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Copper(II) Triflate: A Versatile Catalyst for the One-Pot Preparation of Orthogonally Protected Glycosides

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Abstract: The development of general and expedient methodologies for the preparation of orthogonally protected glycoside building blocks is essential for the efficient synthesis of complex oligosaccharides. Herein, we describe a new approach that uses copper(II) triflate as a versatile catalyst for the one-pot preparation of orthogonal protected thio- and *O*-glycosides from the corresponding unprotected counterparts. The conditions are mild, easy to handle and applicable to two and three one-pot tandem transformations, which include arylidene acetalation, esterification, regioselective reductive acetal ring opening, glycosylation and silylation processes.

Keywords: carbohydrates; catalysis; copper(II) triflate; oligosaccharide synthesis; one-pot procedure

Recent developments in glycobiology and glycomedicine research have made carbohydrates and their glycoconjugates increasingly popular as lead compounds in drug and vaccine discovery.[1] Furthermore, carbohydrate scaffolds have also been employed as chiral precursors in natural product synthesis with good success.[2] The preparation of structurally defined oligosaccharide scaffolds has remained a major obstacle in the field. The development of expedient methods to efficiently prepare these complex molecules remains essential to make oligosaccharide synthesis available to main stream chemists and for understanding glycan diversity and function.[3]

Oligosaccharide synthesis relies on the ability to link monosaccharide units in a chemo-, regio- and stereoselective manner. This is typically accomplished by the use of orthogonal protecting groups[4] and of building blocks with suitable leaving groups[1a] that can be manipulated under different reaction conditions. However, the synthesis of these differentially protected monosaccharide moieties is still a very labour-intensive process, as it is typically accomplished by the introduction of each functional group in a stepwise fashion. This process tends to increase the linearity and decrease the efficiency of the overall synthesis.

Most methodologies developed for the assembly of complex oligosaccharide structures are aimed at investigating new, improved promoters to catalyze the glycosylation reaction[5] or more efficient coupling strategies such as: one-pot multistep glycosylation reactions,[6] polymer-supported,[7] fluorous tag[8] or ionic liquid-supported[9] oligosaccharide syntheses. However, little effort has been devoted to the development of efficient approaches that can be applied to the preparation of orthogonally protected monosaccharide building blocks.[4] In the last few years, very elegant Lewis acid-catalyzed one-pot regioselective protection strategies by the groups of Beau[10] and Hung[11] have been reported. Still, their approaches require the use of labile per-*O*-trimethylsilyl ether glucosides as their starting materials, since their strategy is not suitable for unprotected glucosides.

Herein, we report the first successful application of copper(II) triflate [$Cu(OTf)_2$] to catalyze arylidene acetalation reactions. Furthermore, we show the versatility of this catalyst in the application of sequential one-pot catalyzed orthogonal functionalization of unprotected glycosides that includes up to three distinct steps.

In the last decade, $Cu(OTf)_2$ has been used in a battery of extended synthetic applications, including numerous examples where $Cu(OTf)_2$ gives better results than other popular metal triflates such as $Yb(OTf)_3$ and $Sc(OTf)_3$.[12] Furthermore, $Cu(OTf)_2$ has been

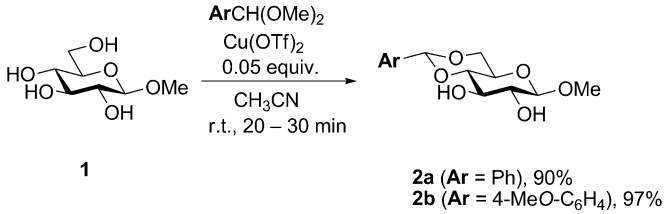
found in a variety of highly useful applications in carbohydrate chemistry. For instance, $Cu(OTf)_2$ has been used to catalyze acetylation reactions,[13] and more recently was used as a mild glycosylation promoter.[14] In general, $Cu(OTf)_2$ is used in catalytic amounts and is water-stable, hence it can be easily recycled and reused without loss of activity,[15] which makes it very attractive for the synthetic chemist.

