Carbohydrate Mimics

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Flexible Synthesis of 2-Deoxy-*C*-Glycosides and (1→2)-, (1→3)-, and (1→4)-Linked *C*-Glycosides**

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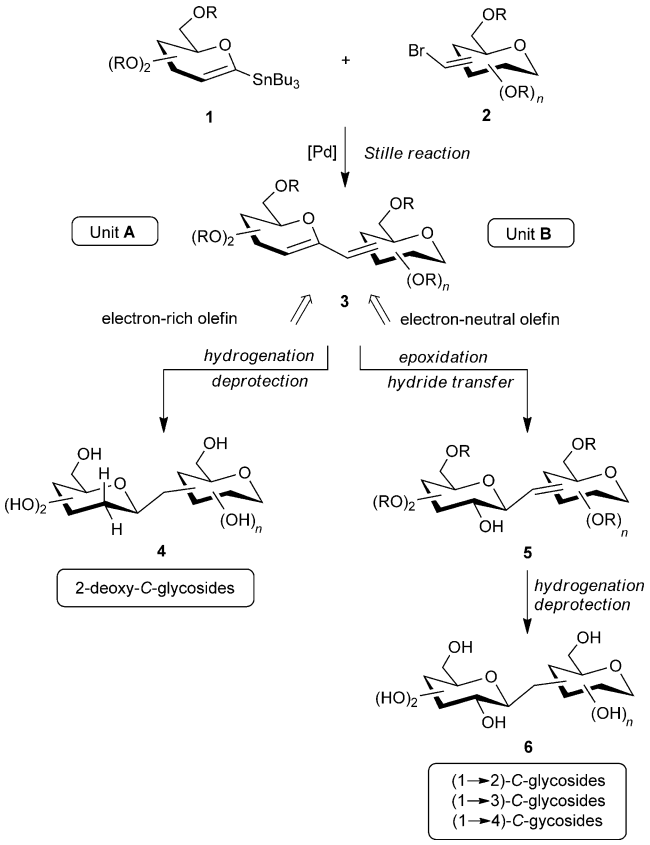
C-Glycosides are an important class of carbohydrate mimics.[1] In these compounds the monosaccharide units are linked by a methylene unit instead of an oxygen atom, rendering the disaccharide highly stable towards enzymatic and chemical hydrolysis. The conformational differences between *C*- and *O*-glycosides have been the subject of debate in the recent past because of the absence of *exo* and *endo* anomeric effects in *C*-glycosides; however, a general conclusion cannot be drawn to date.[2] The difficulties associated with the synthesis of a *C*-glycosidic bond between two monosaccharide moieties are readily apparent. Several groups have addressed the synthesis of such structures in the past decade.[3] Typically, methods have been developed only for specific linkages[4,5] or have required elaborate building blocks. Thus, a modular and robust approach for the synthesis of a variety of different *C*-glycosidic linkages would be of high synthetic and biochemical interest. Recently, we reported a Sonogashira reaction to promote the synthesis of α- and β-linked (1→6)-*C*-disaccharides.[3a] Herein we focus on the preparation of more challenging *C*-glycosidic bonds and present a strategy to build α- and β-linked (1→2)-, (1→3)-, and (1→4)-*C*-disaccharides.

Our approach relies on the use of two monosaccharide units. Starting from 1-stannylglucal **1** and exocyclic bromo-olefins **2**, a Stille cross-coupling would generate pseudo-disaccharides **3** bearing a diene subunit (Scheme 1). The diene subunit consisting of an endocyclic electron-rich and an exocyclic less-electron-rich double bond sets the stage for several functionalization reactions. A global reduction leads to (1→*n*)-linked 2-deoxy-*C*-glycosides of type **4**, whilst an oxidative–reductive functionalization of the endocyclic enol ether would regenerate the native hydroxy group pattern of the monosaccharide unit **A** (generation of **5**). A further reduction of the remaining exocyclic double bond forms the methylene bridge between the two monosaccharide units and completes the sequence. In the case of the (1→*n*)-linked



Scheme 1. Modular approach for the synthesis of 2-deoxy-*C*-glycosides and (1→2)-, (1→3)-, and (1→4)-linked *C*-disaccharides.

2-deoxy-*C*-glycosides **4** two stereocenters are generated. In the synthesis of *C*-disaccharides **6** from dienes **3** three stereocenters are installed, making the approach relatively flexible in establishing the stereochemical configuration at these centers.

