Carbohydrates

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Tandem Catalysis for a One-Pot Regioselective Protection of Carbohydrates: The Example of Glucose**

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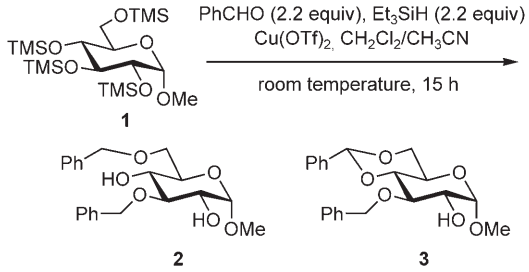
In the assembly of oligosaccharide structures from monosaccharide building blocks, the major focus logically centers on the challenge of developing the stereoselective formation of glycosidic bonds.[1] Much less attention is given to elaborating monomeric building blocks (glycosyl donors and acceptors) that usually require designing a multistep sequence of transformations that involves several protecting-group manipulations.[1,2] Replacing these lengthy multistep approaches by new strategies that rely on the minimal use of separate steps would be highly attractive. In particular, the development of one-pot, catalyzed tandem processes without intermediate separation steps is a desirable strategy to carry out a sustainable multistep synthesis with high efficiency.[3]

Over the past few years, our laboratory has presented several strategic options that have drastically shortened the synthetic route to bioactive glycoconjugates.[4] As part of this work, we report here the successful development of a sequential tandem Lewis acid catalysis which includes two or more distinct steps promoted by a single catalyst in a single reaction vessel.[5]

Acetal formation, regioselective reductive opening of arylidene acetals or reductive etherification, and acylation are reactions widely used on carbohydrate templates that can all be readily catalyzed by triflate salts or trimethylsilyl triflate (TMSOTf).[6–9] The possibility then emerges that these reactions could be programmed in tandem.[5] This intriguing approach would, however, require an absolute fine-tuning of the experimental conditions that would be compatible with all three reactions conducted in the same vessel. Particularly crucial would be to exploit the kinetic/thermodynamic preferences that would lead to a clean regioselective protection of sugars.[10,11]

We decided to implement a one-pot regioselective benzylation of a glucopyranoside, a procedure seen as a balanced complement to the highly regioselective de-*O*-benzylation of benzylated sugar derivatives promoted by excess amounts of isobutylaluminum reagents[12] or oxidizing agents.[13] Results outlined in Table 1 present our initial attempts to prepare regioselectively 3,4-di-*O*-benzyl-D-glucopyranoside **2** using a one-pot procedure from the per-*O*-trimethylsilylated derivative **1** as the substrate sugar for model studies.[14] When [$Cu(OTf)_2$] was used as the sole catalyst [$Cu(OTf)_2$] and "easy" conditions were maintained (0 °C to room temperature with a minimum loading of catalyst), success resulted from a subtle choice of solvent conditions (cf. entries 1 and 2, Table 1).

Table 1: Persilylated D-glucopyranoside **1** under reductive alkylation conditions.[a]



1 **2** **3**

Entry	$Cu(OTf)_2$ [mol%]	CH_2Cl_2/CH_3CN	Yield [%]	**2/3**
1	0.5	98:2	57	1:7
2	0.5	0:100	32	3:2
3	0.5	80:20	65	1:3
4	1	80:20	44	2:3

[a] TMS = trimethylsilyl.

This preliminary study, although not synthetically useful, proved that the tandem process was indeed operating with a low loading of the catalyst (0.5–1 mol%). This also indicated that adjusting the reaction conditions for the regioselective one-pot preparation of 3-*O*-benzyl-4,6-*O*-benzylidene-D-glucopyranoside **3** would be easily feasible. This was next examined using the same substrate but with different triflate catalysts (Table 2). With a selected set of solvent conditions, we were pleased to discover that the addition of an excess of benzaldehyde (3 equiv), Et_3SiH (1.1 equiv), and 1 mol% of $Cu(OTf)_2$ in CH_3CN to a solution of silylated α-methyl glucopyranoside **1** in CH_2Cl_2 (final CH_2Cl_2/CH_3CN ratio of 4:1) resulted in the clean formation of compound **3** in 78% yield (entry 3, Table 2). Lower loadings of the catalyst resulted in lower yields of **3** with the concurrent formation of only the acetal **4** (47 and 18% with 0.25 and 0.5 mol% of $Cu(OTf)_2$, respectively, entries 1 and 2, Table 2). In constrast, the decreased yields of **3** with higher catalyst loadings (2.5 and 5 mol%) are explained by the surprising formation of the mono-*O*-benzyl derivative **5** (25 and 38%, respectively, entries 4 and 5, Table 2). The use of the other triflate catalysts (entries 6–9, Table 2) under the same conditions (1 mol% catalyst in the same solvent at room temperature) was less

