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A Pd-Catalyzed Approach to (1→6)-Linked *C*-Glycosides

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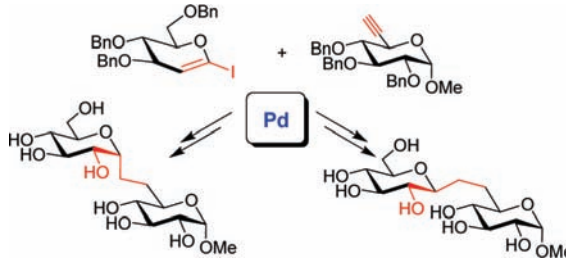
ABSTRACT



A flexible and robust method for the assembly of (1→6)-linked *C*-glycosidic disaccharides is presented. The key reaction is a Pd-catalyzed coupling of 1-iodo- or 1-triflato-glycals with alkynyl glycosides. Reinstallation of the native hydroxyl group pattern is achieved after selective hydrogenation of the triple bond using Raney-nickel. Epoxidation with DMDO and reductive epoxide opening gives access to either the α- or the *β*-derivative, depending on the hydride source.

Carbohydrates have become a major focus of current biological, biochemical, and medicinal research.[1] Besides their hydrophilicity and complexity, a particular problem for the application of carbohydrates as drugs is the *in vivo* lability of the glycosidic bond. To address this issue stable mimetics have to be prepared. One possibility *inter alia* is the replacement of the anomeric oxygen by carbon functionalities to provide carbohydrate mimetics that are called *C*-glycosides.[2] Aryl *C*-glycosides are often found in natural products;[3] however, *C*-glycosidic bonds between monosaccharide units are only rarely found in nature. In recent decades several synthetic approaches to access *C*-glycosidic bonds have been developed.[4,5] The stability of such compounds against hydrolysis, acids, and especially enzymatic degradation makes their synthesis and biological evaluation an interesting journey in the realm of medicinal chemistry.[6]

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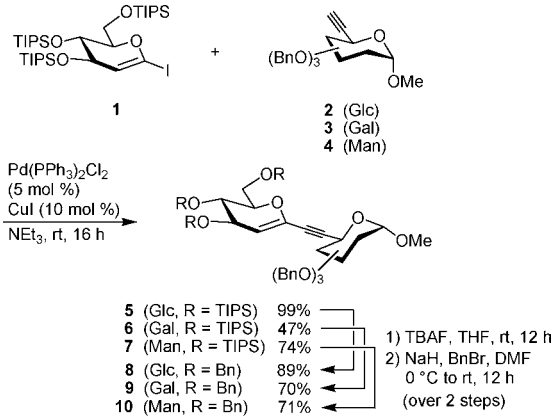
Therefore, a flexible and robust approach for the assembly of a variety of *C*-glycosides (α- and *β*-anomers) starting from relatively simple building blocks would be highly desirable. In this communication we present our recent studies that address this issue with respect to the (1→6)-linkage.

We made use of Pd-catalyzed coupling reactions in assembling the subunits, these being appropriately functionalized monosaccharide building blocks. The two coupling partners, the 1-iodoglycal **1** and the alkynyl glycosides (**2**−**4**), underwent Sonogashira−Hagihara-type reaction to afford the pseudodisaccharides **5**−**7** (Scheme 1).

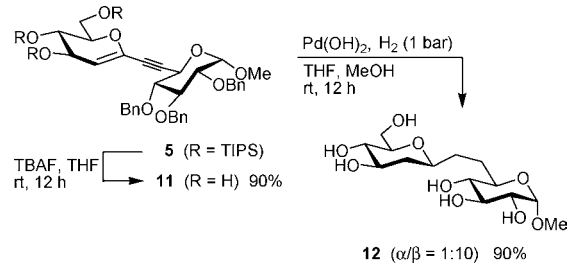
Scheme 1. Sonogashira−Hagihara Reaction for the Synthesis of *C*-Glycosidic Pseudodisaccharides **5**−**7**



