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Microwave-Assisted One-Pot Synthesis of 1,6-Anhydrosugars and Orthogonally Protected Thioglycosides

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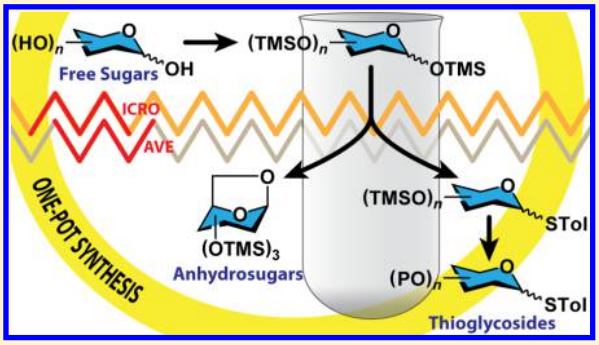
Supporting Information

ABSTRACT: Living organisms employ glycans as recognition elements because of their large structural information density. Well-defined sugar structures are needed to fully understand and take advantage of glycan functions, but sufficient quantities of these compounds cannot be readily obtained from natural sources and have to be synthesized. Among the bottlenecks in the chemical synthesis of complex glycans is the preparation of suitably protected monosaccharide building blocks. Thus, easy, rapid, and efficient methods for building-block acquisition are desirable. Herein, we describe routes directly starting from the free sugars toward notable monosaccharide derivatives through microwave-assisted one-pot synthesis. The procedure followed the in situ generation of per-*O*-trimethylsilylated monosaccharide intermediates, which provided 1,6-anhydrosugars or thioglycosides upon treatment with either trimethylsilyl trifluoromethanesulfonate or trimethyl(4-methylphenylthio)silane and ZnI_2, respectively, under microwave irradiation. We successfully extended the methodology to regioselective protecting group installation and manipulation toward a number of thioglucosides and the glycosylation of persilylated derivatives, all of which were conducted in a single vessel. These developed approaches open the possibility for generating arrays of suitably protected building blocks for oligosaccharide assembly in a short period with minimal number of purification stages.



INTRODUCTION

Biological systems display glycan scaffolds with enormous diversity and complexity.[1] While these biopolymers are built from only a few types of monosaccharide units, the multiple chiral centers available, the branching possibilities, the regio- and stereochemical aspects of the glycosidic linkages, and the potential for further enzymatic modifications supply extensive structural information that prove vital in recognition, adhesion, and signal transduction events. Insights on the character of the interactions involving glycans could drive the development of novel therapeutic and diagnostic agents. Nonetheless, sufficient quantities of well-defined sugar constructs required by structure−activity relationship studies could not be readily acquired from nature, and chemical syntheses remain the most common manner of access.[2] Notably, the characteristics that made sugars so complex are also the prevailing reasons for the unfortunate hardships encountered in carbohydrate syntheses.

Despite various efforts to develop efficient strategies for the synthesis of oligosaccharides and glycoconjugates, no standard synthetic methods akin to protein and nucleic acid acquisitions are available. Traditional synthesis as well as the promising preactivation,[3] programmable one-pot,[4] and automated[5] strategies supplied numerous well-defined complex oligosaccharide sequences. These methods, however, rely on suitably protected monosaccharide building blocks to achieve proper chain assembly and the introduction of the necessary functionalizations in the target compounds. The preparations of glycosyl building blocks are often painstaking, laborious, and time-consuming multistep processes involving regioselective protection of hydroxy groups and functionalization at the anomeric carbon.

Use of microwave (MW) as an unconventional heat source was shown to provide fast, clean, and high-yielding reactions.[6] Specialized MW devices enable the flash heating of reaction solutions even at temperatures well above the boiling points of commonly used organic solvents, rendering conditions that are not feasible under typical means. Because MW-enhanced

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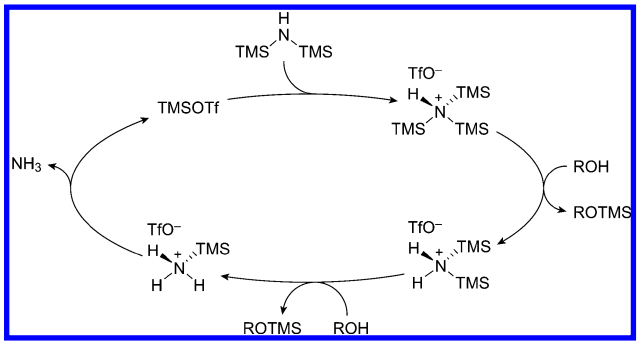
synthesis has yet to fully permeate the carbohydrate field,[7] we decided to explore MW in the preparation of monosaccharide building blocks.