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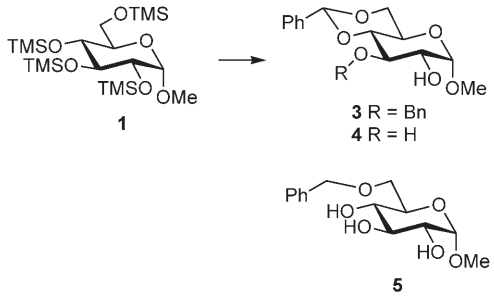
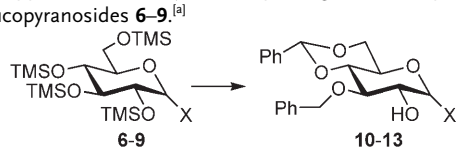
Table 2: One-pot regioselective protection of α-methyl D-glucopyranoside **1**.[a]



Entry	Catalyst	Mol %	Yield of **3** [%][b]
1	$Cu(OTf)_2$	0.25	[c]
2	$Cu(OTf)_2$	0.5	70
3	$Cu(OTf)_2$	1	78
4	$Cu(OTf)_2$	2.5	48[d]
5	$Cu(OTf)_2$	5	45[e]
6	TMSOTf	1	49[f]
7	$Bi(OTf)_3$[g]	1	36[f]
8	$Hf(OTf)_4$	1	52[f]
9	$VO(OTf)_2$	1	57[f]

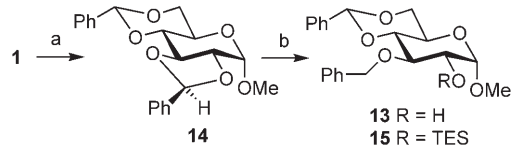
[a] General reaction conditions: 3 equiv benzaldehyde, 1.1 equiv Et_3SiH, *x* mol% $M(OTf)_n$ in CH_2Cl_2/CH_3CN (4:1) at room temperature, 10 min. [b] Yield of **3** after silica gel chromatography. [c] Only acetal **4** was formed in 47% yield. [d] Ether **5** was also formed in 25% yield. [e] Ether **5** was also formed in 38% yield. [f] Acetal **4** and ether **5** were also formed. [g] The $Bi(OTf)_3/Et_3SiH$ combination is not stable, see reference [15]. Bn = benzyl.

Table 3: Copper triflate catalyzed one-pot regioselective protection of thio-D-glucopyranosides **6–9**.[a]



Entry	X	Product	Yield [%][b]
1	**6**: β-SPh	**10**	80
2	**7**: β-STol	**11**	79
3	**8**: β-SEt[c]	**12**: X = β-SEt	53
		13: X = α-SEt	12
4	**9**: α-SEt[c]	**12**: X = β-SEt	19
		13: X = α-SEt	60

[a] General reaction conditions: 3 equiv benzaldehyde, 1.1 equiv Et_3SiH, 1 mol% $Cu(OTf)_2$ in CH_2Cl_2/CH_3CN (4:1) at 0°C, 10 min. [b] Yield after silica gel chromatography. [c] Reaction performed at room temperature for 2 h.



Scheme 1. Origin of the one-pot regioselective benzylation at position 3 of α-methyl D-glucopyranoside **1**. a) PhCHO (3 equiv), 1 mol% $Cu(OTf)_2$, CH_2Cl_2/CH_3CN (4:1), room temperature, 0.5 h, 23%; b) Et_3SiH (1.1 equiv), 1 mol% $Cu(OTf)_2$, CH_2Cl_2/CH_3CN (4:1), room temperature, 0.5 h; **3**: 56% yield, **15**: 8% yield (diol **4** also formed in 7% yield). TES = triethylsilyl.

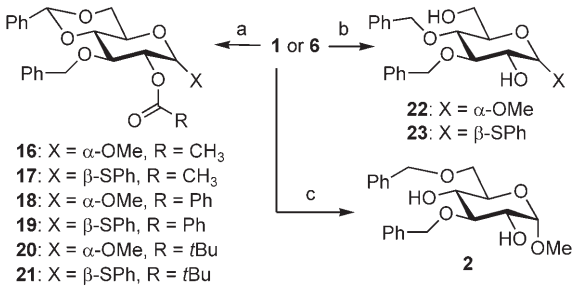
efficient in giving **3**, and both acetal **4** and ether **5** were also obtained. Under these reaction conditions, $Ba(OTf)_2$, $Yb(OTf)_3$, and $Sm(OTf)_3$ were inefficient, providing only the 4,6-acetal **4** (results not shown).