Iodoglucal **1** can easily be prepared starting from D-glucose according to methods well documented in the literature.[7] The 6-alkynyl glycoside derivatives were synthesized in one step under Ohira−Bestmann conditions from the respective aldehydes.[8] The coupling reaction that produces **5**−**7** occurs under standard Sonogashira conditions in good to excellent yield (Scheme 1). As alkynyl components congeners with *gluco*-, *galacto*-, and *manno*-configuration were used.[9]

The enyne system in the respective pseudodisaccharides opens up several possibilities for further transformation. Whereas a complete reduction would afford a (1→6)-linked 2-deoxy-*C*-glycoside, a reduction of the alkyne moiety followed by an oxidative−reductive functionalization of the double bond would produce the respective *C*-glycosidic disaccharide with the native hydroxyl group pattern. With **5** we performed a cleavage of the TIPS groups by using TBAF as fluoride source. Afterward a hydrogenation of the enyne system together with a deprotection of the Bn groups yielded the (1→6)-linked 2-deoxy-*C*-glycoside **12**. The reaction under a hydrogen atmosphere using Pearlman's catalyst proceeded smoothly in a highly substrate-controlled fashion to afford **12** in an α/*β* ratio of 1:10 (Scheme 2).

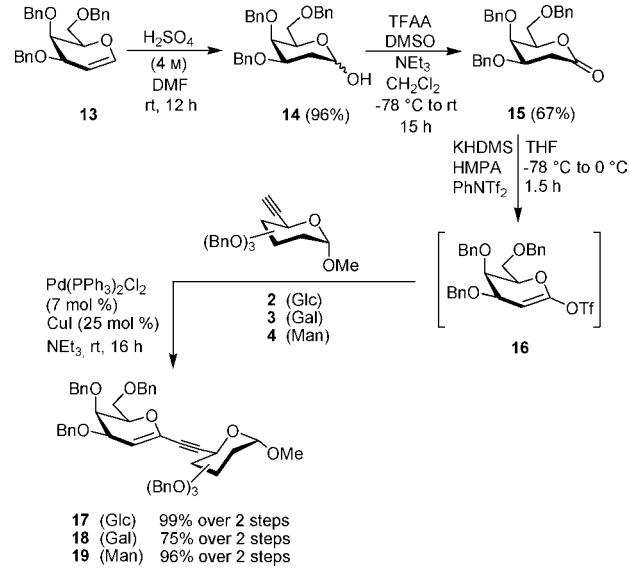
Scheme 2. TIPS Deprotection and Hydrogenation of **5** To Yield (1→6)-Linked 2-Deoxy-*C*-glycoside **12**



We next explored the scope of this approach in accessing (1→6)-linked *C*-glycosides. Attempts to prepare the unknown 1-iodogalactals were fruitless. For this, we had examined lithiation of the anomeric carbon and subsequent iodination of the intermediate carbanion. However, for silylated galactals this procedure resulted in some decomposition.[10] Therefore, we investigated the viability of the process with triflates as electrophiles in the coupling reaction.

The corresponding galactal triflate **16** could be prepared in excellent yield via an acid-mediated addition of water to the perbenzylated galactal **13**, yielding an α:*β*-mixture of the hemiacetal **14**.[11] Subsequent oxidation to the lactone under modified Swern conditions,[12] followed by the final transformation of the corresponding enolate with $PhNTf_2$,[13] gave rise to the respective triflate **16** (Scheme 3). Because

Scheme 3. Synthesis of the Galactal Triflate and Subsequent *in Situ* Cacchi Coupling To Yield **17**−**19**



of concerns regarding the stability of these compounds, they were not isolated but coupled *in situ* with a variety of