One-pot protection strategies have gained traction in recent years as an attractive method in reducing time, wastes, and effort in carbohydrate synthesis.[4,8] Our work on this topic centered on the trimethylsilyl trifluoromethanesulfonate (TMSOTf)-catalyzed regioselective transformations of various per-*O*-trimethylsilylated starting materials into several fully and partially protected building blocks in one pot.[9] In this paper, we examined the utility of MW irradiation in the transformation of persilylated monosaccharide derivatives into anhydrosugars and thioglycosides. Together with an efficient silylation method and our collective experience in one-pot protection, we developed an integrated MW-assisted one-pot procedure that starts from the free sugars, leading to a diverse range of sugar derivatives and presenting an opportunity for the rapid and practical preparations of others.

RESULTS AND DISCUSSION

One-Pot Preparation of Anhydrosugars. Per-*O*-trimethylsilylated monosaccharides are important gateways to a wealth of sugar derivatives.[9,10] The trimethylsilylation of alcohols is traditionally carried out using chlorotrimethylsilane (TMSCl), which require long reaction times (typically overnight for sugars), large excesses of bases, and product purification prior to any succeeding steps. We recently reported a trimethylsilylation procedure using hexamethyldisilazane (HMDS) under TMSOTf catalysis.[10a] As shown in Scheme 1, each activated HMDS can silylate two alcohol groups,

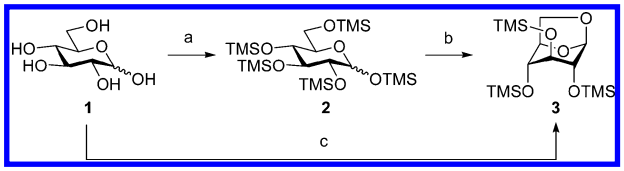
Scheme 1. Proposed Catalytic Cycle for the TMSOTf-Mediated Alcohol Sialylation by HMDS



followed by the liberation of ammonia gas, which also assists in driving the cycle forward. Aside from HMDS being more economical than TMSCl, the reaction is finished in a short period in excellent yields without the need for high excesses of HMDS. The essentially neutral final pH consequently permits the potential integration with our previously developed one-pot procedure.

The initial exposure of D-glucose (**1**) to 2.5 equiv of HMDS and catalytic TMSOTf in CH_2Cl_2 produced the penta-*O*-TMS intermediate **2** in almost quantitative yield (Scheme 2).[10a] We found that the subsequent treatment with 10 mol % TMSOTf under MW irradiation at 100 °C for 5 min resulted in the generation of the 1,6-anhydroglucose **3** in 78% yield after chromatographic purification. The 1,6-anhydropyranose backbone could be readily identified through the HMBC NMR correlations between the anomeric proton and carbon and the respective carbons and protons at the 5- and 6-positions

Scheme 2. MW-Assisted 1,6-Anhydroglucose Formation[a]



[a]Reagents and conditions: (a) HMDS, TMSOTf, CH_2Cl_2, rt, 30 min; (b) TMSOTf, CH_2Cl_2, MW (100 °C), 5 min; 78% (two steps); (c) HMDS, TMSOTf, CH_2Cl_2, rt, 1 h; TMSOTf, CH_2Cl_2, MW (100 °C), 5 min; HMDS, rt, 30 min; 72% (one pot).

(Figure 1a). The $^1C_4$ conformation of the pyranosyl ring is made obvious by the W-coupling between 1-H and 3-H (see