1-Stannylglycals of type **1** are readily synthesized according to established methods.[6] Exocyclic olefins **2** were generated from the corresponding ketones by a Wittig-type reaction using the phosphorus ylide Ph_3PCHBr. However, the bromo-substituted double bond in position 2 of the monosaccharide was preferentially obtained by means of a halocyclopropanation of the respective glycals followed by the opening of the three-membered ring.[7,8]

The subunits **1** and **2** were cross-coupled under standard Stille conditions (Scheme 2).[9] As carbohydrate building blocks, glucose-, galactose-, mannose-, and allose-based systems were employed. Despite steric hindrance pseudo-disaccharides **3** were synthesized in good yields ranging from 63% to 88%. The galactose- and mannose-based building

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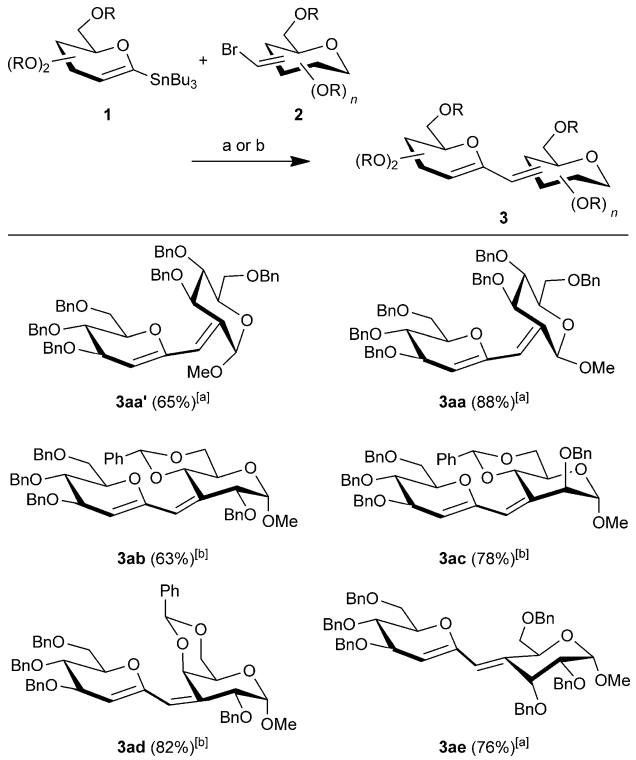
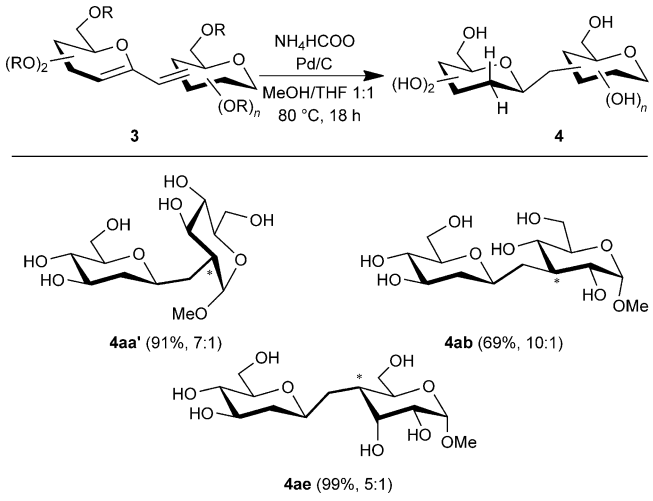


Scheme 2. Stille coupling of **1** and **2** to access (1→2)-, (1→3)-, and (1→4)-linked *C*-glycosidic pseudodisaccharides **3**. Reagents and conditions: a) **1** (1.0 equiv), **2** (1.05 equiv), [Pd(PPh$_3$)$_4$] (10 mol%), CuI (0.4 equiv), LiCl (2.5 equiv), DMF, 80 °C, 5.5–18 h. b) **1** (1.0 equiv), **2** (1.05 equiv), [Pd(PPh$_3$)$_4$] (10 mol%), MeCN/NMP (10:1), 95–105 °C, 6–14 h.

blocks proved to be superb coupling partners for 1-stannylglucal.

