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One-Pot Synthesis of Oligosaccharides by Combining Reductive Openings of Benzylidene Acetals and Glycosylations

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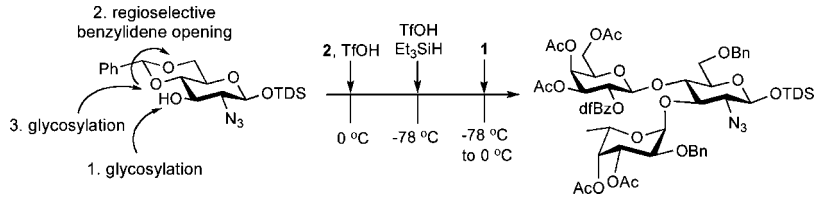
ABSTRACT



Combining triflic acid-promoted glycosylations of trichloroacetimidates with reductive opening of benzylidene acetals with triflic acid and triethylsilane as one-pot procedures provides access to a wide range of disaccharides and 2,4- and 3,4-branched trisaccharides.

Protein- and lipid-bound saccharides are ubiquitous in biological systems involved in many important molecular processes such as fertilization, embryogenesis, neuronal development, hormone activities, and the proliferation of cells and their organization into specific tissues.[1,2] These interactions are also important in health science and are involved in the invasion and attachment of pathogens, inflammation, metastasis, blood group immunology, and xenotransplantation.[3–5] A major obstacle to advances in glycobiology is the lack of pure and structurally well-defined carbohydrates and glycoconjugates. These compounds are often found in low concentrations and in microheterogeneous forms, greatly complicating their isolation and characterization. In many cases, well-defined oligosaccharides can only be obtained by organic synthesis.[6–9]

Although the methods for oligosaccharide synthesis have improved considerably during the past decade, the construction of complex carbohydrates remains a significant challenge due to the combined demands of elaborate procedures for glycosyl donor and acceptor preparation and the requirements of regio- and stereoselectivity in glycoside bond formation. To streamline the preparation of complex oligosaccharides, one-pot multistep approaches for selective monosaccharide protection and oligosaccharide assembly are being pursued, which do not require an intermediate workup and purification step and hence speed-up the process of chemical synthesis considerably.[10,11] For example, the observation that acetal formation, regioselective reductive opening of arylidene acetals, reductive etherification, and acetylation can be catalyzed by triflic acid (TfOH) or trimethylsilyl triflate (TMSOTf) made it possible to program these reactions in tandem by sequential addition of reagents to give easy access to a wide variety of selective protected monosaccharide building blocks. Furthermore, many laboratories have demonstrated that chemoselective, orthogonal and iterative gly-