The use of 4,6-*O*-arylidene acetalations as a protecting group strategy is widely spread on carbohydrate templates in combination with esterification at C-2 and C-3, as it provides a versatile orthogonal protection that allows for regio- and stereocontrol in oligosaccharide assembly. 4,6-*O*-Arylidene acetals can either undergo regioselective ring opening to provide a free 4-OH or 6-OH, or afford both free hydroxy groups upon acetal hydrolysis or hydrogenolysis.[4] 4,6-*O*-Arylidenation is often performed under harsh acidic conditions and the use of a Lewis acid to catalyze acetalation reactions is rarely reported.[16,17] In those instances, the benzaldehyde is used in large excess (i.e., as reaction solvent)[16] or the reaction proceeds slowly requiring long reaction times for completion.[17]

Due to its coordinating as well as Lewis acid properties,[12a] we speculated that $Cu(OTf)_2$ could be a good catalyst for the arylidene acetalation of glycosides, while still providing a mild reaction medium.

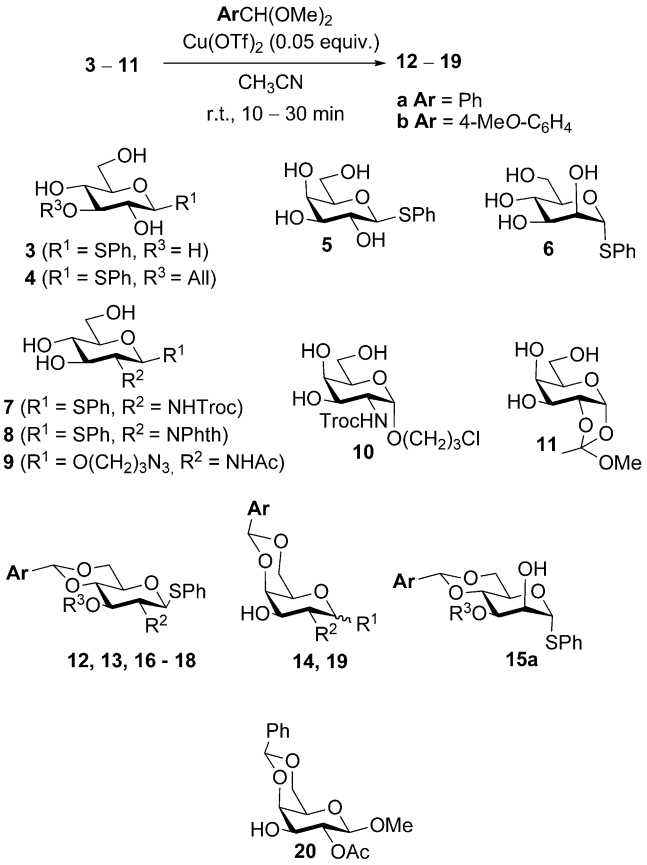
With that in mind, we decided to test our hypothesis with a simple 4,6-*O*-arylidene acetalation of commercial methyl β-D-glucopyranoside **1** in the presence of $Cu(OTf)_2$ (0.05 equiv.) and the corresponding dimethyl arylidene acetal (1.2 equiv.) in CH_3CN (Scheme 1). Conversion to product was achieved within 20 min at room temperature under sonication conditions and 4,6-*O*-benzylidene acetal derivative **2a** and 4,6-*O*-*p*-benzylidene acetal **2b** were obtained in excellent yields of 90% and 97%, respectively.

Encouraged by these results, we then turned our attention to explore the scope of the reaction with other frequently used thio- and *O*-glycosides.[18] To that end, a series of synthetic thiophenyl glycosides, including examples containing allyl protecting groups and a series of common *N*-protecting groups (NHTroc, NPhth, NHAc) (compounds **3**–**8**) were prepared. In addition, a series of *O*-glycosides bearing either a 1-*O*-alkyl azide chain, a 1-*O*-alkyl halide chain or an acid labile 1,2-*ortho* ester (compounds **9**–**11**), were prepared. These two series of compounds were subjected to the same reaction conditions previously described in Scheme 1. In general, the reactions proceeded cleanly, were complete within 10–30 min at room temperature under sonication conditions and products **12**–**20** were isolated in yields of 85–98% (Table 1).