For a rapid and flexible route to (1→*n*)-linked 2-deoxy-*C*-disaccharides **4**, dienes **3** were subjected to a transfer hydrogenation with ammonium formate and Pd on charcoal (Scheme 3).[10] Such conditions provided 2-deoxy-*C*-disaccharides with all conceivable linkages. The use of different heterogeneous catalysts as well as the application of molecular hydrogen not generated in situ did not result in the desired *C*-disaccharides. Although in all cases four stereoisomers have to be considered, we observed high substrate-induced diastereoselectivity. Only two diastereomers in ratios from 5:1 to 10:1 were detectable by NMR analysis. The obtained products **4** have been characterized by 2D-NMR and NOESY methods (see the Supporting Information).

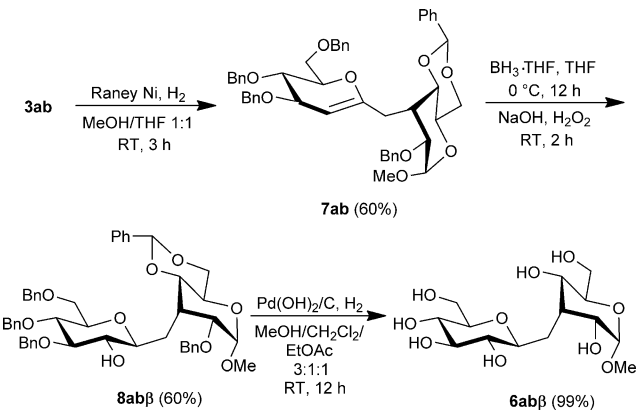


Scheme 3. Synthesis of (1→*n*)-linked 2-deoxy-C-disaccharides **4** (*n* = 2, 3, 4).

In principle there are two conceivable strategies to access the native hydroxy-group pattern starting from **3**. The first approach is a reductive–oxidative refunctionalization in which first the less-electron-rich exocyclic double bond is reduced and then the endocyclic enol ether oxidized to regenerate the native hydroxy-group pattern of the carbohydrate. The second possibility is an inversion of this sequence, first oxidizing the enol ether and then reducing the exocyclic double bond to build the methylene bridge linking the two monosaccharide units.

Recently, we found the reductive–oxidative approach to be superior in the synthesis of (1→6)-*C*-disaccharides and therefore we decided to pursue the first approach.[3a] However, pivotal differences cannot be ignored. In contrast to (1→6)-linkages, the synthesis of (1→2)-, (1→3)-, and (1→4)-linkages requires a diene subunit, which in terms of electronics differs from the enyne motif employed in the prior case. A further major difference is that the reduction of the exocyclic double bond generates a stereocenter, whereas in the reduction of the exocyclic alkyne in (1→6)-*C*-disaccharides there are no diastereoselectivity issues.

In our initial experiments we tried a Raney nickel catalyzed reduction which had proved successful in the synthesis of (1→6)-*C*-disaccharides.[3a] The application of this heterogeneous catalyst in combination with molecular hydrogen afforded **7ab** in good yield (Scheme 4). We found the diastereoselectivity to be surprisingly high and only the *allo* configuration could be detected at C-3. A subsequent hydroboration[3h,4g,11] led to the β-*C*-disaccharide in moderate yield and high diastereoselectivity. However, this strategy could not be transferred to other systems and we found a reduced enol ether as the product of the first step. Hence, we had to pursue the second strategy.

