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Regioselective One-Pot Protection of D-Glucosamine

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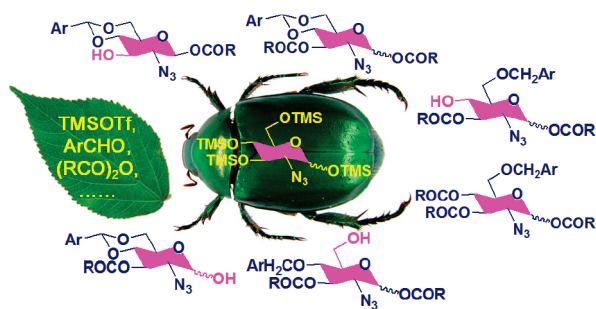
A highly regioselective one-pot transformation of 2-azido-2-deoxy-1,3,4,6-tetra-*O*-trimethylsilyl-D-glucopyranose via sequential additions of various reagents was systematically studied, yielding the fully protected derivatives and the 1-, 3-, 4-, as well as 6-alcohols, respectively.

The chirality of the anomeric center along with the polyhydroxylated character of several monosaccharide units has enabled Nature to generate carbohydrate polymers of staggering complexity.[1] The information embedded in these structures that are exploited in living systems attracted keen interest and fueled the advance of the emerging field of glycomics.[2] Among the widely distributed sugar components, D-glucosamine and its *N*-acetylated and *N*-sulfonated derivatives, are found in numerous biologically potent molecules such as cell surface *N*-glycoproteins, proteoglycans (heparan sulfate, heparin), hyaluronic acid, glycosphingolipids (Lewis a/x), glycosylphosphatidylinositol (GPI) anchors, blood group antigens, bacterial cell wall, lipopolysaccharides, and chitin/chitosan.[2c,3] The 3-O and 4-O positions of the glucosamine residues are typically involved in the recurring linear assemblies as is the case in hyaluronic acid, chitin, and heparan sulfate.[4] The more decorated *N*-glycoproteins and glycolipids have branching structures occupying not only the 3-O and 4-O, but also the 6-O portions as well.[5] The reducing side attachments are frequently β-oriented, although α-linkages are also common.
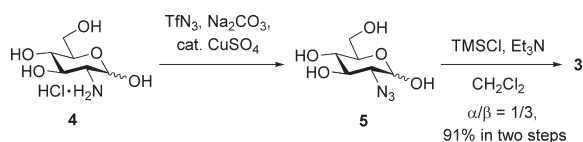
Carbohydrate structure−activity relationship (SAR) studies require well-defined molecules which may only be reasonably acquired through chemical synthesis.[6] Such preparation necessitates the acquisition of properly protected monosaccharide assembly units. Traditional protocols rely on independent preparative routes and step-by-step protection−deprotection schemes with focus on the careful differentiation of the multiple hydroxyls of an unprotected starting material, often suffering tedious workups and time-consuming purifications. To tackle these problems and efficiently create a library of suitable monosaccharide synthons for glycomics study, a trimethylsilyl trifluoromethanesulfonate (TMSOTf)-mediated regioselective one-pot protection strategy was recently developed by us.[7] There, a variety of D-glucose derivatives with different protecting group patterns was prepared from the simple per-*O*-trimethylsilylated glucopyranosides with anomeric fixed α-OMe (**1**) and β-STol (**2**).
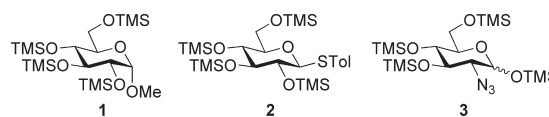
In continuation of this effort, we disclose herein the application of our novel approach on the anomeric nonfixed D-glucosamine unit **3** to synthesize a series of building blocks that include fully protected sugars and 1-, 3-, 4-, as well as 6-alcohols. In this case, the azido group was selected to mask the 2-C position of the glucosamine unit due to its dual utility in forming either α- (by nonparticipating effect)[8] or β-glycosidic linkage (by nitrile solvent effect).[9] Other amino