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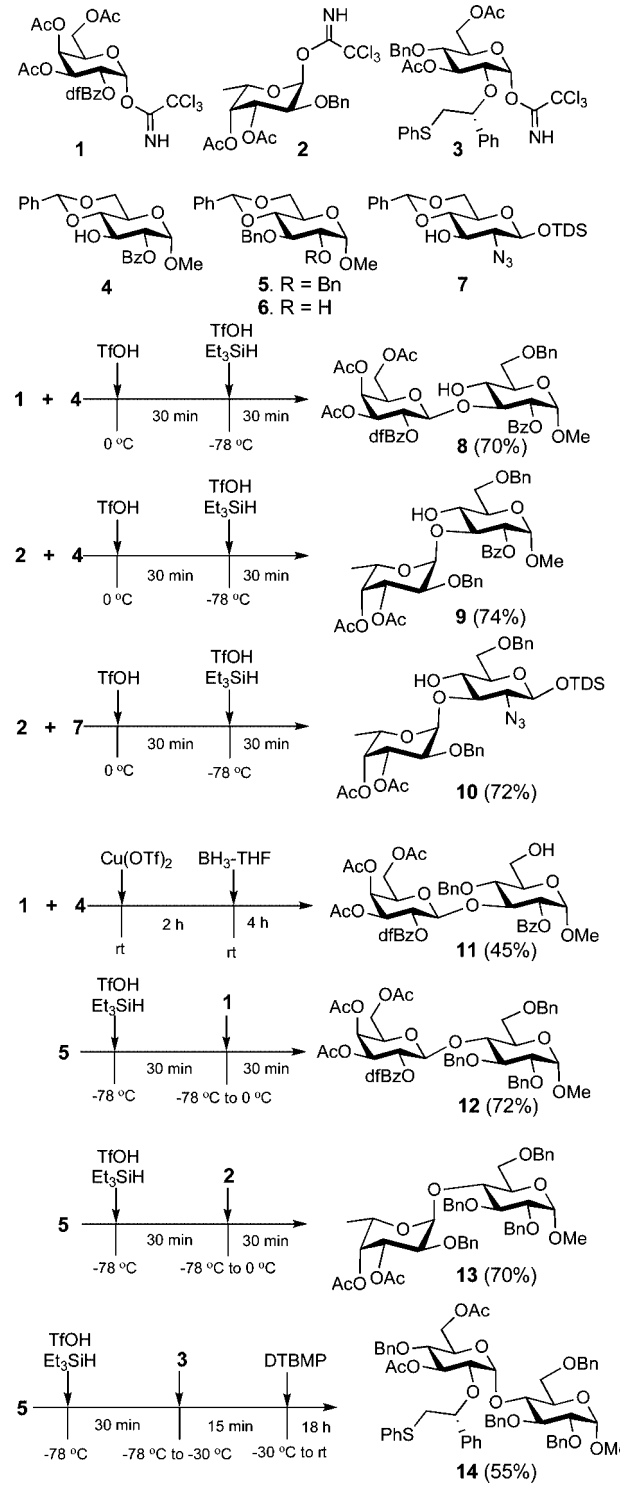
cosylation strategies, which exploit differential reactivities of anomeric leaving groups, allow several selected glycosyl donors to react in a specific order resulting in a single oligosaccharide product.[12–18]

Several reports have also shown that removal of silyl and trityl ethers can be combined with glycosylations.[19–22]

To further streamline the process of oligosaccharide assembly, we report here a strategy whereby a regioselective opening of a benzylidene acetal and glycosylations are combined in a one-pot multistep synthetic procedure (Scheme 1). The attraction of the approach is that it makes it possible to assemble branched oligosaccharides by a one-pot procedure, a task that cannot readily be accomplished by chemoselective, orthogonal, and iterative glycosylations. In this respect, differential reactivities of hydroxyls have been exploited for the synthesis of branched oligosaccharides by one-pot procedures[23–30] but the scope of this approach is limited because of the need of exceptional high regioselectivities.

Trichloroacetimidates were selected as glycosyl donors because their activation requires only catalytic TfOH or TMSOTf.[31] Furthermore, TfOH combined with triethylsilane (Et_3SiH) was employed for the opening of a 4,6-*O*-benzylidene acetals[32,33] because these conditions provide in general high regioselectivies and excellent yields, and furthermore it was anticipated that these reaction conditions would be compatible with TfOH mediated glycosylations of trichloroacetimidates.

Scheme 1. One-Pot Synthesis of Disaccharides by Glycosylation and Benzylidene Acetal Opening



Thus, a mixture of trichloroacetimidate **1**[34] (1.5 equiv) and benzylidene acetal protected glycosyl acceptor **4**[35] (1.0 equiv)

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in dichloromethane at 0 °C was treated with a catalytic amount of TfOH. After a reaction time of 30 min, TLC and MALDI-MS analysis indicated consumption of the starting material and the formation of the expected disaccharide. The reaction mixture was cooled to −78 °C followed by addition of TfOH (1.8 equiv) and Et_3SiH (2.0 equiv). After being stirred for 30 min at −78 °C, the reaction was quenched by the addition of triethylamine and methanol, and purification by silica gel column chromatography gave disaccharide **8** in a yield of 70%. As expected, only a *β*-galactoside was formed due to the presence of a 2,5-difluorobenzoyl group[36] at C-2 of the galactosyl donor **1**.[34] This protecting group is an excellent neighboring group participant and unlike benzoyl and pivaloyl esters can be cleaved under mild conditions by using a catalytic amount of sodium methoxide in methanol.