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(10) We assume that in the case of the galactal a deprotonation at the C-4 followed by subsequent ring opening occurs. The proton H-4 is acidified due a parallel arrangement of the C4-H and the C5-O bonds.
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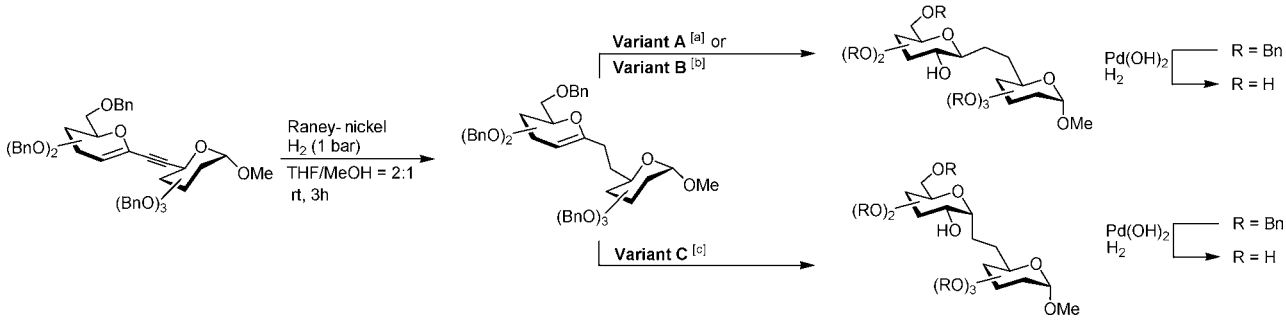
Table 1. Synthesis of *C*-Glycosidic Disaccharides



entry	enyne	enol ether	*C*-glycosidic disaccharide
1	**8**	**20** (84%)	**21** (R = Bn) 53%[a]; **22** (R = H) 99%
2	**10**	**23** (80%)	**24** (R = Bn) 67%[a]; **25** (R = H) 99%
3	**9**	**26** (61%)	**27** (R = Bn) 52%[b]; **28** (R = H) 99%
4	**8**	**20** (84%)	**29** (R = Bn) 67%[c]; **30** (R = H) 99%
5	**10**	**23** (80%)	**31** (R = Bn) 56%[c]; **32** (R = H) 81%
6	**19**	**33** (75%)	**34** (R = Bn) 69%[b]; **35** (R = H) 99%
7	**18**	**36** (38%)	**37** (R = Bn) 63%[b]; **38** (R = H) 99%

[a] **Variant A:** 1) DMDO, CH_2Cl_2, -78 °C to 0 °C, 30 min 2) DIBAL, CH_2Cl_2, -78 °C, 1 h

[b] **Variant B:** 1) $BH_3 \cdot$ THF, THF, 0 °C to rt, 12 h 2) H_2O_2, NaOH, 2 h

[c] **Variant C:** 1) DMDO, CH_2Cl_2, -78 °C to 0 °C, 30 min 2) $LiBHEt_3$, THF, 0 °C, 3 h

different glycosyl alkynes to yield the desired pseudodisaccharides **17**−**19**.[5] In order to reinstall the native hydroxyl group pattern, we became interested in the behavior of the enyne system with respect to oxidation and reduction. Attempts to epoxidize the electron-rich double bond without affecting the triple bond proved to be unsuccessful. In contrast, a screening of various hydrogenation catalysts revealed that Raney-nickel under hydrogen atmosphere was able to reduce the triple bond much faster to an ethano unit than it affected the more electron-rich double bond. Encouraged by this result, we further tried to optimize the reaction conditions in order to obtain only the enol ether system and not the fully reduced disaccharides. Finally, a mixture of MeOH and THF (2:1) and a reaction time of about 3 h under an atmosphere of hydrogen proved to be the best choice for effecting the desired transformation (Table 1).