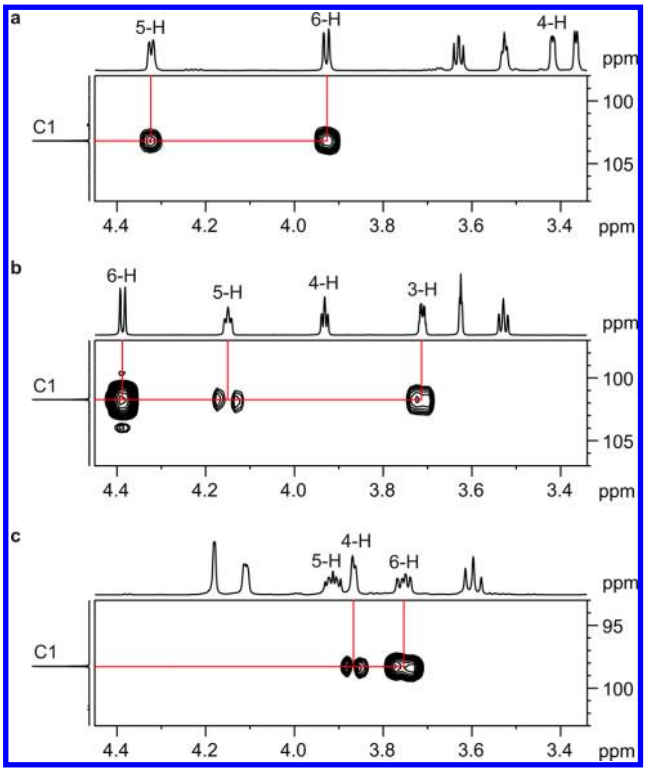


Figure 1. HMBC spectra identifying the backbone structure of the (a) 1,6-anhydroglucopyranose **3**, (b) 1,6-anhydrogalactopyranose **11**, and (c) 1,6-anhydrogalactofuranose **12**.

the Supporting Information). A sharp drop in yield was observed when the MW temperature is set to 90 °C (32%). When the same starting mixture was refluxed with CH_2Cl_2 for 30 min, only the partially desilylated compounds were produced. Following this discovery, a one-pot approach to synthesize **3** by adopting the fruitful MW condition was pursued. Thus, the per-*O*-TMS **2**, generated in situ by using HMDS and TMSOTf, was mixed with 10 mol % of TMSOTf, and the mixture was exposed to similar MW heating. While the 1,6-anhydroglucose formation is successful, MW irradiation unfortunately cleaved some TMS groups. After another treatment with HMDS in the same flask to reinstall the lost TMS groups, compound **3** was attained in 72% yield.

Anhydrosugars are useful intermediates in the synthesis of natural products, biologically potent oligosaccharides and glycoconjugates, and polymers.[11] The rigid [3.2.1]-bicyclic structure of 1,6-anhydropyranoses reorients the hydroxy groups and, hence, forces a sometimes handy reversal of their reactivity

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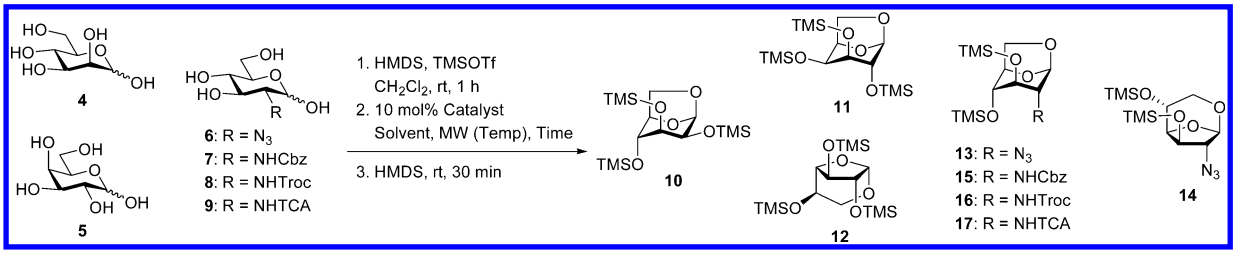
Table 1. Microwave-Assisted One-Pot Synthesis of Different 1,6-Anhydrosugars



entry	starting material	catalyst	temp (°C)	time (min)	solvent	product	yield (%)
1	**4**	TMSOTf	100	5	CH_2Cl_2	**10**	78
2	**4**	TfOH	180	20	EtCN	**10**	90
3	**5**	TMSOTf	100	5	CH_2Cl_2	**11/12**	46/46[a]
4	**5**	TMSOTf	100	5	$ClCH_2CH_2Cl$	**11/12**	59/23[a]
5	**5**	TMSOTf	150	10	$CHCl_3$	**11/12**	11/61[a]
6	**5**	TMSOTf	100	5	$MeNO_2$	**12**	72
7	**6**	TMSOTf	150	10	CH_2Cl_2	**13/14**	62/8[a]
8	**6**	TfOH	100	3	MeCN	**13**	57
9	**7**	TMSOTf	150	10	CH_2Cl_2	**15**	68
10	**8**	TfOH	100	3	MeCN	**16**	68
11	**9**	TfOH	100	3	MeCN	**17**	70

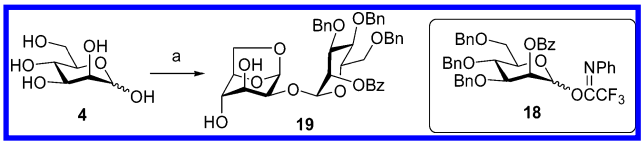
[a]Products were chromatographically isolated as mixtures of isomers, and the yields shown are estimates using the ratios of peaks corresponding to the respective anomeric protons in ^{1}H NMR: Cbz, benzyloxycarbonyl; Troc, 2,2,2-trichloroethoxycarbonyl; TCA, trichloroacetyl.

