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PII: S0008-6215(18)30580-9

DOI: <https://doi.org/10.1016/j.carres.2018.10.010>

Reference: CAR 7620

To appear in: *Carbohydrate Research*

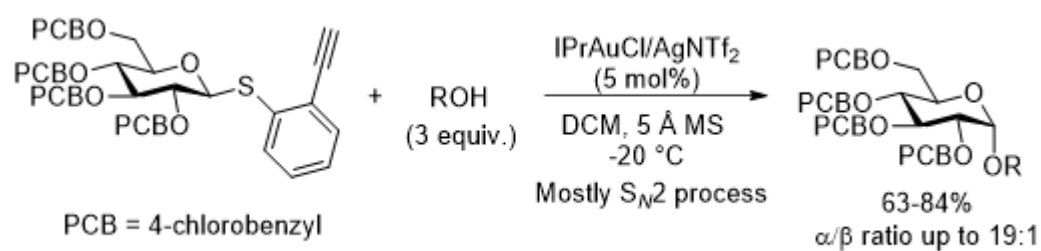
Received Date: 7 October 2018

Revised Date: 25 October 2018

Accepted Date: 25 October 2018

Please cite this article as: Z. Zheng, L. Zhang, Gold-catalyzed synthesis of 1,2-*cis* glucosides using an *o*-ethynylphenyl thioglucoside donor, *Carbohydrate Research* (2018), doi: <https://doi.org/10.1016/j.carres.2018.10.010>.

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# Gold-Catalyzed Synthesis of 1,2-*cis* Glucosides Using an *o*-Ethynylphenyl Thioglucoside Donor

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## Keywords:

Glycosylation; 1,2-*cis* glucosidic bond; *o*-ethynylphenyl thioglucoside; gold catalysis; S<sub>N</sub>2 pathway

## Abstract:

A glucosylation method featuring gold catalysis-activated *o*-ethynylphenyl thioglucosides as donors is described. With donor design and condition optimization, the reaction proceeds in a mostly S<sub>N</sub>2 pathway. A series of 1,2-*cis* glucosides are obtained in good yields and with up to 19:1  $\alpha$ -selectivity.

## 1. Introduction

Stereoselective construction of 1,2-*cis* glycosidic bonds remains challenging despite recent advances.[1, 2] Glycosylation reactions often involve oxocarbenium intermediates, which frequently result in the formation of anomeric mixtures of low to moderate selectivities (Scheme 1a). Previous achievements in selective construction of 1,2-*cis* glycosidic bond entail employing donor directing groups,[3-9] harnessing different reactivities of equilibrating donor anomers,[10-12] or exploiting conformational preferences of the reactive intermediates to minimize the formation of undesirable anomers (Scheme 1b).[13-16] Notwithstanding, these methods still rely on specific structural features of the donor molecule and, therefore, often fall short in generality.

An arguably more general approach to stereoselective glycosylation and in particular to the formation of 1,2-*cis* glycosides is to engineer a S<sub>N</sub>2-type process solely based on the leaving

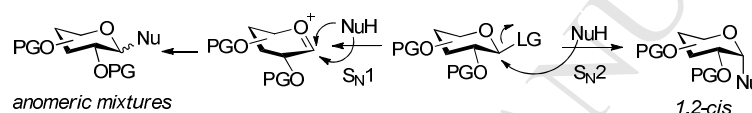
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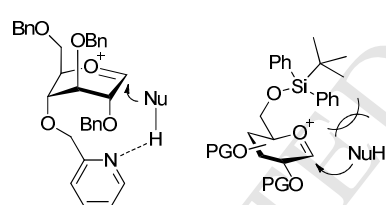
group and regardless of the remaining donor structure. As such, the stereochemistry of the newly

formed glycosidic bond would in theory only depend on the anomeric configuration of a donor molecule (Scheme 1a).[2]  $S_N2$  or “ $S_N2$ -like” reactions have been realized between deprotonated/anionic acceptors and glycosyl halide[17, 18] or sulfonate[19-25] donors and via a macrocyclic bisthiourea-catalyzed cooperative activation strategy,[26] but much advance in this area is still desired. We attempted to develop activation strategies to generate anomeric leaving groups that would permit  $S_N2$ -type glycosylations. Herein, we report our preliminary results on a gold-catalyzed synthesis of 1,2-glucosides using *o*-ethynylphenyl thioglucoside donors.