Scheme 1. $Cu(OTf)_2$-catalyzed 4,6-*O*-arylidene acetalations.

Table 1. $Cu(OTf)_2$-catalyzed 4,6-*O*-arylidene acetalations.



Entry	Ar	Substrate	Product	Yield[b] [%]
1	Ph	**3**	**12a**	94[c]
2	PMP[a]	**3**	**12b**	85
3	Ph	**4**	**13a**	98[c]
4	Ph	**5**	**14a**	90
5	PMP	**5**	**14b**	86
6	Ph	**6**	**15a**	70[d]
7	Ph	**7**	**16a**	85[c]
8	PMP	**7**	**16b**	85
9	Ph	**8**	**17a**	90[c]
10	Ph	**9**	**18a**	95
11	Ph	**10**	**19a**	91[c]
12	Ph	**11**	**20**	45

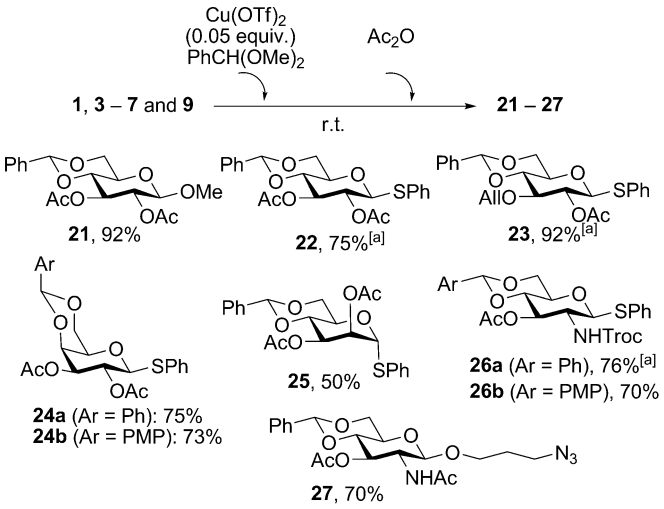
[a] PMP = *p*-methoxyphenyl.
[b] Isolated yield.
[c] The reaction was carried out in a gram-scale.
[d] Performed with 2 equivalents of $PhCH(OMe)_2$

In all cases, the reactions proceeded with excellent regioselectivity with only the 4,6-*O*-arylidene product observed, without any trace of the undesired 3,4-*O*-acetal in the case of galactosides **5** and **10** (entries 4, 5 and 11, Table 1) or 2,3-*O*-acetal in the case of mannoside **6** (entry 6, Table 1).[19] Moreover, the reaction conditions are compatible with different protecting groups such as allyl ethers (entry 3, Table 1) and amino protecting groups (entries 7–10, Table 1) demonstrating the generality of use of this approach. Interestingly, when orthoester **11** was treated with $Cu(OTf)_2$ in the presence of benzaldehyde dimethyl acetal, concomitant formation of the 4,6-*O*-acetal with orthoester rearrangement gave the unexpected product **20**, containing the 4,6-*O*-benzylidene, an acetyl group at C-2 and a free 3-OH, in a moderate yield of 45%. This exciting outcome offers a very useful and non-toxic entry into selective C-2/C-3 glycoside functionalization that is otherwise generally achieved by toxic stannylene

These encouraging results combined with our interest in developing new and improved approaches for the preparation of versatile glycoside building blocks, led us to the investigation of a new, general and efficient multistep synthesis of orthogonally functionalized glycosides.

One-pot synthetic strategies offer a very attractive alternative to sequential approaches, since several synthetic steps can be performed in the same reaction vessel, without any need for work-up and purification between the steps. One-pot 4,6-arylidene acetalation/acetylation of sugar derivatives has been reported under acidic conditions using immobilized $HClO_4$[21] and H_2SO_4,[22] respectively, or *p*-toluenesulfonic acid.[23] However, all of these strategies are based on the use of harsh, and in some cases, difficult to handle acidic systems to catalyze the reactions. Our group has recently reported the iodine (I_2)-catalyzed one-pot tandem acetalation/esterification reaction of unprotected thio- and *O*-glycosides.[24] However, 0.4 equivalents of I_2 were needed to drive the reaction to completion and catalytic 4-dimethylaminopyridine was required to accelerate the esterification step.