pattern. Furthermore, the opening of the 1,6-anhydrobridge for further functionalization is a simple operation.[12] With this in mind, we applied our MW-assisted procedure to other monosaccharides (Table 1). Application of the TMSOTf-catalyzed condition on D-mannose (**4**) with MW irradiation similar to that used for **1** produced the 1,6-anhydromannose **10** in good yield (entry 1). Alternatively, a better result was obtained under a more drastic reaction condition (entry 2). For D-galactose (**5**), treatment with TMSOTf under MW heating at 100 °C in CH_2Cl_2 resulted in a 1:1 mixture of the anhydropyranose **11** and the anhydrofuranose **12** (entry 3). The backbone connectivities of these isomers were recognized through the relevant correlations in the HMBC spectra (Figure 1b,c). Different solvents apparently affect the product preference. A solvent change to dichloroethane furnished the pyranose **11** (59%) as the major product (entry 4). With $CHCl_3$, the product preference was somehow reversed, favoring the formation of the anhydrofuranose **12** with 61% yield and with compound **11** generated in 11% yield (entry 5). Compound **12** was exclusively obtained in good yield when the solvent is $MeNO_2$ (entry 6).

We also applied the one-pot procedure to several D-glucosamine derivatives. The azide **6** was transformed into the anhydropyranose **13** in 62% yield with the minor furanoside side product through treatment with TMSOTf in CH_2Cl_2 under MW heating to 150 °C (entry 7). When trifluoromethanesulfonic acid (TfOH) and MeCN were used under 100 °C (entry 8), the anhydropyranose **13** was exclusively obtained. Entries 9−11 show the synthesis of several *N*-protected 1,6-anhydrohexopyranoses **15**−**17** from their corresponding starting materials in good yield. Interestingly, ultrasonication in a bath kept at 25 °C for 50 min and plain heating in an oil bath at 60 °C for 30 min, instead of MW irradiation in the one-pot reaction sequence in entry 11, delivered the target product **17**, albeit in much lower yields of 45% and 35%, respectively. Use of CH_2Cl_2 in place of MeCN for these latter cases did not generate the anhydrosugar.

The extension of the MW-assisted anhydrosugar formation to glycosylation in one pot was next examined. We opted to form the dimannose derivative **19**, which holds the crucial $\alpha(1 \rightarrow 2)$ linkage found in important glycan structures such as glycosylphosphatidylinositol anchors[13] and bacterial cell-wall phosphatidylinositol mannosides[14] (Scheme 3). D-Mannose (**4**) was silylated with HMDS and then subjected to MW irradiation to furnish the desired anhydro-intermediate **10**. Here, the equatorial orientation of O2 in derivative **10** makes it more susceptible to glycosylation than the other positions. Thus, the activation of the mannosyl donor **18**[15] with $BF_3{\cdot}Et_2O$ in the same flask, followed by desilylation resulted to the disaccharide **19** in a 53% overall yield. Compound **19** can be easily functionalized to act as a building block in glycan assembly.

Scheme 3. One-Pot Synthesis of a $\alpha(1 \rightarrow 2)$-Linked Mannose Disaccharide via the MW-Assisted Anhydrosugar Formation[a]



[a]Reagents and conditions: (a) HMDS, TMSOTf, CH_2Cl_2, rt, 1 h; TMSOTf, CH_2Cl_2, MW (100 °C), 5 min; **18** (1.0 equiv), $BF_3{\cdot}Et_2O$, −60 °C, 3 h; TBAF, rt, 1 h, 53% (one pot). Bn. benzyl; Bz. benzoyl; TBAF. tetrabutylammonium fluoride.

One-Pot Preparation of Thioglycosides. Thioglycosides[16] are common and useful building blocks in carbohydrate synthesis. Their stability in numerous protection and deprotection steps as well as their ability to act as acceptors in various glycosylation conditions offer immense synthetic value. Furthermore, programmable one-pot glycosylation, which relies on the relative reactivities of glycosyl donors, are mainly carried out using thioglycosides.[17] We have demonstrated the utility of persilylated thioglycosides in regioselective

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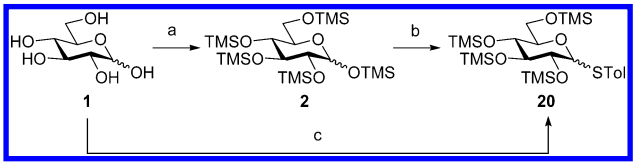
one-pot protection.[9] However, the traditional preparation of these silylated thioglycosides from unprotected starting materials is laborious. This procedure usually involves a number of separate steps, including per-acetylation, thioglycosylation, deacetylation, and silylation.[9a,18] In this regard, the MW-assisted one-pot thioglycosylation was further explored and then later expanded to provide a number of differentially functionalized thioglycosides in a fast and convenient manner.