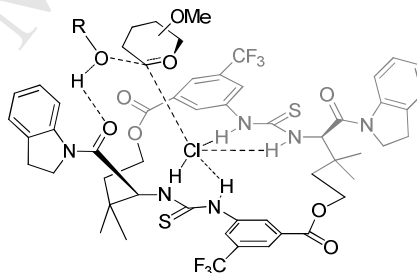
a. glycosylation pathways



b. directing effect and steric control



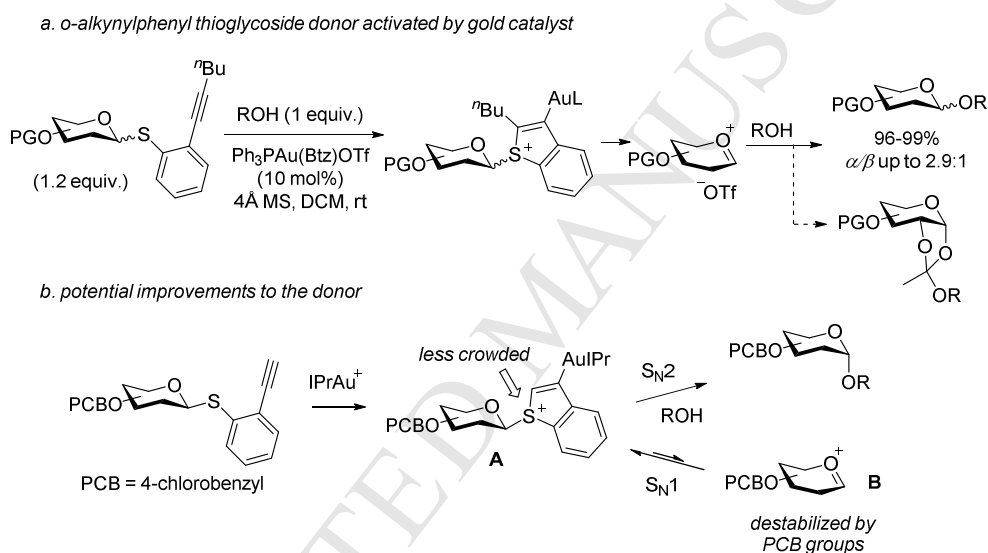
c.  $\beta$ -selective glycosylation catalyzed by macrocyclic bis-thioureas



**Scheme 1.** Glycosylation reactions and selected approaches to forming 1,2-*cis* glycosidic bonds.

Gold catalysis has been increasingly applied in glycoside synthesis for the past decade.[27-37] In 2012, Yu et al reported the use of *o*-alkynylphenyl thioglycoside as donor in a gold(I)-catalyzed glycosylation reaction. In this chemistry, the cationic and acidic Au(I) complex promotes the cyclization of the sulfur atom to the C-C triple bond, which results in the formation of a benzothiophenium intermediate. This reactive species is then susceptible to nucleophilic attack by acceptors (Scheme 2a).[38] However, the reaction suffers from low stereoselectivity and moderate yields due to side reactions and mostly proceeds through an oxocarbenium intermediate. We reasoned that modifying this system might render this type of activation

suitable for  $S_N2$ -type glycosylation and hence could circumvent those drawbacks (Scheme 2b). Firstly, we proposed to replace the donor benzyl protecting groups with more electron-withdrawing 4-chlorobenzyl groups (PCB),<sup>[39]</sup> aiming to inductively discourage the formation of oxocarbenium intermediate **B**. Secondly, we would employ (2-ethynylphenyl)thio group, which differs from Yu's version by the absence of alkyne terminus substituent, as the latent leaving group to 1) decrease the steric hindrance around the sulfur in the activated donor **A**, which should discourage the expulsion of the benzothiophene, and 2) ensure a faster gold-catalyzed cyclization reaction. Finally, we reasoned that a less acidic  $\text{IPrAu}^+$  catalyst would further stabilize the sulfonium intermediate **A** and favor the  $S_N2$  pathway.



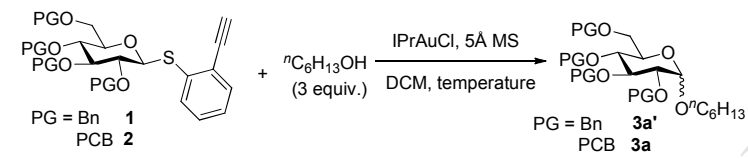
**Scheme 2.** Redesigning *o*-Alkynylphenyl thioglycoside donors.