This tandem transformation was successfully extended to the corresponding thioglucopyranosides, representative building blocks of a widely used class of glycosyl donors (Table 3). With the thioaryl substrates **6** and **7**, the best results were obtained at 0°C, with a tetrabutylammonium fluoride treatment at the end of the reaction for g-scale preparations. (entries 1 and 2, Table 3). However, reactions of the corresponding thioethyl glycosides **8** and **9** produced a mixture of anomers **12** and **13** (65–79%, total yield), as a consequence of an acid-catalyzed anomerization (entries 3 and 4, Table 3).

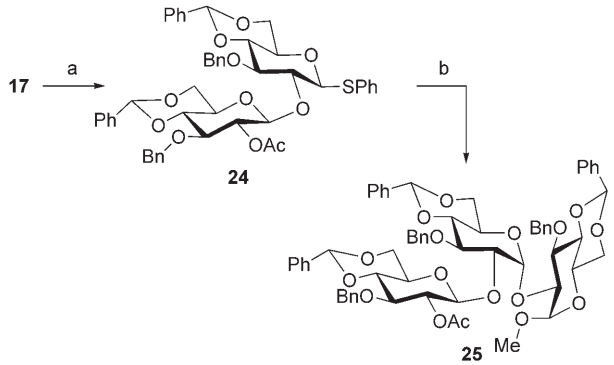
In order to clarify the key regioselective benzylation at position 3 of the tandem process the same conditions were applied to **1** omitting the reducing Et_3SiH (step a, Scheme 1). This gave the bis-benzylidene acetal **14** as only one diastereomer as shown which, after treatment with our standard reductive procedure, provided only 3-*O*-benzyl derivatives **3** and **15** in 64% total yield with no detectable amounts of the regioisomeric 2-*O*-benzyl derivative. This indicates that the one-pot regioselective alkylation at position 3 most probably arises from a regioselective reductive opening of a transient 2,3-acetal, with the other 4,6-acetal being stable under these reaction conditions.[16]

With this one-pot procedure in hand in which all reagents are present at the onset of the reaction, we then explored the possibility of extending further the "tandem" process by sequential addition of reagents that would be active under copper triflate catalysis. Thus further acylation proceeded in good overall yields (69–79%) with the anhydrides, either at room temperature (Ac_2O, 3 equiv) or at reflux temperature (Bz_2O and Piv_2O, 4 equiv) to provide the corresponding fully protected carbohydrates **16–21** (Scheme 2). For example β-thiophenyl glycoside **17** was provided as a crystalline material in 79% yield without the need for column chromatography. Similarly, when the same procedure was followed by the copper triflate catalyzed regioselective ring opening of the 4,6-*O*-benzylidene in the presence of the BH_3·THF complex, the 3,4-di-*O*-benzyl derivatives **22** and **23** were obtained highly selectively in good yields (Scheme 2). Switching from this borane-promoted reductive opening to the silane-promoted reductive cleavage in CH_3CN[7d] furnished the 3,6-di-*O*-benzyl-D-glucopyranoside **2** (step c, Scheme 2).[17]

The utility of these diverse one-pot syntheses of monomeric building blocks was highlighted in an efficient iterative construction[18] of protected trimeric oligosaccharide **25**, using the fully protected β-selective glycosyl donor **17**, acceptor **10** as the precursor of the internal unit, and acceptor **3** as the terminating building block (Scheme 3). Phenylsulfenyl-promoted assembly of **17** and **10** following the procedure of Crich and Smith[19] provided exclusively β-dimeric glycosyl donor **24** in 70% yield (β/α > 95:5), which on further activation and coupling with the acceptor **3** yielded with unexpected exclusive α-selectivity α,β-triglucoside **25** (α/β > 95:5) in 66% yield.



Scheme 2. Copper triflate catalyzed one-pot regioselective protection of D-glucopyranosides **1** and **6**. a) PhCHO (3 equiv), Et_3SiH (1.1 equiv), 1 mol% $Cu(OTf)_2$, CH_2Cl_2/CH_3CN (4:1), room temperature (X = α-OMe) or 0 °C (X = β-SPh), 10 min (procedure a), then Ac_2O (3 equiv), CH_2Cl_2, room temperature, 1 h (**16**: 78%; **17**: 79% after direct recrystallization) or Bz_2O (4 equiv), CH_2Cl_2, reflux, 24 h (**18**: 71%; **19**: 69%) or Piv_2O (4 equiv), CH_2Cl_2, reflux, 24 h (**20**: 74%; **21**: 70%). b) procedure (a) then BH_3·THF (5 equiv), 10 mol% $Cu(OTf)_2$, room temperature, 3 h (**22**: 75%; **23**: 77%); c) procedure (a) then Et_3SiH (5 equiv), 5 mol% $Cu(OTf)_2$, room temperature, 2 h (**2**: 58%). Bz = benzoyl, Piv = pivaloyl.