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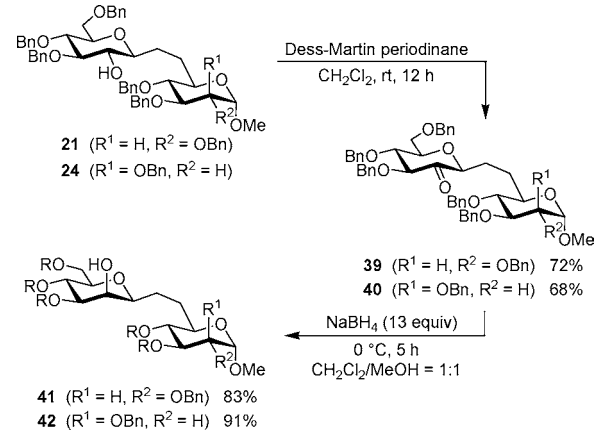
Having reduced the triple bond of the enyne system selectively, the remaining enol ether was targeted for reinstallation of the native hydroxyl group pattern. Formally a regio- and diastereoselective addition of water to the enol ether was needed. Studies with different borane complexes revealed that hydroboration with BH_3·THF diastereoselectively gave access to β-configured *gluco* products (Table 1, entries 3, 6, and 7).[14] However, we sought a method that would allow for the formation of both α- and β-configured pseudoanomeric centers, depending only on the reagents used. For unsubstituted glycals dimethyldioxirane (DMDO) is the reagent of choice to convert these compounds into *gluco*-configured glycosyl building blocks.[15] Therefore, we tested the DMDO-mediated epoxidation with our compounds as well. Indeed, high facial selectivity in favor of the *gluco* configuration (>20:1) was observed. We were optimistic that the epoxide opening by a hydride would afford only α- or β-configured pseudoanomeric centers, which could be adjusted by the right choice of the hydride source.

First we elucidated the potential of DIBAL as a hydride transfer reagent.[16] We anticipated the formation of β-products due to coordination of the aluminum with the epoxide oxygen and resulting hydride transfer from the same side (Table 1, entries 1 and 2). By contrast, the use of superhydride ($LiBHEt_3$) exclusively led to installation of the α-linkage.[17] As a result of its high nucleophilicity, an S_N2-type ring opening of the three-membered ring occurs. With these methods in hand a variety of (1→6)-linked *C*-glycosides were created (Table 1). Global deprotection to afford the disaccharide mimetics was performed in almost quantitative yield by using a hydrogen atmosphere and Pearlman' s catalyst (Table 1). The stereochemistry of the products was confirmed by HOMO-decoupling NMR experiments (see Supporting Information).

The epoxidation procedure with DMDO led only to *gluco*-configured products. Because of the highly sensitive acetalic epoxide that is formed, acidic or basic epoxidation reagents that might lead to a different facial selectivity are not suitable. Therefore, we employed a well-known trick to convert glucose moieties into mannose moieties.[18] An oxidation of the newly formed 2-hydroxyl group of **21** or **24**, respectively, with Dess−Martin periodinane (DMP) to the respective ketone **39** or **40** and subsequent diastereoselective reduction by sodium borohydride afforded the *C*-glycosidic β-mannoses **41** or **42** (Scheme 4). The chiral induction resulted exclusively from the substrate.[19]

Scheme 4. Synthesis of *C*-Glycosidic β-Mannosides



In summary, we have developed a robust and flexible approach for the synthesis of various (1→6)-linked *C*-glycosidic disaccharides starting from appropriately functionalized monosaccharide building blocks. The key to our sucess was a Pd-catalyzed coupling of an 1-iodo or 1-triflato glycal with an alkynyl glycoside. Further transformation of the resulting enyne system provides access to α- and β-configured *C*-glycosidic disaccharides, as well as 2-deoxy-*C*-glycosides. Extension of this approach to other *C*-glycosidic bonds such as (1→4)-linkages using different Pd-mediated coupling reactions is in progress.

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Supporting Information Available: Experimental procedures, spectroscopic data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Attempts to reduce the corresponding ketone arising from the corresponding α-derivative (see **39**α in Supporting Information) led back to the starting material indicating an inverted chiral induction.