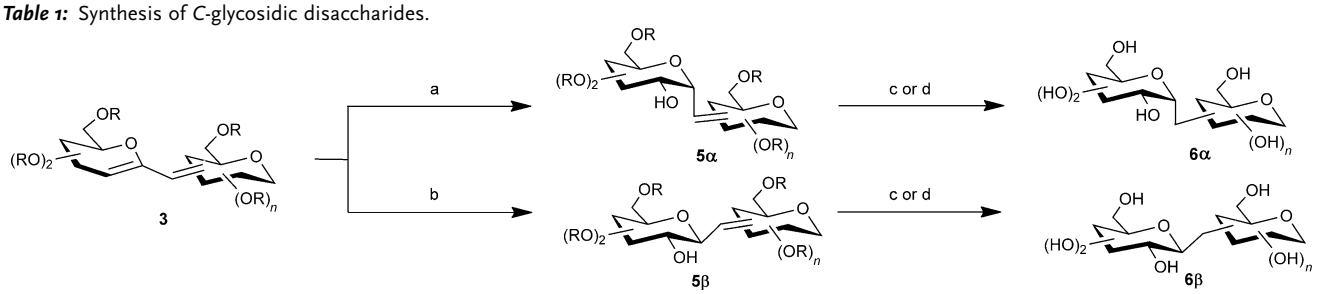


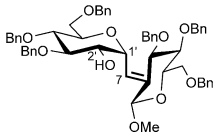
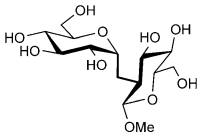
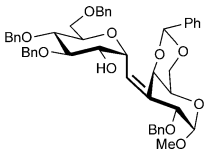
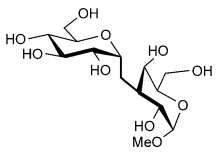
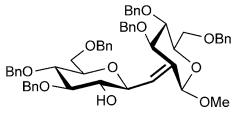
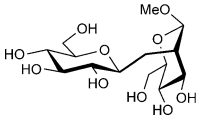
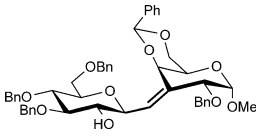
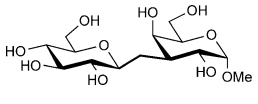
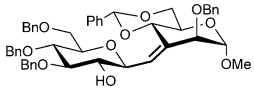
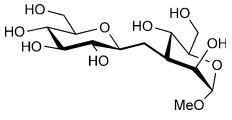
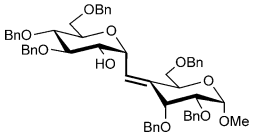
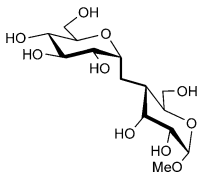
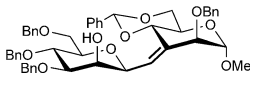
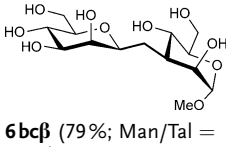
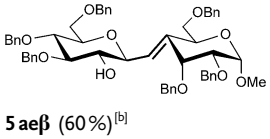
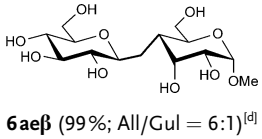
Scheme 4. Refunctionalization of diene **3ab** by means of a reduction–oxidation sequence and subsequent deprotection to yield **6abβ**.

The new strategy relies on the refunctionalization of the enol ether as the first step. To prove the viability of this approach we initially examined the epoxidation of the (1→3)-linked *C*-disaccharide **3ac**. We found conditions that yielded high chemo- and diastereoselectivity (Table 1, entry 3). The utilization of only one equivalent of dimethyldioxirane (DMDO) at −78 °C led to complete control of chemoselectivity: exclusively the enol ether double bond was attacked. The epoxidation with DMDO proceeds with high facial selectivity and solely leads to the *gluco*-configured carbohydrate framework (d.r. > 20:1).[12] In the subsequent ring-opening of the acetalic epoxide, the stereochemical configuration of the pseudoanomeric carbon can be adjusted by the choice of the nucleophilic hydride agent. Coordinating hydrides such as diisobutylaluminum hydride (DIBAL) set the stage for the β-anomer in high diastereoselectivities, whereas strongly nucleophilic hydride sources such as superhydride ($LiBHEt_3$) generated exclusively the α-product in an S_N2-type fashion.[3a,13,14]

Applying this strategy provides access to a variety of different α- and β-linked *C*-disaccharides (Table 1). Even under Shi conditions the generation of an epoxide with *manno* configuration proved not to be feasible. Thus, the newly generated 2-hydroxy group has to be inverted to prepare *manno*-configurated *C*-disaccharides. A Mitsunobu inversion failed, possibly because of high steric hindrance. To access β-linked mannosyl derivatives a two-step sequence can be employed. The oxidation of the 2-hydroxy group leads to a ketone that can be easily reduced with sodium borohydride[15] to obtain a β-*manno*-configurated *C*-disaccharide

Table 1: Synthesis of *C*-glycosidic disaccharides.