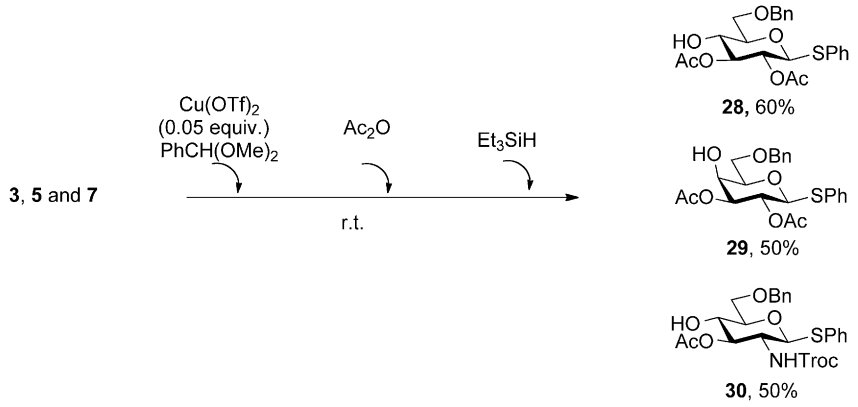
Having shown that acetal formation could be effectively catalyzed by $Cu(OTf)_2$, we decided to apply the developed conditions to the preparation of orthogonally protected glycosides in one-pot acetalation/acetylation tandem reactions. To that purpose, glycosides **1**, **3**–**7** and **9** were first subjected to the $Cu(OTf)_2$-catalyzed acetalation reaction. Upon completion as shown by TLC, acetic anhydride (Ac_2O)[25] and another 0.05 equivalents of $Cu(OTf)_2$ were added to the reaction mixture, which was left stirring at room temperature overnight to afford products **21**–**27** (Scheme 2). Reactions proceeded in good to excellent yields ranging from 70–92% over 2 steps, with the exception of mannose derivative **25** that was obtained in



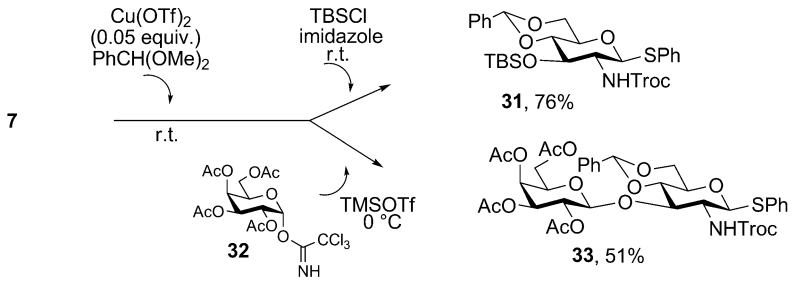
Scheme 2. One-pot $Cu(OTf)_2$-catalyzed tandem acetalation/acetylation reactions. [a] The reaction was carried out in a gram-scale.

a moderate yield of 50%. It is noteworthy that *p*-methoxybenzylidene acetals, which undergo acid hydrolysis 10 times faster than the benzylidene counterparts,[26] could withstand the reaction conditions and products **24b** and **26b** were isolated in yields of 73% and 70%, respectively, demonstrating that our mild set of conditions are compatible with this more labile class of acetals. Moreover, the tandem one-pot reaction was also compatible with the use of amino protecting groups, as demonstrated for substrates **7** and **9** which afforded products **26a** and **27** in yields of 76% and 70%, respectively. In addition allyl ether bearing **23** was obtained in 92% yield from **4**.