We found that the penta-*O*-TMS intermediate can be directly transformed into a thioglycoside in the presence of trimethyl(4-methylphenylthio)silane (TMSSTol) and ZnI_2 under MW irradiation (Scheme 4). Again using D-glucose (**1**) as the model

Scheme 4. MW-Assisted One-Pot Thioglucoside Formation[a]



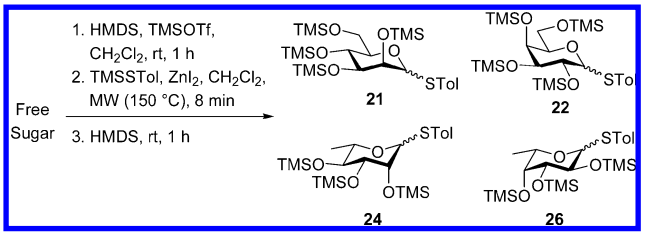
[a]Reagents and conditions: (a) HMDS, TMSOTf, CH_2Cl_2, rt, 30 min; (b) TMSSTol, ZnI_2, CH_2Cl_2, MW (150 °C), 8 min, 83% (two steps, α/β = 4.2/1); (c) HMDS, TMSOTf, CH_2Cl_2, rt, 1 h; TMSSTol, ZnI_2, CH_2Cl_2, MW (150 °C), 8 min; HMDS, rt, 1 h; 76% (one pot, α/β = 5/1). Tol, 4-tolyl.

system, MW-induced heating to 150 °C furnished the per-*O*-TMS thioglucoside **20** in 83% yield. In contrast, no target products were formed upon MW heating to 100 °C as well as the plain CH_2Cl_2 reflux conditions. Interestingly, while the conventional route using the D-glucose pentaacetate as starting material and $BF_3{\cdot}Et_2O$ exclusively furnish the β-anomer,[18] the MW-assisted transformation above provided the α-anomer as the major product (α/β = 4.2/1). In the absence of a participating acyl moiety, such stereoselectivity probably came as a result of the anomeric effect. Following the same sequence of reactions, a one-pot approach was performed, supplying compound **20** in 76% yield after chromatographic purification with relatively similar stereoselectivity (α/β = 5/1). Like the MW-assisted 1,6-anhydrosugar formation, MW irradiation also resulted in the partial cleavage of the silyl groups, which were reinstalled by another treatment with HMDS. This novel route thus enabled access to the persilylated thioglucoside from the unprotected sugar in just a few hours as opposed to several days using the conventional procedure.

The feasibility of our MW-assisted one-pot thioglycosylation procedure was further explored for other monosaccharides (Table 2). Manipulation of D-mannose (**4**, entry 1) and D-galactose (**5**, entry 2) provided the corresponding thioglycosides **21** and **22** in excellent 71% and 62% yields, respectively. Conversely, thioglycosylation of L-rhamnose (**23**, entry 3) and L-fucose (**25**, entry 4) conveniently afforded compounds **24** and **26**, in 71% and 66% yields, respectively. In all these cases, the predominant stereochemical orientation of the thiotolyl group is biased toward the thermodynamically favored axial position.

Whether thioglycosides can be made to act as either donor or acceptor in glycan assembly depends on their level of protection. The formation of compound **19** displayed the potential of persilylated derivatives as direct acceptors in glycosylation. A related work by Gervay–Hague showed the successful application of persilylated glycosyl iodide as glycosyl donor.[19] In these regards, we examined whether our

Table 2. One-Pot Synthesis of Per-*O*-silylated Thioglycosides



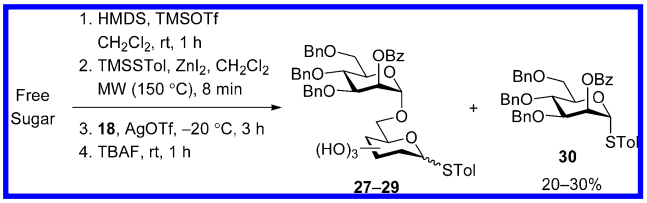
entry	free sugar	product	yield (%)	α/β ratio[a]
1	D-mannose (**4**)	**21**	71	4.5/1
2	D-galactose (**5**)	**22**	62	4.5/1
3	L-rhamnose (**23**)	**24**	71	1.7/1
4	L-fucose (**25**)	**26**	66	2.5/1