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SCHEME 1. **Preparation of 2-Azido-2-deoxy-1,3,4,6-tetra-***O*-trimethylsilyl-ᴅ-glucopyranose 3

TABLE 1. **Acid-Promoted Regioselective One-Pot 4,6-*O*-Arylidenation and Acetylation**

entry	acid	x	T (°C)	Ar	product (yield, %)
1	TMSOTf	1.1	0 to rt	Ph	**6** (7) + **7** (36) + **8** (11) + **9** (15)
2	TMSOTf	1.1	0 to rt	2-Naph	**10** (8) + **11** (34) + **12** (13) + **13** (17)
3	Cu(OTf)$_2$	1.1	0 to rt	Ph	**6** (11) + **7** (23) + **8** (15) + **9** (31)
4	Cu(OTf)$_2$	1.1	0 to rt	2-Naph	**10** (9) + **11** (19) + **12** (12) + **13** (25)
5	TMSOTf	2.5	40	Ph	**9** (32)
6	Cu(OTf)$_2$	2.5	40	Ph	**9** (57)
7	Cu(OTf)$_2$	5	40	Ph	**9** (69)
8	Cu(OTf)$_2$	7.5	40	Ph	**9** (74)
9	Cu(OTf)$_2$	10	40	Ph	**9** (77)
10	Cu(OTf)$_2$	10	40	2-Naph	**13** (74)

protecting groups, e.g. Boc, Cbz, Troc, Phth, ClAc, CF$_3$CO, and CCl$_3$CO, all prefer the β-form because of the participating effect by the carbonyl group.[10] The azido group can also be easily transformed into *N*-acetyl or free amine by using thioacetic acid[11] or a series of reductants, respectively. The next encountered problem is the differentiation of four hydroxy groups on the ᴅ-glucosamine unit, which contains one primary alcohol at 6-C and three secondary alcohols at 1-C, 3-C, and 4-C. Conceptually, the 4,6-dihydroxyls can be blocked by arylidene formation, and the remaining 1-OH and 3-OH can be distinguished by their differences in acidity.

To initiate this one-pot approach, the per-*O*-silylated ether **3** needs to be synthesized and the two-step procedure is depicted in Scheme 1. Commercially available ᴅ-glucosamine hydrochloride **4** was first reacted with freshly prepared triflic azide (TfN$_3$) in the presence of copper sulfate as catalyst to afford the corresponding azido derivative **5**.[12] After partial purification, the crude tetraol **5** underwent per-*O*-silylation to furnish the product **3**, which was recrystallized from ethanol[13] as a white solid with a 91% overall yield.

Having acquired the common intermediate **3**, we went forward with the regioselective one-pot protection strategy. The general protocols involved the following: (1) selective protection of 4,6-dihydroxyl groups as arylidene acetals followed by regioselective 1-*O*-acylation to provide the 3-alcohols; (2) 4,6-*O*-arylidenation, 1,3-di-*O*-acylation to obtain the fully protected derivatives; (3) 4,6-*O*-arylidenation, 1,3-di-*O*-acylation, and regioselective ring-opening of arylidene acetals to furnish the 6-alcohols, fully protected derivatives, and 4-alcohols, respectively; and (4) 4,6-*O*-arylidenation, 1,3-di-*O*-acylation, and regioselective removal of the protecting group at 1-O to yield the 1-alcohols. 4,6-*O*-Arylidene formation and the subsequent acylation are core steps in the one-pot process. Treatment of compound **3** with 1.05 equiv of benzaldehyde and catalytic TMSOTf smoothly implemented the first transformation. With the already acid-containing mixture, it is convenient to pursue the acylation stage under acid catalysis. Promoted by TMSOTf, acetylation was attempted with 1.1 equiv of Ac$_2$O initially at ice bath temperature and then gradually warmed to room temperature. Regrettably, as detailed in entry 1 of Table 1, the one-pot reaction led to the 1-acetylated 3-alcohol **6**, 3-acetylated