## 2. Results and Discussion

Based on this design, we synthesized anomerically pure *o*-ethynylphenyl thioglucosides **1** and **2** and performed a series of initial studies with *n*-hexanol as the acceptor (Table 1). To our delight, glycoconjugate **3a'** was obtained in an encouraging  $\alpha/\beta$  ratio of 7:1 when the substrate **1** bearing benzyl protecting groups was employed as donor. Lowering the reaction temperature to  $-20\text{ }^\circ\text{C}$  improved the ratio to 13:1. Eventually, the donor **2** bearing 4-chlorobenzyl groups gave an excellent 19:1 ratio at  $-20\text{ }^\circ\text{C}$ , confirming the value of employing inductive destabilization of the oxocarbenium intermediate to improve the reaction's  $S_N2$  characteristics. Later, we were glad to find that lowering the catalyst loading to 5% does not change the reaction outcome. Following these encouraging results, a quick screening of counterion indicated that  $\text{NTf}_2^-$  gave the best

result. Notably, little selectivity was observed with OTf (Table 1, entry 5), which is in accordance with the previously reported counterion effect of OTf.[40, 41]

**Table 1.** Reaction condition optimization



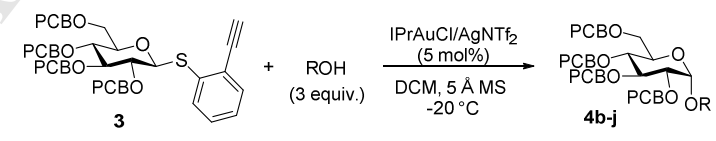
Entry	Donor	IPrAuCl loading	Halide abstractor (5 mol %)	Temperature	Yield and Selectivity ( $\alpha/\beta$ ) <sup>b</sup>
1	<b>1</b>	10 mol%	AgNTf <sub>2</sub>	rt	60%, 7/1
2	<b>1</b>	10 mol%	AgNTf <sub>2</sub>	-20 °C	66%, 13/1
3	<b>2</b>	10 mol%	AgNTf <sub>2</sub>	-20 °C	83%, 19/1
4	<b>2</b>	5 mol%	AgNTf <sub>2</sub>	-20 °C	84%, 19/1
5	<b>2</b>	5 mol%	AgOTf	-20 °C	80%, 0.8/1
6	<b>2</b>	5 mol%	AgSbF <sub>6</sub>	-20 °C	90%, 15/1
7	<b>2</b>	5 mol%	NaBARF	-20 °C	65%, 16/1

<sup>a</sup> Concentration: 0.05M. Reaction was stirred in a cooling bath for 6 hours before being quenched by <sup>n</sup>Bu<sub>4</sub>NCl. <sup>b</sup>

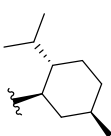
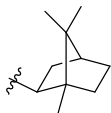
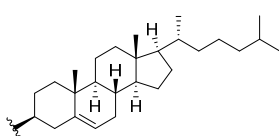
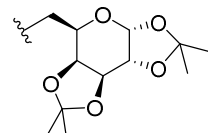
Combined yield and anomeric ratio determined by NMR with internal references.

With optimal conditions in hand, we investigated the scope of this gold-catalyzed glucosylation reaction. Like *n*-hexanol, benzyl alcohol was converted to the corresponding benzyl glucoside **3b** in excellent yield and selectivity. When secondary and tertiary alcohols were used, a slight drop in yield and selectivity was observed (Table 2, **3c**, **3d**, and **3e**), most likely due to the increased steric hindrance that hampers the S<sub>N</sub>2 attack. A moderate 66% yield and 10:1 selectivity was obtained with benzoic acid as nucleophile (Table 2, **3f**). Cholesterol was also successfully converted to the corresponding glycoconjugate **3g** in moderate yield and a 5:1  $\alpha/\beta$  selectivity. Finally, the galactose-derived acceptor with a free 6-OH group reacted smoothly under the optimal conditions, yielding the disaccharides **3h** in 68% yield and a decent anomeric selectivity.