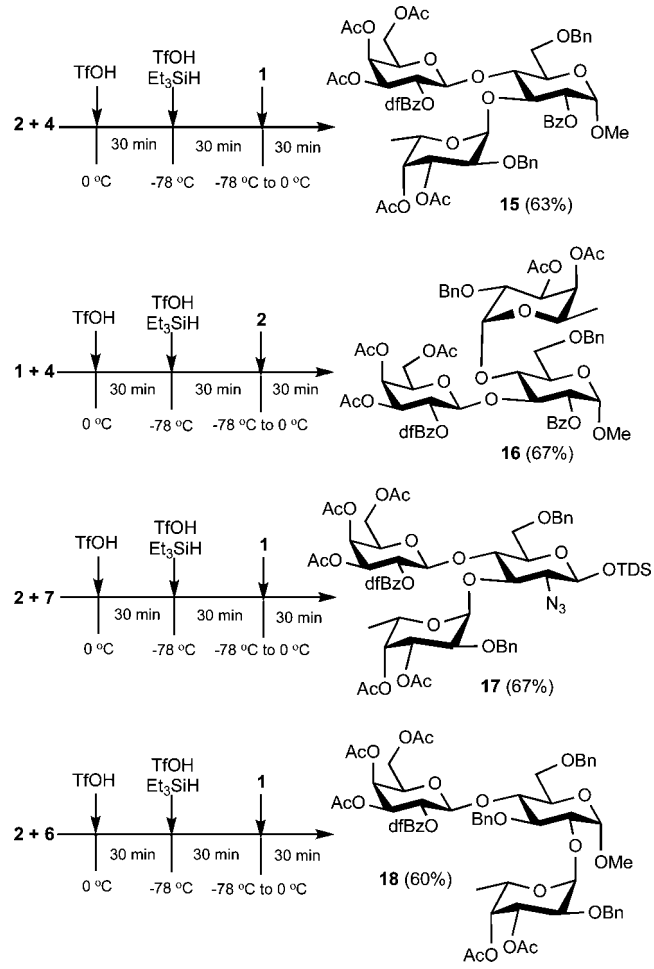
In the next set of experiments, the sequence of reactions was repeated; however, in this case the fucosyl donor **2**[37] was employed instead of **1**. Fortunately, disaccharide **9** was isolated in an overall yield of 74% as a single regio- and stereoisomer demonstrating that the methodology is compatible with acid-sensitive fucosides. It was also found that fucosylation of 2-azido-containing glycosyl acceptor **7**[38] followed by a regioselective opening of the benzylidene acetal, using standard conditions, of the resulting disaccharide led to the facile formation of disaccharide **10**.

It has been established that the regioselective ring opening of 4,6-*O*-benzylidene acetals can be reversed to provide saccharides with a free C-6 hydroxyl by employing $Cu(OTf)_2$ in combination with borane[39] instead of TfOH and Et_3SiH. Furthermore, it was anticipated that trichloroacetimidates can be activated by $Cu(OTf)_2$ and thus it may be possible to glycosylate the C-3 hydroxyl of **4** followed by a regioselective opening of the benzylidene acetal of the resulting product to give a disaccharide having a C-6 hydroxyl. Indeed, a $Cu(OTf)_2$ (0.15 equiv) mediated glycosylation of glucosyl donor **1** (1.5 equiv) with acceptor **4** (1.0 equiv) gave, after a reaction time of 2 h at room temperature, a disaccharide, which was treated with borane−THF complex (2.0 equiv) to provide after an additional 4 h of stirring at ambient temperature disaccharide **11** in a yield of 45%. In our efforts to improve the reaction yield, it was found that prolonged reaction times led to decomposition and formation of byproduct.

Next, attention was focused on a reaction sequence whereby a regioselective benzylidene acetal opening is followed by glycosylation. Thus, Et_3SiH (2.0 equiv) and TfOH (1.8 equiv) were added to a cooled (−78 °C) solution of compound **5** (1.0 equiv) in dichloromethane and after a reaction time of 30 min, glycosyl donor **1** or **2** (1.8 equiv) was added followed by gradually raising the temperature to 0 °C over a period of 30 min. Standard workup and purification by silica gel column chromatography gave regio- and stereoisomerically pure disaccharides **12** and **13**, respectively, in yields of 72% and 70%.