1-TMS ether **7**, 1-alcohol **8**, and 1,3-diacetate **9** in 7%, 36%, 11%, and 15% yields, respectively. Similar results were obtained in the case of 2-naphthaldehyde (entry 2), and the acetylated derivatives **10**−**13** were individually isolated in 8%, 34%, 13%, and 17% yields. Alternatively, copper(II) trifluoromethanesulfonate [Cu(OTf)$_2$][14] in place of TMSOTf registered marginal improvements under the same conditions (entries 3 and 4). When the amount of Ac$_2$O was raised to 2.5 equiv and the temperature to 40 °C, a better yield was delivered by Cu(OTf)$_2$ (57%, entry 6) than TMSOTf (32%, entry 5) for the 1,3-diacetate **9**. Further increase in the amount of Ac$_2$O in a Cu(OTf)$_2$-catalyzed acetylation[15] resulted in yield enhancement (entries 7 and 8) and at 10 equiv, the fully protected derivatives **9** and **13** were generated in 77% (entry 9) and 74% (entry 10) yields, respectively. Notably, mixtures of anomers were afforded in these reactions.

Since the regioselective 1-*O*-acylation could not be efficiently executed with acid catalysis, this second stage conversion was attempted utilizing the basic approach.[16] The reaction conditions and results are outlined in Table 2. After protecting the 4-O and 6-O positions with a benzylidene acetal, the TMS groups at the 1-O and 3-O positions were removed by treatment with tetra-*n*-butylammonium fluoride (TBAF) together with acetic acid to control the pH value of the solution.[17] Without quenching the reaction, the 1-*C*-hydroxy group was regioselectively acetylated employing triethylamine (Et$_3$N) and 1.1 equiv of Ac$_2$O to afford only the β-form[18] 3-alcohol **6β** in 91% yield (entry 1). Here, the carboxylic acid used to moderate the basicity of TBAF should be the parent acid of the anhydride reagent used to protect 1-O in order to prevent undesirable mixed anhydride

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TABLE 2. Regioselective One-Pot 4,6-*O*-Arylidenation Followed by Basic Acylation

1. 0.15 equiv TMSOTf,
   1.05 equiv ArCHO,
   CH$_2$Cl$_2$, 0 °C, 1.5 h

2. ZOH, TBAF,
   0 °C, 4 h

3. x equiv Z$_2$O, Et$_3$N

6β: Ar = Ph, R = H, Z = Ac
10β: Ar = 2-Naph, R = H, Z = Ac
14: Ar = Ph, R = H, Z = Bz
15: Ar = 2-Naph, R = H, Z = Bz
9: Ar = Ph, R = Z = Ac
13: Ar = 2-Naph, R = Z = Ac
16: Ar = Ph, R = Z = Bz
17: Ar = 2-Naph, R = Z = Bz

entry	Ar	x	Z	product	yield (%)
1	Ph	1.1	Ac	**6β**	91
2	2-Naph	1.1	Ac	**10β**	90
3	Ph	1.1	Bz	**14**	89
4	2-Naph	1.1	Bz	**15**	87
5	Ph	3	Ac	**9**[a]	94[c]
6	2-Naph	3	Ac	**13**[b]	92[c]
7	Ph	3	Bz	**16**	92[c]
8	2-Naph	3	Bz	**17**	91[c]

[a] α/β = 1/6. [b] α/β = 1/6. [c] Acylation was carried out together with DMAP.