**Table 2.** Scope study of the glycosylation method

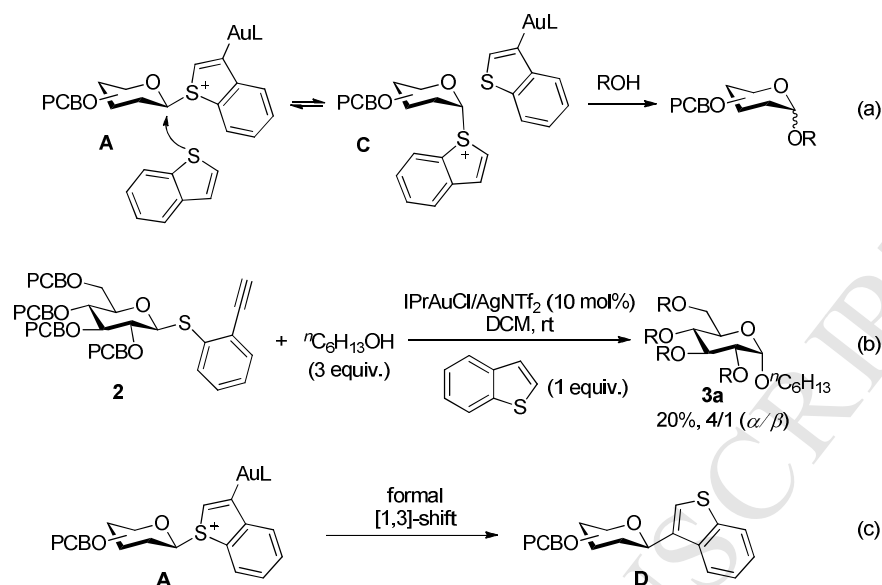


Product	R group	Yield	Selectivity ( $\alpha/\beta$ )
<b>3b</b>	Bn	80%	19/1

<b>3c</b>		72%	15/1
<b>3d</b>		74%	16/1
<b>3e</b>	<sup>t</sup> Bu	73%	15/1
<b>3f</b>	Bz	66%	10/1
<b>3g</b>		63%	5/1
<b>3h</b>		68%	12/1

<sup>a</sup> Reactions were stirred in cooling bath for 10 hours. All yields are combined isolated yield. Anomeric ratio was determined by NMR.

The scope studies reveal that the nucleophilicity and the steric hindrance of an acceptor, as expected, affect the reaction outcome. As a general trend, a less nucleophilic and sterically more hindered acceptor tends to give a lower yield and a poorer selectivity. We hypothesized that as the reaction proceeds, the benzothiophene byproduct accumulated in the reaction mixture may in turn react with the activated donor **A**, resulting in racemization of the donor (Scheme 3a). Additionally, the benzothiophene may coordinate to the cationic gold(I) catalyst and therefore slow the reaction, as corroborated by the reaction shown in Scheme 3b. Additionally, the side product **D** generated from a formal [1,3] shift[38] of the intermediate **A** could be detected in almost all cases (Scheme 3c), which accounts for the moderate yields in some of the challenging cases.



**Scheme 3.** Involvement of benzothiophene byproduct in the reaction

### 3. Conclusions

In summary, we have developed an improved gold catalysis for the construction of 1,2-*cis* glucosidic bonds using *o*-ethynylphenyl thioglucoside donors. The method improves upon the previously reported approach and realizes largely  $S_N2$  glucosylation. Good to excellent level of  $\alpha$ -selectivities can be realized. The employment of 4-chlorobenzyl group instead of the typical benzyl group as sugar OH protecting group permits enhanced levels of  $S_N2$  due to inductive destabilization of the  $S_N1$  oxocarbenium intermediate.

### 4. Acknowledgements

This work was supported by the NIH Glycoscience Common Fund program (1U01GM125289). The research reported here made use of a 400 MHz NMR instrument funded by NIH S10OD012077 and the shared facilities of the UCSB MRSEC (NSF DMR 1720256).

