*, 55.

(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.

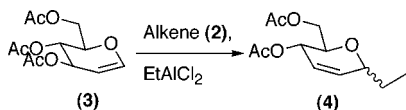
(8) Horton, D.; Werckle, W. *Carbohydr. Res.* **1975**, *44*, 227.

Scheme 1



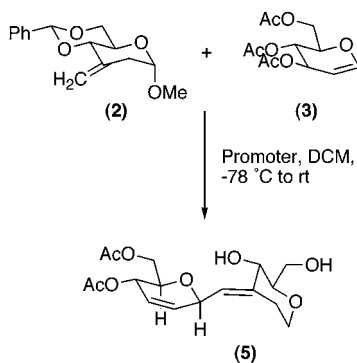
and use of EtAlCl_2 only succeeded in forming 2,3-dideoxy *C*-glycoside **4** in 30% yield (Scheme 2).

Scheme 2



More useful results, however, were obtained when $\text{BF}_3 \cdot \text{OEt}_2$ or I_2 was used to effect reaction. In these cases, the desired carbon-Ferrier reaction occurred between alkene **2** and glycol **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.

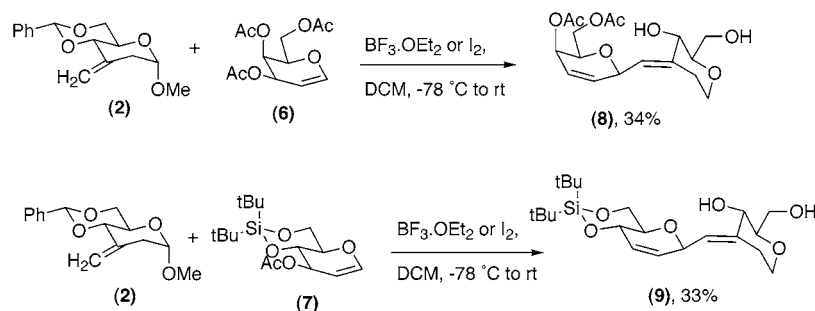
Table 1.

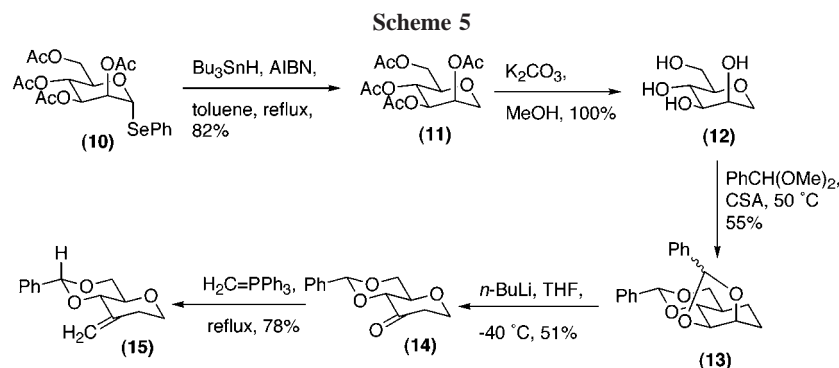
equiv of 2	equiv of 3	lewis acid	yield of 5 (%)
1	1	$\text{BF}_3 \cdot \text{OEt}_2$	22
1	2	$\text{BF}_3 \cdot \text{OEt}_2$	45
1	1	I_2	25
1	2	I_2	55

Optimum conversion yields were obtained when alkene **2** and glycol **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 glycol. Therefore, to ensure that sufficient glycol 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 glycol only served to promote self-condensation of the glycol, 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 glycol donors **6** and **7**¹⁰ were also utilized for the carbon-Ferrier reaction with alkene **2**. Pleasingly, both glycols allowed entry to the 1-deoxy *C*-linked disaccharides **8** and **9**, respectively, in moderate synthetic yield (Scheme 4).

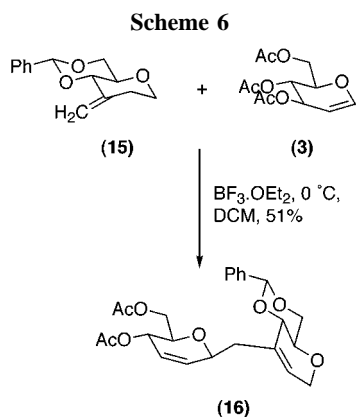
Scheme 4





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.

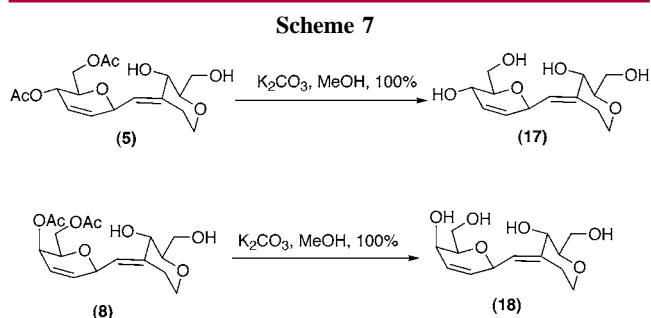
Removal of the phenyl selenide functionality was easily achieved in excellent yield under homolytic conditions to afford 1-deoxy derivative **11**.¹² Deprotection of the acetate esters and reprotection of tetrol **12** thus formed with benzaldehyde dimethyl acetal under acidic conditions then furnished 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



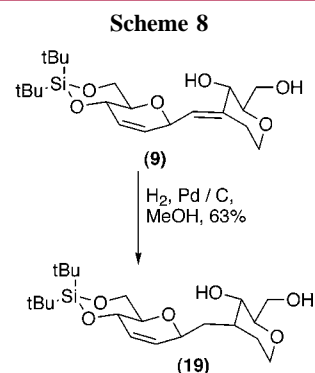
the reaction with alkene **2**, the benzylidene group proved to be stable to the reaction conditions, the alkene functionality

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**.

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).



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



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.

(9) Brimble, M. A.; Brenstrum, T. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1612.

(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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