[a]Determined by using ^{1}H NMR.

persilylated thioglycosides could be useful as direct donors and acceptors. Our activation of the tetra-*O*-TMS thioglucoside **20** with either *N*-iodosuccinimide/TMSOTf or *p*-toluenesulfenyl chloride/silver(I) trifluoromethanesulfonate (AgOTf) promoter system in the presence of a 6-alcohol acceptor (methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside[20]) unfortunately did not generate the expected disaccharide (see Table S1 in the Supporting Information). Instead, the anhydroglucose **3** was isolated as the main product together with the acceptor (as a TMS derivative due to the resilylation step). Apparently, the intramolecular attack of the C6 TMS ether on the oxocarbenium ion occurs so much faster than the approach of a separate primary alcohol nucleophile.

The acceptor potential of the persilylated thioglycosides was next evaluated under a one-pot setting starting from the free sugars **1**, **4**, and **5** (Table 3). After persilylation and MW-induced thioglycosylation, the sugar derivatives were treated with the imidate **18**, which was selectively activated by AgOTf. The addition of TBAF was then performed to remove all TMS groups. Consequently, the α1 → 6 disaccharides **27**–**29** were acquired in moderate yields with no other regioisomers found. Moreover, about 20–30% of the thiomannoside **30** was isolated from the reaction solution. This side-product was, however, not recovered after separate condensations of **18** and the purified thioglycosides **20**–**22**, indicating that the thio group in **30** came from the remaining TMSSTol reagent in the reaction flask. In this latter single step procedure, disaccharides **27**, **28**, and **29** were acquired in 51%, 65%, and 71% yields, respectively.

Table 3. Glycosylation of the in Situ Generated Persilylated Thioglycosides



entry	free sugar	product	yield (%)	α/β ratio[a]
1	D-glucose (**1**)	**27**	36	2/1
2	D-mannose (**4**)	**28**	49	4/1
3	D-galactose (**5**)	**29**	44	10/1

[a]Determined by using ^{1}H NMR.

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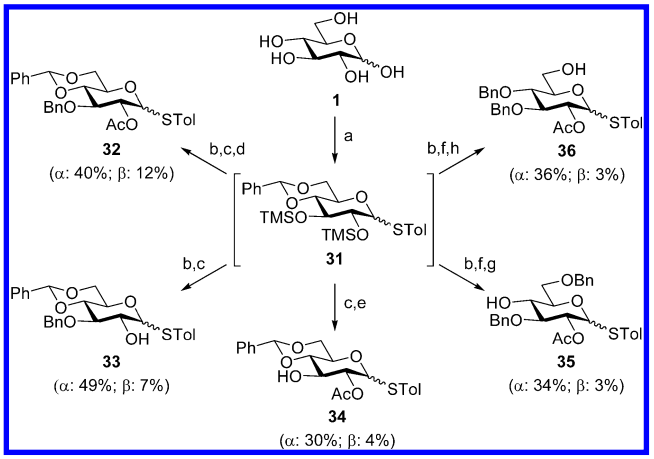
We then considered the merging and compatibility of the MW-based approach and our established regioselective and combinatorial one-pot protection strategy (Scheme 5). A

Scheme 5. One-Pot Synthesis of Thioglucoside Deviratives via the MW-Assisted Thioglycosylation[a]

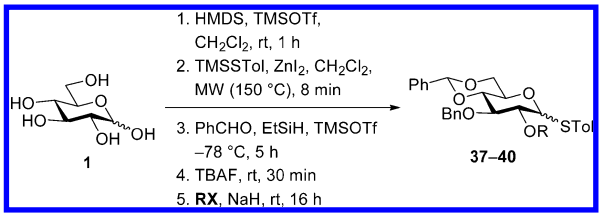


[a]Reagents and conditions: (a) HMDS, TMSOTf, CH_2Cl_2, rt, 1 h; TMSSTol, ZnI_2, CH_2Cl_2, MW (150 °C), 8 min; PhCHO, TMSOTf, 0 °C, 2 h; (b) PhCHO, Et_3SiH, TMSOTf, −78 °C, 5 h; (c) TBAF, rt, 30 min; (d) Ac_2O, Et_3N, rt, 16 h; (e) AcOH, Ac_2O, Et_3N, 0 °C, 16 h; (f) Ac_2O, TMSOTf, 0 °C, 16 h; (g) TfOH, Et_3SiH, −78 °C, 30 min; (h) BH_3·THF, TMSOTf, 0 °C, 16 h. Ac, acetyl.