Recently, we demonstrated that glycosylations with glycosyl donors modified at C-2 with a (*S*)-(phenylthiomethyl)benzyl moiety give exclusively α-anomeric selectivity due to neighboring group participation resulting in an intermediate trans-fused 1,2-sulfonium ion.[40,41] To explore the possibility of a one-pot procedure involving benzylidine acetal opening and glycosylation with such a donor, compound **5**[42] (1.0 equiv) was treated with TfOH (1.8 equiv) and Et_3SiH (2.0 equiv) followed by subsequent addition of **3**[40] (1.8 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) (3.0 equiv) to give **14** as only the α-anomer.

Scheme 2. One-Pot Synthesis of Trisaccharides by Glycosylations and Benzylidene Acetal Opening



Next, we explored the possibility of synthesizing branched trisaccharides by a reaction sequence involving glycosylation,

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reductive benzylidene acetal opening, followed by another glycosylation (Scheme 2). Thus, a mixture of trichloroacetimidate **2** (1.5 equiv) and benzylidene protected glycosyl acceptor **4** (1.0 equiv) in dichloromethane at 0 °C was treated with a catalytic amount of TfOH. After a reaction time of 30 min, the reaction mixture was cooled to −78 °C followed by addition of TfOH (1.8 equiv) and Et_3SiH (2.0 equiv), and after a further reaction time of 30 min, galactosyl donor **1** (1.8 equiv) was added and the reaction mixture was allowed to warm to 0 °C over a period of 30 min, to give after standard workup and purification by silica gel column chromatography trisaccharide **15** in a yield of 63%. A similar procedure gave trisaccharide **16** by a glycosylation of **1** with **4**, followed by reductive opening of the benzylidene acetal and glycosylation of the resulting acceptor with fucosyl donor **2**. Furthermore, a TfOH-promoted glycosylation of 2-azido-2-deoxyglucoside **7** with **2** followed by benzylidene acetal opening with TfOH/Et_3SiH gave a disaccharide acceptor, which was glycosylated with galactosyl donor **1** to give protected Lewis^x trisaccharide **17** in an excellent yield of 67%. Removal of the anomeric thexyldimethylsilyl (TDS) protecting group of **17** followed by conversion of the resulting lactol into the leaving group provides an opportunity to prepare more complex oligosaccharides. Finally, it was demonstrated that the methodology can also be employed for the preparation of 2,4-branched trisaccharides by glycosylation of acceptor **6**[43] with fucosyl donor **2** to give a 2,4-linked disaccharide, which was subjected to Et_3SiH/TfOH to regioselectively open the benzylidene to afford a glycosyl acceptor having a C-4 hydroxyl. Addition of galactosyl donor **1** to the latter compound followed by standard workup and purification by silica gel column chromatography gave trisaccharide **18** in 60% yield.

In conclusion, it has been demonstrated that one-pot procedures involving reductive opening of benyzlidene acetals and glycosylations can give easy access to a wide range of di- and trisaccharides. It is to be expected that the utility of the methodology can be further extended by combining acid-catalyzed reductive etherifications and acetylations with glycosylations. Also the use of a thioglycoside as the initial acceptor may provide an opportunity to prepare more complex structures by employing the resulting thioglycoside product as a glycosyl donor.

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Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(43) **Methyl 4,6-*O*-benzylidene-3-*O*-benzyl-α-D-glucopyranoside (6):** To a solution of methyl 4,6-benzylidene-α-D-glucopyranoside (50 mg, 0.18 mmol) in DCM (1.0 mL) was added benzaldehyde (22 μL, 0.21 mmol) and triethylsilane (34 μL, 0.21 mmol), and the mixture was stirred under an atmosphere of argon for 30 min. The mixture was cooled (−78 °C) and TfOH (0.3 eq) was added. The reaction mixture was quenched after 30 min with pyridine (50 μL), diluted with DCM (5 mL), and washed with sat. aq $NaHCO_3$ (3 mL) and brine (3 mL). The organic layer was dried ($MgSO_4$), concentrated in vacuo, and purified by silical gel column chromatography (hexane/ethyl acetate, 4/1, v/v) to give **6** as a white solid in 50% yield.