Et_3SiH is frequently used in the presence of a protic acid or $Cu(OTf)_2$ as a hydride source in reductive 4,6-*O*-benzylidene ring opening of carbohydrates to form 4-OH, 6-OBn bearing derivatives.[27] Based on our preliminary data, we proposed that a 4,6-O-benzylidene reductive opening step could be incorporated into the one-pot sequence. Consequently, glucosyl **3**, galactosyl **5** and NHTroc protected glucosaminyl **7** thioglycosides, were subjected to the one-pot $Cu(OTf)_2$-catalyzed acetalation/esterification conditions previously described, once the two-step process was complete as shown by TLC, Et_3SiH was added to the reaction mixture and the expected products **28**, **29** and **30** were obtained cleanly in yields of 50–60% over the 3-step conversion (Scheme 3). It is important to note that the strategy affords, in one-pot and at room temperature, thioglycoside products that are differentially protected, that is, each orthogonal protecting group can be chemoselectively unmasked. For instance, the C-3 acetate group is base labile, while the C-6 benzyl group is susceptible to hydrogenolysis and



Scheme 3. One-pot $Cu(OTf)_2$-catalyzed tandem acetalation/acetylation/reductive opening reactions.



Scheme 4. One-pot $Cu(OTf)_2$-catalyzed tandem acetalation/silylation and acetalation/glycosylation processes.

the glycosides are ready to be used as both glycosyl donors and acceptors.[5b]

Another synthetically useful protecting group combination is that of acetalation/silylation. This was achieved by acetalation of **7** in the presence of $Cu(OTf)_2$ followed by addition of chloro(*tert*-butyl)dimethylsilane and imidazole to afford **31** in 76% isolated yield, after two steps.

In order to showcase further the versatility of $Cu(OTf)_2$, the one-pot acetalation/glycosylation reaction was also investigated. For that purpose, benzylidenation of NHTroc protected glycosaminyl **7** was carried out with $Cu(OTf)_2$ as described before. Upon completion of the 4,6-*O*-acetalation, glycosyl donor **32** and TMSOTf (0.05 equiv.) were added at 0 °C (Scheme 4). Disaccharide **33** was obtained after 1 hour in a yield of 51% over the 2 steps.[29]

These results highlight the wide range of transformations possible in the presence of mild $Cu(OTf)_2$.

In summary, we have shown a versatile and fast one-pot $Cu(OTf)_2$-catalyzed strategy for the orthogonal protection of *O*- and thio-glycosides. The conditions are mild, easy to handle and applicable to two- and three-step one-pot tandem transformations, including arylidene acetalation, esterification, reductive acetal ring-opening, silylation and glycosylation processes. The reaction conditions are tolerant of most common amino protecting groups (Ac, Phth, Troc and N_3) and scalable to gram quantitities. This approach simplifies greatly the preparation of orthogonally protected building blocks ready to be used in oligosaccharide assembly and represents a significant step forward towards simplifying oligosaccharide synthesis and making it more accessible to main stream chemists.

Experimental Section

General Procedure for 4,6-*O*-Arylidenation

To a mixture of benzaldehyde (or 4-methoxybenzaldehyde) dimethyl acetal (1.2 mmol) in CH_3CN (10 mL) and the unprotected saccharide (1 mmol) was added $Cu(OTf)_2$ (0.05 mmol) and the system was sonicated at room temperature (10–30 min) under a nitrogen atmosphere. Upon completion as monitored by TLC, the solvent was concentrated and the residue was purified by flash chromatography to give the 4,6-arylidene product with the corresponding yield as shown in Table 1.

General Procedure for One-Pot 4,6-*O*-Arylidenation/Acetylation Reaction

To a mixture of benzaldehyde (or 4-methoxybenzaldehyde) dimethyl acetal (1.2 mmol) and the unprotected saccharide (1 mmol) in CH_3CN (10 mL) was added $Cu(OTf)_2$ (0.05 mmol) and the system was sonicated at room tempera-

ture (10–30 min) under a nitrogen atmosphere. Acetic anhydride (5 mmol, 5 equiv.) was then added and the obtained solution was stirred for a further 18 h. The reaction was quenched with Et_3N (0.1 mL) and the solvent was evaporated. The crude product was purified by flash chromatography to give the protected monosaccharides with corresponding yields as shown in Scheme 2.