TABLE 3. Regioselective One-Pot Protection to Synthesize the 6-Alcohols

1. 0.15 equiv TMSOTf,
   1.05 equiv ArCHO,
   CH$_2$Cl$_2$, 0 °C, 1.5 h

2. 0.2 equiv Cu(OTf)$_2$,
   x equiv Ac$_2$O, 40 °C, 3 h

3. 0.2 equiv Cu(OTf)$_2$,
   BH$_3$/THF, 0 °C to RT

18: Ar = Ph, R = Ac
19: Ar = 2-Naph, R = Ac

entry	x	Ar	product	yield (%)
1	2.5	Ph	**18**	38
2	2.5	2-Naph	**19**	35
3	10	Ph	**18**	59
4	10	2-Naph	**19**	57

formation. By applying this method with other combinations of aryl aldehyde (2-naphthaldehyde, benzaldehyde) and acid anhydrides (Ac$_2$O, Bz$_2$O), the target 3-alcohols (**10β**, **14**, **15**) were obtained as single isomers in excellent yields all in one pot (entries 2−4). To drive the 1,3-di-*O*-acylation, the previously obtained arylidene acetals were treated with Et$_3$N and 3 equiv of acid anhydride under catalytic 4-*N*,*N*-dimethylaminopyridine (DMAP) at room temperature (entries 5−8). DMAP is necessary to provide excellent product turnover, but in the case of acetylation, addition of this catalyst supplied a mixture of the α- and β-anomers **9** (94%) and **13** (92%), whereas only the β-isomers **16** (92%) and **17** (91%) were isolated after benzoylation.

We next tackled the preparation of 6-alcohols via the fully protected derivatives in one pot (Table 3). Efforts to regioselectively open the 4,6-*O*-arylidene acetal after full protection using the above-mentioned basic conditions turned out unsuccessful. Following the route through the Cu(OTf)$_2$-mediated 1,3-di-*O*-acetylation, the regioselective 6-*O*-ring-opening of the originally formed arylidene acetal was, then,

TABLE 4. Regioselective One-Pot Protection To Synthesize the Fully Protected Derivatives and 4-Alcohols

1. 0.15 equiv TMSOTf,
   1.05 equiv ArCHO,
   CH$_2$Cl$_2$, 0 °C, 1.5 h

2. 0.2 equiv Cu(OTf)$_2$,
   x equiv Ac$_2$O, 40 °C, 3 h

3. 0.2 equiv Cu(OTf)$_2$,
   Me$_2$EtSiH, CH$_3$CN,
   0 °C, 2 h

20: Ar = Ph, R = Ac
21: Ar = 2-Naph, R = Ac
22: Ar = Ph, R = H
23: Ar = 2-Naph, R = H

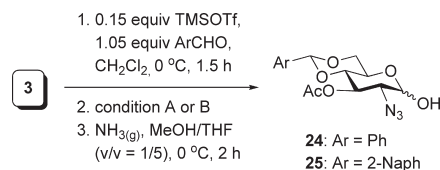| entry	x	Ar	product	yield (%)
1	10	Ph	**20**	62
2	10	2-Naph	**21**	60
3	2.5	Ph	**22**	45
4	2.5	2-Naph	**23**	44

explored by using BH$_3$/THF[7,19] as the reductant in the presence of 0.2 equiv of Cu(OTf)$_2$ initially at 0 °C and gradually warmed to room temperature. In entries 1 and 2, when 2.5 equiv of Ac$_2$O was used for acetylation, the desired 6-alcohols **18** and **19** were obtained in 38% and 35% yields, respectively. Increasing the amount of Ac$_2$O to 10 equiv would benefit the reactions, and the yields of products **18** and **19** were improved to 59% (entry 3) and 57% (entry 4), respectively.