Entry	Diene	*C*-Glycosidic olefin	*C*-Disaccharide	Entry	Diene	*C*-Glycosidic olefin	*C*-Disaccharide
(1→2)-linked C-glycosidic disaccharides							
1	**3aa**			5	**3ad**		
		3aaα (61%)[a]	**6aaα** (99%; Glc/Man = 3:1)[c]			**5adα** (58%)[a]	**6adα** (99%; Gal)[d]
2	**3aa**			6	**3ad**		
		5aaβ (61%)[b]	**6aaβ** (99%; Glc/Man = 2:5)[c]			**5adβ** (53%)[b]	**6adβ** (75%; Gal/Gul = 7:1)[d]
(1→3)-linked C-glycosidic disaccharides				*(1→4)-linked C-glycosidic disaccharides*			
3	**3ac**			7	**3ae**		
		5acβ (79%)[b]	**6acβ** (99%; Man)[d]			**5aeα** (65%)[a]	**6aeα** (99%; All)[d]
4	**3ac**			8	**3ae**		
		5bcβ (50% over three steps)[b,e]	**6bcβ** (79%; Man/Tal = 4:1)[d]			**5aeβ** (60%)[b]	**6aeβ** (99%; All/Gul = 6:1)[d]

Reagents and conditions: [a] **3** (1.0 equiv), DMDO (1.0 equiv), CH_2Cl_2, −78 °C, 1 h, →0 °C, 20 min, $LiBHEt_3$ (15.0–40.0 equiv), THF, 0 °C, 3 h. [b] **3** (1.0 equiv), DMDO (1.0 equiv), CH_2Cl_2, −78 °C, 1 h, →0 °C, 20 min, DIBAL (5.0 equiv), CH_2Cl_2, −78 °C. [c] NH_4HCOO (10.0 equiv), Pd/C, MeOH/THF = 1:1, 80 °C, 1.5–3 h. [d] $Pd(OH)_2/C$, H_2, $MeOH/CH_2Cl_2/EtOAc = 3:1:1$, 25 °C, 18 h. [e] Inversion of the OH group for substrate **5acβ** over two steps: 1) DMP (5.0 equiv), CH_2Cl_2, 25 °C, 18 h; 2) $NaBH_4$ (18 equiv), $MeOH/CH_2Cl_2$ = 1:1, 0 °C, 3 h. DMP = Dess–Martin periodinane.

(Table 1, entry 4). The diastereoselectivity is controlled by chiral induction of the substrate.

The stereochemistry of *C*-glycosidic olefins **5** could be determined by analysis of the coupling constant of the pseudoanomeric proton 1′-H to 2′-H. The signal of proton 1′-H is a doublet of doublets, in which one coupling addresses 7-H and the other coupling addresses 2′-H (for designation of the protons, see Table 1, entry 1). The coupling constant to 7-H, which gives rise to a doublet with a characteristic chemical shift, is easily extracted; thus, the other coupling constant in the doublet of doublets results from the coupling to 2′-H. A large coupling constant of $J \geq 9$ Hz indicates a β-linkage, whilst $J \leq 4$ Hz suggests an α-configuration (for details see the Supporting Information).

The formed *C*-glycosidic olefins were subsequently reduced. Attempts to hydrogenate the exocyclic double bond with homogeneous catalysts such as Wilkinson's or Crabtree's catalyst were in vain, even at high pressure.[16] The heterogeneously catalyzed reduction with Raney nickel did not lead to the desired product under high pressure in a continuous-flow hydrogen reactor. Finally, promising results were obtained by using Pearlman's catalyst. The application of this catalyst has a major advantage in that the double bond is reduced and all of the protecting groups are removed simultaneously. In most cases we observed high selectivities in the formation of *C*-disaccharides **6**. The stereochemical configuration of the products was determined by careful analysis of the coupling constants and by 1D-NOESY experiments (see the Supporting Information). In the case of the (1→2)-linkage we again found the transfer hydrogenation to be the key to success.[10] We did not observe the desired *C*-disaccharides when we applied heterogeneous catalysis with molecular hydrogen not generated in situ.

In conclusion, we have reported a rapid and flexible entry to (1→2)-, (1→3)-, and (1→4)-*C*-disaccharides. The key step is a Stille-type reaction of the functionalized subunits, in which stannylglycals and exocyclic bromoolefins are employed as coupling partners. The resulting highly substituted diene system can be either completely reduced to 2-deoxy-*C*-disaccharides or refunctionalized in an oxidative–reductive manner to regenerate the native hydroxy-group pattern of the respective carbohydrate moiety. The reported approach should be applicable in the synthesis of complex oligosaccharides and glycoconjugates. The generation of amino sugars and the synthesis of more complex *C*-*O*-glycosides are under investigation in our laboratory.

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