successful integration is expected to further alleviate building block preparation. Accordingly, after the MW-assisted one-pot thioglycosylation of D-glucose, the 4,6-*O*-benzylidene group was introduced using benzaldehyde and TMSOTf to afford the supposed intermediate **31**. Subsequent treatment with benzaldehyde, Et_3SiH, and TMSOTf at −78 °C then regioselectively introduced a benzyl group at the 3-O-position. The inductive effect by the two oxygens attached to the anomeric carbon contributes to the lower nucleophilicity of O2 and, therefore, the regioselective reductive 3-O-benzylation in this acidic condition. By the same reason, the typical base-assisted benzylation as well as acylation theoretically favors the 2-O-position. Further desilylation using TBAF and treatment with Ac_2O and Et_3N in the same pot furnished the fully protected thioglycoside **32** as a mixture of separable anomers in a combined yield of 52%. The 2-alcohol **33** was synthesized in five transformations using a similar procedure as that for compound **32**, except for acetylation.[21] On the other hand, the 3-alcohol **34** can be obtained in a one-pot manner by first converting D-glucose into the intermediate **31**, followed by desilylation and regioselective 2-O-acetylation under basic condition.[9c] The preparations of the 4- and 6-alcohols were carried out in the same flask by regioselective 4,6-*O*-benzylidene ring-opening at O4 and O6, respectively, after the TMSOTf-catalyzed 3-O-benzylation and 2-O-acetylation stages. The addition of TfOH and Et_3SiH furnished the 4-glycosyl alcohol **35**, whereas BH_3·THF and TMSOTf afforded the 6-alcohol **36**.[20]

Aside from the participating acetyl group, nonparticipating orthogonal protecting groups were also introduced at O2 using the one-pot procedure to show the flexibility of the method in providing a diverse set of fully protected thioglycosides. As shown in Table 4, the O2 position was readily masked in a one-pot setting with 2-NAP, PMB, *p*-BrBn, and allyl protecting

Table 4. Regioselective One-Pot Protection of Fully Protected Thioglucosides



			yield (%)	
entry	RX[a]	product[a]	α	β
1	2-NAPBr	**37**: R = 2-NAP	38	7
2	PMBCl	**38**: R = PMB	37	8
3	*p*-BrBnBr	**39**: R = *p*-BrBn	38	5
4	AllBr	**40**: R = All	42	10

[a]Notation: 2-NAP, 2-naphthylmethyl; PMB, *p*-methoxybenzyl; All, allyl.

groups under Williamson's condition. While the introduction of these groups at O2 is feasible under our acidic and reductive procedure, a basic condition is utilized here to avoid the side products that might be produced because of the presence of the remaining benzaldehyde reagent in the reaction solution. The fully protected thioglucosides **37**−**40** were obtained in good one-pot yields, with the α-isomer as major product, after six transformation stages and a single chromatographic purification.

CONCLUSIONS

We have developed an efficient and rapid method for preparing 1,6-anhydrosugars and thioglycosides directly from unprotected monosaccharides via the MW-assisted one-pot reaction. The faster reaction times, minimal purification step, high preference to α-thioglycosides, and the fact that the process starts from the free sugars are among the attractive qualities of this approach. In addition, the extension of the synthetic method to glycosylation and the regioselective and combinatorial one-pot protection protocol developed by us offer ready access to numerous suitably protected thioglycoside building blocks for the synthesis of essential glycans. Further applications of this method to broader sugar systems are now under study.

EXPERIMENTAL SECTION

General Procedure for the MW-Assisted One-Pot Synthesis of 1,6-Anhydrosugars. In a microwave tube, TMSOTf (0.2 equiv) was added at room temperature (rt) under N_2 atmosphere to a suspension of the free sugar (1.0 equiv) and HMDS (2.5 equiv) in dry CH_2Cl_2 (10 mL per gram of the free sugar). The reaction was stirred for at least 30 min and monitored by thin layer chromatography. Once the reaction was completed, the mixture was purged with dry N_2 gas, which eliminated the ammonia byproduct and also vaporized most of the solvent. Then, the per-*O*-trimethylsilylated intermediate was dissolved in CH_2Cl_2 (20 mL per gram of the free sugar) followed by the addition of 10 mol % of TMSOTf or TfOH. The resulting reaction mixture was subjected to MW irradiation in the respective mode for the time interval described in Table 1. The reaction mixture was further treated with HMDS (2 equiv) and stirred for 30 min at room temperature. The crude reaction mixture was purified in a short column using silica gel (ethyl acetate/hexanes = 1/25 to 1/15).