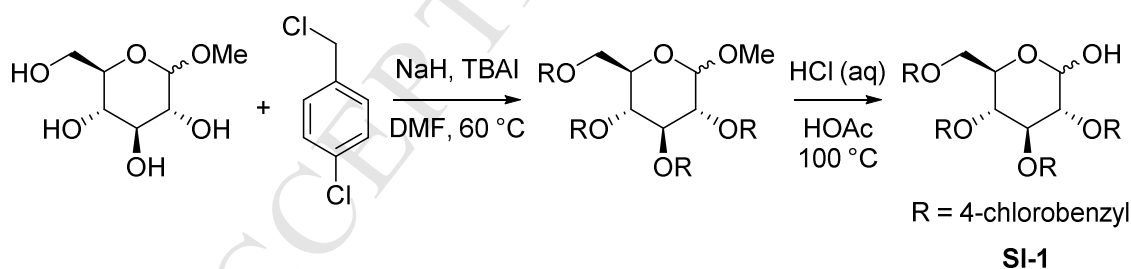
### 5. Experimental

#### General



Ethyl acetate (ACS grade), hexanes (ACS grade), dichloromethane (ACS grade) were purchased from Fisher Scientific and used without further purification. ACS grade 1,2-dichloroethane were purchased from Acros Organics and used directly. Commercially available reagents were used without further purification. Reactions were monitored by thin layer chromatography (TLC) using Silicycle precoated silica gel plates. Flash column chromatography was performed over Silicycle silica gel (230-400 mesh).  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on a Varian 400 MHz spectrometer, a Varian 500 MHz Unity plus spectrometer, and a Varian 600 MHz Unity plus spectrometer, using residue solvent peaks as internal standards ( $\text{CDCl}_3$ ,  $^1\text{H}$ : 7.26 ppm;  $^{13}\text{C}$ : 77.00 ppm). Infrared spectra were recorded with a Perkin Elmer FT-IR spectrum 2000 spectrometer and are reported in reciprocal centimeter ( $\text{cm}^{-1}$ ). Mass spectra were recorded with Waters (Micromass) LCT premier #1, using electrospray method and TOF detector.

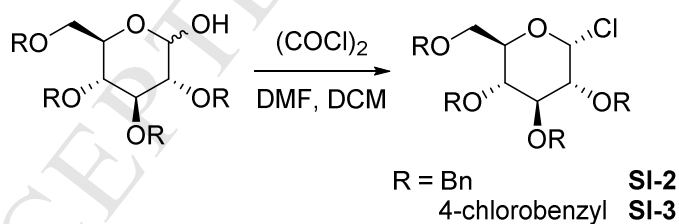
#### Preparation of 2,3,4,6-tetra-*O*-(4-chlorobenzyl)-D-glucopyranose (SI-1)



To a cooled (0 °C) mixture of 1-methyl-D-glucopyranose (1.94 g, 10 mmol), TBAI (369 mg, 1 mmol), and DMF (25 mL) was added NaH (60% in mineral oil, 2 g, 5 equiv.). The mixture was then stirred vigorously for 20 min, and 4-chlorobenzyl chloride (8 g, 5 equiv.) was added in small portions. The reaction was warmed up to room temperature gradually, heated at 60 °C for 12 hours, and quenched by careful addition of saturated  $\text{NH}_4\text{Cl}$  solution at 0 °C. The crude product was extracted by DCM, washed with water and brine, and concentrated under vacuum.

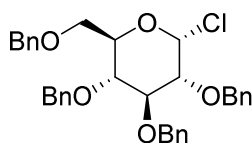
To the crude product of the first step was added HOAc (50 mL) and HCl (6M, 10 mL), and the mixture was stirred at 100 °C until TLC showed complete transformation of the starting material. The reaction was concentrated under vacuum, dissolved by DCM, washed with saturated NaHCO<sub>3</sub>, and dried with MgSO<sub>4</sub>. Upon removal of DCM under vacuum, the crude product was purified by silica gel column chromatography to give the product as a colorless oil (4.1 g, 61%, mixture of both anomers). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.35 – 6.96 (m, 16H), 5.24 (d, J = 3.5 Hz, 0.7H, α-anomer), 4.93 – 4.36 (m, 8.3H), 4.01 (ddd, J = 10.1, 4.1, 2.1 Hz, 0.7H, α-anomer), 3.92 (t, J = 9.3 Hz, 0.7H, α-anomer), 3.68 – 3.46 (m, 4.3H), 3.34 (dd, J = 9.0, 7.7 Hz, 0.3H, β-anomer). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 136.99, 136.81, 136.69, 136.49, 136.16, 133.88, 133.69, 133.63, 133.54, 133.44, 129.34, 129.26, 129.23, 128.93, 128.92, 128.84, 128.81, 128.70, 128.64, 128.59, 128.55, 128.54, 97.52, 91.07, 84.31, 82.91, 81.49, 80.03, 77.68, 74.71, 74.68, 74.54, 74.04, 73.75, 72.74, 72.69, 72.33, 70.17, 68.84, 68.58. HRMS (ESI+, C<sub>34</sub>H<sub>32</sub>Cl<sub>4</sub>O<sub>6</sub>Na): calculated 699.0851, 701.0827, 703.0806, found 699.0848, 701.0836, 703.0839.