General Procedure for One-Pot 4,6-*O*-Arylidenation/Acetylation/Reductive Ring Opening Reaction

To a mixture of benzaldehyde (or 4-methoxybenzaldehyde) dimethyl acetal (1.2 mmol) and the unprotected saccharide (1 mmol) in CH_3CN (10 mL) was added $Cu(OTf)_2$ (0.05 mmol) and the system was sonicated at room temperature (10–30 min) under a nitrogen atmosphere. Acetic anhydride (5 mmol, 5 equiv) was then added and the obtained solution was stirred for a further 18 h. Upon complete acetylation as shown by TLC, Et_3SiH (10 mmol, 10 equiv.) was added at 0 °C before adding a further quantity of $Cu(OTf)_2$ (0.05 mmol). The mixture was kept at room temperature for 3–4 h. After quenching the reaction with Et_3N (0.1 mL), the solvent was concentrated and the residue was purified by flash chromatography to give the 4-OH, 6-OBn products.

Procedure for One-Pot $Cu(OTf)_2$-Catalyzed Tandem Acetalation/Silylation Reaction; Synthesis of 31

To a solution of monosaccharide **6** (86 mg, 0.193 mmol), and benzaldehyde dimethyl acetal (35 μL, 0.232 mmol) in dry CH_3CN (2.0 mL) was added $Cu(OTf)_2$ (3.5 mg, 9.65 μmol). The reaction mixture was then sonicated for 30 min. Chloro(*tert*-butyl)dimethylsilane (146 mg, 0.967 mmol) and imidazole (66 mg, 0.967 mmol) were added and the reaction mixture was stirred for 2 h at 60 °C. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography (*n*-hexane/EtOAc, 95:5, v/v) to give the title product **31**; yield: 95 mg (76%); $[\alpha]_D^{22}$: −15 (*c* 0.9, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.50–7.46 (m, 4H, Ph), 7.38–7.30 (m, 6H, Ph), 5.52 (s, 1H, PhC*H*), 5.19 (d, 1H, $J_{NH,2}$ = 9.0 Hz, N*H*), 5.07 (d, 1H, $J_{1,2}$ = 10.5 Hz, H-1), 4.78 (d, 1H, *J* = 12.0 Hz, C*H*H, *Troc*), 4.71 (d, 1H, *J* = 12.0 Hz, CH*H*, *Troc*), 4.37 (dd, 1H, dd, 1H, $J_{6a,5}$ = 4.5 Hz, $J_{6a,6b}$ = 10.5 Hz, H-6a), 4.06 (t, 1H, $J_{3,2} = J_{3,4}$ = 9.0 Hz, H-3), 3.79 (t, 1H, $J_{6b,5}$ = 10.5 Hz, H-6b) 3.56–3.41 (m, 3H, H-2, H-4, H-5), 0.93 (s, 6H, 2 × C*H*$_3$, *TBS*) 0.11, 0.03, −0.03 (3 s, 9H, 3 × C*H*$_3$, *TBS*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 153.7 (CO, *Troc*), 137.0, 132.7 (C_q), 132.4, 129.1, 129.0, 128.1, 128.0, 126.3 (*C*H, *Ph*), 101.9 (Ph*C*H), 95.2 (CCl_3, *Troc*), 87.0 (C-1), 81.9 (C-4), 74.8 (*C*H$_2$, *Troc*), 72.0 (C-3), 70.4 (C-2), 68.6 (C-6), 58.5 (C-5), 25.7, 25.6 (2 × *C*H$_3$, *TBS*), 18.1 (C_q, *TBS*), −3.6, −4.2, −5.0 (3 × *C*H$_3$, *TBS*); ESI-HR-MS: *m/z* = 670.0990, calcd. for for $C_{28}H_{36}Cl_3NNaO_6S^+$ $(M+Na)^+$: 670.0996.