General Procedure for the MW-Assisted One-Pot Synthesis of Thioglycosides. In a microwave tube, TMSOTf (0.2 equiv) was added to a mixture of the free sugar (1.0 equiv) and HMDS (2.6 equiv) in CH_2Cl_2 (10 mL per gram of the free sugar) under N_2 atmosphere. After stirring at room temperature for 30 min, the mixture

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was purged with dry N_2 gas, which eliminated the ammonia byproduct and also vaporized most of the solvent. CH_2Cl_2 (20 mL per gram of the free sugar), ZnI_2 (0.2 equiv), and TMSSTol (1.1 equiv) were consecutively added to the reaction mixture, and the resulting mixture was heated to 150 °C by MW irradiation for 8 min. The reaction was then cooled down to room temperature and HMDS (1.8 equiv) was added to the mixture, which was further stirred for another hour. The mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. Purification of the crude residue was carried out by flash column chromatography in silica gel (ethyl acetate/hexanes = 1/150).

General Procedure for the MW-Assisted One-Pot Synthesis of Disaccharides Bearing a Thiotolyl Aglycone Function. In a microwave tube, TMSOTf (0.2 equiv) was added to a mixture of the free sugar (1.0 equiv) and HMDS (2.6 equiv) in CH_2Cl_2 (10 mL per gram of the free sugar) under N_2 atmosphere. After being stirred at room temperature for 30 min, the mixture was purged with dry N_2 gas, which eliminated the ammonia byproduct and also vaporized most of the solvent. CH_2Cl_2 (20 mL per gram of the free sugar), ZnI_2 (0.2 equiv), and TMSSTol (1.05 equiv) were consecutively added to the reaction mixture, and the resulting mixture was heated to 150 °C by MW irradiation for 8 min. The reaction was cooled to room temperature, and activated 3 Å molecular sieves (2 g per gram of the free sugar) and compound **18** (1.1 equiv) were added to the reaction. The mixture was further cooled down to −20 °C. AgOTf (3 equiv) was then added, and the mixture was stirred for 3 h. Afterward, TBAF (1 M solution in THF, 3 equiv) was added, and the resulting mixture was stirred for 1 h at room temperature. The mixture was filtered through a pad of Celite and concentrated under reduced pressure. The products were separated and purified by flash column chromatography (ethyl acetate/hexanes =1/1 to 1/3) in silica gel.

General Procedure for the MW-Assisted One-Pot Synthesis of Fully Protected Thioglucosides with Various Ether-Type Protection at O2. In a microwave tube, TMSOTf (0.2 equiv) was added to a mixture of D-glucose (**1**) and HMDS (2.6 equiv) in CH_2Cl_2 (10 mL per gram of the free sugar) under a N_2 atmosphere. After stirring at room temperature for 30 min, the reaction was purged with N_2 gas, which eliminated the ammonia byproduct and also vaporized most of the solvent. CH_2Cl_2 (20 mL per gram of sugar), ZnI_2 (1.12 equiv), and TMSSTol (0.2 equiv) were added to the reaction flask, and the mixture was heated in the microwave reactor at 150 °C for 8 min. The reaction was cooled to room temperature and activated 3 Å molecular sieves (2.5 g per gram of the free sugar) was added. The solution was further cooled down to 0 °C, and PhCHO (1.2 equiv) and TMSOTf (0.2 equiv) were subsequently added to the solution. After stirring for another 2 h, the reaction mixture was cooled to −78 °C and stirred for another 15 min. Et_3SiH (1.12 equiv), PhCHO (1.12 equiv), and TMSOTf (0.2 equiv) were consecutively added to the reaction mixture and stirred for another 5 h. TBAF (1 M solution in THF, 1.0 equiv) was added to the solution and the reaction flask was warmed up to room temperature and stirred for 1 h. Then, NaH (10 equiv) and the alkyl halide (5.0 equiv) were sequentially added to the reaction mixture, and the resulting solution was stirred at room temperature for another 16 h. The whole mixture was filtered through a pad of Celite, the filtrate was diluted with H_2O, and the crude product was extracted with CH_2Cl_2. The organic layer was washed with brine and concentrated under reduced pressure to furnish the crude residue, which was purified by flash column chromatography in silica gel (ethyl acetate/hexanes = 1/5).

■ ASSOCIATED CONTENT

Supporting Information

Additional experimental procedures and characterization data for relevant compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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