### Preparation of Glucopyranosyl Chlorides (SI-2 and SI-3)



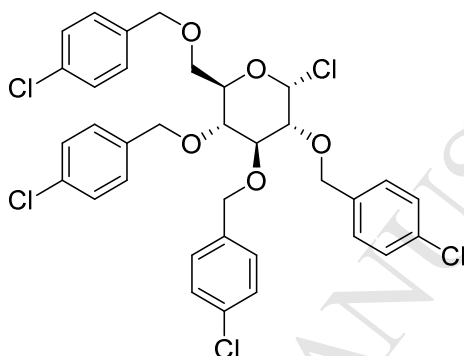
5 mmol of corresponding D-glucopyranose and 10 mmol of oxalyl chloride was mixed in DCM (20 mL) at room temperature, and 3 drops of DMF was added into the solution. Gas evolution was observed immediately, and the reaction was stirred at room temperature for 2 hours. The reaction was then concentrated under vacuum and purified with silica gel column chromatography to give the corresponding glucopyranosyl chlorides as colorless oil.

### 2,3,4,6-tetra-O-benzyl-D-glucopyranosyl chloride (SI-2)



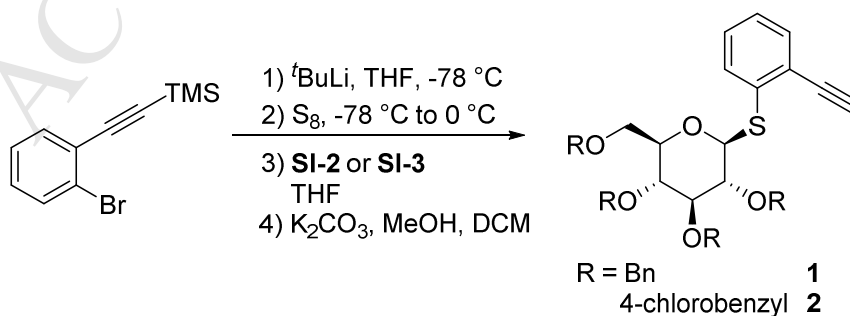
Prepared in 70% yield from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose. Its NMR data is in accordance with those reported by Takeo et al.[32]

### 2,3,4,6-tetra-*O*-(4-chlorobenzyl)-D-glucopyranosyl chloride (SI-3)



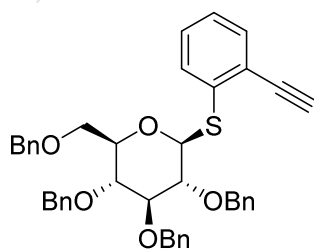
Prepared in 59% yield from **SI-1**.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33 – 7.03 (m, 14H), 6.12 (d,  $J$  = 3.7 Hz, 1H), 4.88 (d,  $J$  = 11.3 Hz, 1H), 4.74 (dd,  $J$  = 11.3, 4.5 Hz, 2H), 4.70 – 4.59 (m, 2H), 4.55 (d,  $J$  = 12.2 Hz, 1H), 4.46 (d,  $J$  = 11.3 Hz, 1H), 4.42 (d,  $J$  = 12.3 Hz, 1H), 4.11 – 4.04 (m, 1H), 3.99 (t,  $J$  = 9.2 Hz, 1H), 3.76 – 3.61 (m, 4H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  136.83, 136.35, 136.08, 135.79, 134.00, 133.71, 133.63, 133.54, 129.28, 129.27, 129.23, 129.22, 129.03, 128.84, 128.77, 128.64, 128.60, 128.60, 93.02, 81.16, 79.90, 76.33, 74.83, 74.23, 73.28, 72.71, 71.98, 67.76. . HRMS (ESI $^+$ ,  $\text{C}_{34}\text{H}_{31}\text{Cl}_5\text{O}_5\text{Na}$ ): calculated 717.0512, 719.0487, 721.0464, found 717.0659, 719.0513, 721.0464.