To synthesize the alternate ring-opening product, BH$_3$/THF was replaced by Me$_2$EtSiH[20] as the reductant with Cu(OTf)$_2$ still acting as a promoter. The results are summarized in Table 4. Again, the acetylation conditions played a critical role in the outcome of the one-pot process. Following acetylation carried out with 10 equiv of Ac$_2$O in a Cu(OTf)$_2$-catalyzed reaction, subsequent addition of Me$_2$EtSiH and Cu(OTf)$_2$ at ice-bath temperature provided the unanticipated fully protected 1,3,4-tri-*O*-acetylated derivatives **20** (entry 1) and **21** (entry 2) in 62% and 60% yields, respectively. The reaction presumably went through regioselective ring-opening at 4-O followed by 4-*O*-acetylation in situ owing to the large excess of Ac$_2$O. This phenomenon was not observed in the borane-reductive 6-*O*-opening (Table 3, entries 3 and 4). When the amount of acetylating reagent was reduced to 2.5 equiv and then followed by the Me$_2$EtSiH-mediated regioselective 4-*O*-ring-opening of the arylidene acetals in the same flask, the 4-alcohols **22** (entry 3) and **23** (entry 4) were acquired in 45% and 44% yields, respectively.

In carrying out the one-pot strategy to prepare the 1-alcohols, the basic and acidic conditions used for 1,3-di-*O*-acetylation in generating fully protected derivatives were handy in accessing the target molecules. As illustrated in Table 5, when the arylidene acetals were treated with Ac$_2$O in the presence of Et$_3$N and DMAP followed by regioselective 1-*O*-deacetylation with ammonia in MeOH/THF at 0 °C, the expected hemiacetals **24** (entry 1) and **25** (entry 2) were only isolated in 25% and 21% yields, respectively. The side products include an α,β-unsaturated aldehyde presumably generated through an open ring elimination reaction involving the 3-*O*-acetate. On the other hand, employing Cu(OTf)$_2$ and 10 equiv of Ac$_2$O for 1,3-di-*O*-acetylation resulted in the much better 59% yield for **24** (entry 3) and 53% for **25** (entry 4) after 1-*O*-deacetylation.

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TABLE 5. Regioselective One-Pot Protection To Synthesize the 1-Alcohols

entry	condition^a	Ar	product	yield (%)
1	A	Ph	**24**	25
2	A	2-Naph	**25**	21
3	B	Ph	**24**	59
4	B	2-Naph	**25**	53

^{a}Condition A: AcOH, TBAF, 0 °C, 2 h, then 3 equiv of Ac$_2$O, Et$_3$N, DMAP, 0 °C to rt. Condition B: 0.2 equiv of Cu(OTf)$_2$, 10 equiv of Ac$_2$O, 40 °C, 3 h.

In summary, efficient conversion of D-glucosamine into various synthons bearing chemically differentiable protecting groups was, therefore, demonstrated by employing properly applied one-pot protocols. These synthons can be readily used as glycosyl building blocks in oligosaccharide assembly.

Experimental Section

General Procedure for the One-Pot Synthesis of 3-Alcohols 6β, 10β, 14, and 15. To a solution of compound **3** (0.265 g, 0.536 mmol) and ArCHO (0.562 mmol) in dichloromethane (3 mL) containing freshly dried 3 Å molecular sieves (300 mg) was slowly added trimethylsilyl trifluoromethanesulfonate (80.4 μmoL) at 0 °C under nitrogen atmosphere. The mixture was stirred at the same temperature for 1.5 h, and acetic acid/benzoic acid (1.17 mmol) and tetra-*n*-butylammonium fluoride (1.17 mmol) were sequentially added to the reaction solution. After stirring for another 4 h at 0 °C, acetic anhydride/benzoic anhydride (0.589 mmol) and Et$_3$N (5.36 mmol) were added to the solution, and the reaction mixture was stirred overnight at 0 °C. The whole mixture was filtered through a pad of Celite, and the filtrate was consecutively washed by water (3 mL) and saturated NaHCO$_{3(aq)}$ (3 mL). The aqueous layer was extracted with ethyl acetate (3 × 5 mL), and the combined organic layers were washed with brine, dried over anhydrous MgSO$_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/Hex = 1/3) to provide the desired 3-alcohol. For the preparation of the per-*O*-trimethylsilylated ether **3** and other regioselective one-pot procedures, please see the Supporting Information.

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