Procedure for One-Pot $Cu(OTf)_2$-Catalyzed Tandem Acetalation/Glycosylation Processes: Synthesis of 33

To a solution of **7** (37 mg, 0.08 mmol) and benzaldehyde dimethyl acetal (14 μL, 0.095 mmol) in dry CH_3CN (0.8 mL) was added $Cu(OTf)_2$ (1.5 mg, 3.95 μmol) and the solution was sonicated for 30 min. The solvents were then carefully evaporated under reduced pressure. After redissolving the obtained residue in CH_2Cl_2 (1.0 mL), the donor **32** (46 mg, 0.093 mmol) in dry CH_2Cl_2 (0.5 mL) was added followed by 4 Å MS. The reaction mixture was stirred for 1 h at room temperature before being cooled to 0 °C and TMSOTf (10% in CH_2Cl_2, 8.0 μL) was then added. The reaction was kept at 0 °C for 1 h, quenched with Et_3N (50 μL, 0.36 mmol) and purified by flash chromatography (Tol/EtOAc, 9:1→8:2, v/v), to afford disaccharide **33**; yield: 36 mg (51%) and phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside;[30] yield: 10 mg (28%).

Data for 33: $[\alpha]_D^{22}$: −13 (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.50–7.46 (m, 4H, Ph), 7.39–7.36 (m, 3H, Ph), 7.35–7.31 (m, 3H, Ph), 5.54 (s, 1H, PhC*H*), 5.36 (d, 1H, $J_{NH,2}$ = 8.0 Hz, N*H*), 5.30 (bd, 1H, $J_{4',3'}$ = 3.5 Hz, H-4′), 5.19 (dd, 1H, $J_{2',1'}$ = 8.0 Hz, $J_{2',3'}$ = 10.5 Hz, H-2′), 5.18 (d, 1H, $J_{1,2}$ = 10.5 Hz, H-1), 4.93 (dd, 1H, H-3′), 4.83 (d, 1H, d, 1H, *J* = 12.0 Hz, C*H*H *Troc*), 4.73 (d, 1H, *J* = 12.0 Hz, CH*H* *Troc*), 4.70 (d, 1H, H-1′), 4.38 (dd, 1H, $J_{6a,5}$ = 5.0 Hz, $J_{6a,6b}$ = 10.5 Hz, H-6a), 4.30 (t, 1H, $J_{3,2} = J_{3,4}$ = 9.5 Hz, H-3), 4.05 (dd, 1H, $J_{6a',5'}$ = 8.0 Hz, $J_{6a',6b'}$ = 11.0 Hz, H-6a′), 3.83 (dd, 1H, $J_{6b',5'}$ = 6.0 Hz, H-6b′), 3.81 (t, 1H, $J_{6b,5} = J_{6b,6a}$ = 10.5 Hz, H-6b), 3.66 (t, 1H, $J_{4,3} = J_{4,5}$ = 9.5 Hz, H-4), 3.63 (dd, 1H, H-5′), 5.55 (ddd,1H, H-5), 3.38 (m, 1H, H-2). 2.11, 2.00, 1.96, 1.95 (4 s, 4 × 3H, 4 × C*H*$_3$, 4 × *OAc*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.2, 170.1, 169.4 (CO, *Ac*), 153.6 (CO, *Troc*), 136.9, (C_q, Ph), 132.9, 131.7, 129.3, 129.1, 129.0, 128.4, 128.3, 128.2 126.0 (CH, Ph), 101.3 (*C*HPh), 100.7, (C-1′), 95.3 (*C*Cl_3, *Troc*), 86.0 (C-1), 79.8 (C-4), 79.0 (C-3), 74.4 (*C*H$_2$ *Troc*), 70.9 (C-3′), 70.5 (C-5′), 70.4 (C-5), 69.3 (C-2′), 68.5 (C-6), 66.7 (C-4′), 60.8 (C-6′), 56.4 (C-2), 20.7, 20.6, 20.6, 20.5 (*C*H$_3$, *OAc*); ESI-HR-MS: *m/z* = 886.1076, calcd. for $C_{36}H_{40}Cl_3NNaO_{15}S^+$ $(M+Na)^+$: 886.1082.

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