### Preparation of Glycosyl Donors (1 and 2)



2-Bromo-1-(trimethylsilylethynyl)benzene was synthesized quantitatively according to method reported by Ohno group.[35] A solution of 2-bromo-1-(trimethylsilylethynyl)benzene (860 mg, 3.4 mmol) in THF (10 mL) was cooled to  $-78^{\circ}\text{C}$ , and  $t\text{BuLi}$  (1.7 M in hexanes, 4 mL, 6.8 mmol) was added dropwise. The solution was stirred at  $-78^{\circ}\text{C}$  for another 30 minutes, and sulfur (109 mg, 3.4 mmol) was added in one portion at  $-78^{\circ}\text{C}$ . The reaction was then kept at  $0^{\circ}\text{C}$  for 1 hour and cooled down again to  $-78^{\circ}\text{C}$  before a solution of corresponding glucopyranosyl chloride (**SI-2** or **SI-3**, 2.5 mmol) in THF (5 mL) was added in one portion. The reaction was then warmed up to room temperature and stirred for 10 hours or until complete consumption of the glucopyranosyl chloride. The mixture was quenched by water, concentrated under vacuum, dissolved in a mixture of methanol and DCM (1:1, 10 mL in total), added  $\text{K}_2\text{CO}_3$  (200 mg), and stirred for 2 hours. Upon completion, the mixture was partitioned in DCM and water, extracted by additional DCM, dried with  $\text{MgSO}_4$ , and concentrated under vacuum. Column chromatography with silica gel gave the desired product **1** and **2**.

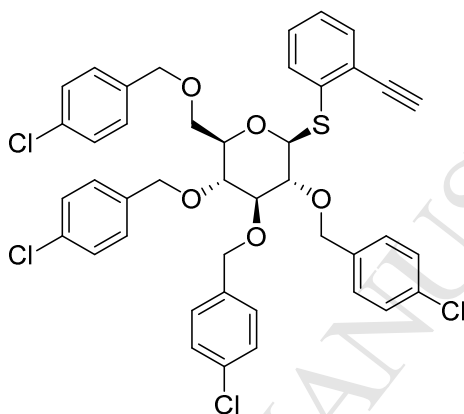
**1**



Prepared in 72% overall yield from **SI-2**.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.76 – 7.66 (m, 1H), 7.54 – 7.48 (m, 1H), 7.48 – 7.42 (m, 2H), 7.40 – 7.28 (m, 16H), 7.27 – 7.21 (m, 2H), 7.20 – 7.14 (m, 2H), 5.03 – 4.93 (m, 2H), 4.92 – 4.81 (m, 3H), 4.80 – 4.73 (m, 1H), 4.67 – 4.52 (m, 3H), 3.88 – 3.56 (m, 6H), 3.40 (s, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  138.36, 138.20, 138.11, 137.95, 137.84, 133.26, 129.71, 129.44, 128.59, 128.48, 128.46, 128.34, 127.96, 127.91, 127.86, 127.82, 127.75, 127.68, 127.57, 126.26, 122.61, 86.69, 86.30, 83.34, 83.31, 81.37, 80.97, 79.10, 77.75,

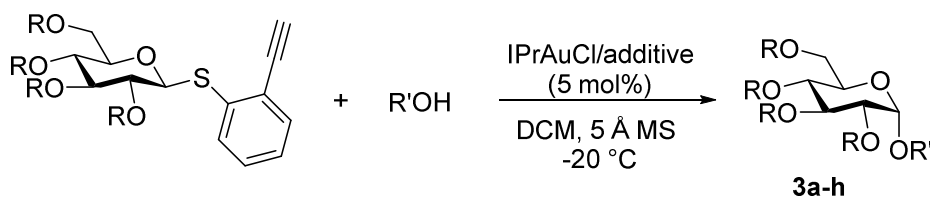
75.89, 75.64, 75.10, 73.42, 69.02. HRMS (ESI<sup>+</sup>, C<sub>42</sub>H<sub>40</sub>O<sub>5</sub>SNa): calculated 679.2494, 680.2527, found 679.2479, 680.2546.