Scheme 3. Iterative preparation of α,β-triglucoside **25**. a) 1-Benzenesulfinyl piperidine (1 equiv), Tf_2O (1.1 equiv), 2,4,6-tri-*tert*-butylpyrimidine (2 equiv), MS 4 Å, CH_2Cl_2, −60 °C, 15 min, then **10** (1.25 equiv) 1 h, 70%. b) The same conditions as in (a) but with **3** (1.25 equiv), 66% (81% based on recovered donor **24**).

In conclusion, we have developed a regioselective one-pot protection of carbohydrates, which has been optimized on D-glucopyranosides, by using a single catalyst in a single reaction vessel. Different building blocks with different substitution patterns can be obtained in a single flask by fine-tuning the reaction conditions. This approach should simplify the synthetic sequences to oligomers as demonstrated by a rapid iterative assembly that incorporates these building blocks into a trisaccharide.

Experimental Section

17: A solution of freshly dried copper(II) trifluoromethanesulfonate in acetonitrile (80 mM, 0.50 mL) was added to an ice-cold solution of the persilylated thioglucoside **6** (2.32 g, 3.98 mmol) and benzaldehyde (1.21 mL, 11.95 mmol) in dichloromethane (2 mL). Then, triethylsilane (0.70 mL, 4.38 mmol) was added, and over 30 min the solution was concentrated to dryness under an argon flow. The resulting yellow solid was dissolved in dichloromethane (2.00 mL), and the acetic anhydride (1.13 mL, 11.95 mmol) was added. The mixture was stirred for 1 h at room temperature. A saturated aqueous $NaHCO_3$ solution was added, and the reaction mixture was extracted twice with dichloromethane. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Crystallization from EtOH (70 mL) gave **17** (1.56 g, 79%) as a white solid. $[\alpha]_D^{25} = +5$ ($c = 1\ g\,cm^{-3}$ in $CHCl_3$) [lit. $[\alpha]_D^{25} = +1.4$ ($c = 1\ g\,cm^{-3}$ in $CHCl_3$)];[20] m.p. 173–175 °C; ^1H NMR ($CDCl_3$, 360 MHz): $\delta = 7.59$–7.26 (m, 18H, Ar-H), 5.61 (s, 1H, CH-Ph), 5.09 (dd, $J_{2,1} = 9.7$ Hz, $J_{2,3} = 9.0$ Hz, 1H, H-2), 4.91 (d, $J = 12.2$ Hz, 1H, CH_2-Ph), 4.75 (d, $J_{1,2} = 9.7$ Hz, 1H, H-1), 4.71 (d, $J = 12.2$ Hz, 1H, CH_2-Ph), 4.43 (dd, $J_{6',5} = 5.0$ Hz, $J_{6',6} = 10.4$ Hz, 1H, H-6′), 3.84 (dd, $J_{6,5} = 10.2$ Hz, $J_{6,6'} = 10.4$ Hz, 1H, H-6), 3.81 (t, $J_{3,2} = J_{3,4} = 9.0$ Hz, 1H, H-3), 3.78 (t, $J_{4,3} = J_{4,5} = 9.0$ Hz, 1H, H-4), 3.55 (ddd, $J_{5,4} = 9.0$ Hz, $J_{5,6} = 10.2$ Hz, $J_{5,6'} = 5.0$ Hz, 1H, H-5), 2.06 ppm (s, 3H, CH_3-CO); ^{13}C NMR ($CDCl_3$, 90 MHz): $\delta = 169.3$ (CH_3-CO), 138.1, 132.7, 132.3, 129.1, 129.0, 128.4, 128.3, 128.2, 127.9, 127.8, 126.1 (18C, Ar-C), 101.3 (CH-Ph), 86.8 (C-1), 81.3 (C-4), 79.8 (C-3), 74.4 (CH_2-Ph), 71.4 (C-2), 70.5 (C-5), 68.6 (C-6), 21.0 ppm (CH_3-CO); R_f (pentane/diethyl ether 3:1) = 0.6; ESI HRMS for $C_{28}H_{28}O_6S_1$ $[M+Na]^+$: found 515.1499, calcd 515.1499.

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