2



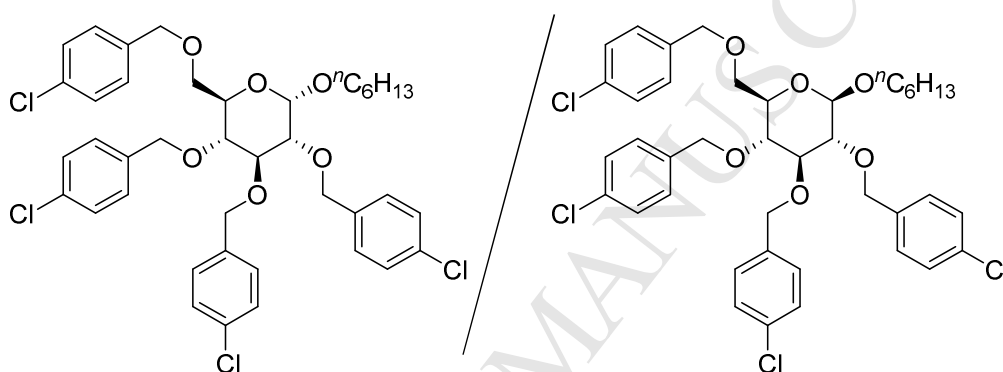
Prepared in 60% overall yield from **SI-3**. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.64 – 7.59 (m, 1H), 7.52 – 7.47 (m, 1H), 7.30 – 7.21 (m, 12H), 7.21 – 7.17 (m, 2H), 7.15 (d, *J* = 8.3 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 4.91 (d, *J* = 10.4 Hz, 1H), 4.84 – 4.68 (m, 4H), 4.62 (d, *J* = 10.4 Hz, 1H), 4.57 – 4.51 (m, 2H), 4.46 (d, *J* = 12.1 Hz, 1H), 3.73 (dd, *J* = 10.9, 1.9 Hz, 1H), 3.69 – 3.48 (m, 5H), 3.36 (s, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 137.70, 136.71, 136.56, 136.34, 136.22, 133.72, 133.66, 133.53, 133.45, 133.41, 129.71, 129.38, 128.97, 128.96, 128.92, 128.75, 128.61, 128.60, 128.56, 128.51, 128.49, 126.51, 122.84, 86.51, 86.28, 83.36, 81.30, 80.94, 79.01, 77.68, 74.82, 74.67, 74.09, 72.67, 68.86. HRMS (ESI<sup>+</sup>, C<sub>42</sub>H<sub>36</sub>Cl<sub>4</sub>O<sub>5</sub>SNa): calculated 815.0935, 817.0914, 819.0894, found 815.0918, 817.0886, 819.0870.

### General Procedure for Glycosylation Reaction



To a vial equipped with screw cap (with septum) was added corresponding glycosyl acceptor (3 equiv.), IPrAuCl (5 mol %), additive (5 mol %), 5 Å molecular sieve (10 mg per 0.5 mmol donor), and dry DCM (0.5 mL per 0.5 mmol donor). The mixture was stirred at room temperature for 15 minutes and was cooled down to -20 °C before a cold solution of glycosyl donor in DCM (0.5 mL per 0.5 mmol donor) was added with syringe. The reaction was stirred at -20 °C until completion. The reaction mixture was then concentrated under vacuum and purified by silica gel column chromatography. Anomeric ratio was determined by  $^1\text{H}$  NMR.

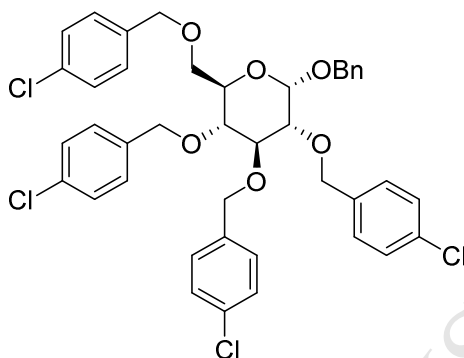
### 3a



Prepared in 84% yield.  $\alpha$ -anomer:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29 – 7.21 (m, 12H), 7.19 (d,  $J$  = 8.4 Hz, 2H), 7.01 (d,  $J$  = 8.3 Hz, 2H), 4.88 (d,  $J$  = 11.3 Hz, 1H), 4.78 (d,  $J$  = 3.6 Hz, 1H), 4.73 – 4.53 (m, 5H), 4.44 – 4.37 (m, 2H), 3.92 (t,  $J$  = 9.2 Hz, 1H), 3.74 (ddd,  $J$  = 10.0, 3.6, 2.0 Hz, 1H), 3.70 – 3.53 (m, 4H), 3.49 (dd,  $J$  = 9.6, 3.6 Hz, 1H), 3.41 (dt,  $J$  = 9.8, 6.7 Hz, 1H), 1.66 – 1.58 (m, 2H), 1.39 – 1.22 (m, 6H), 0.89 (t,  $J$  = 6.7 Hz, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  137.26, 136.67, 136.61, 136.34, 133.67, 133.55, 133.49, 133.32, 129.18, 129.14, 128.91, 128.82, 128.58, 128.54, 128.53, 128.50, 96.61, 81.90, 80.19, 77.71, 74.64, 74.06, 72.68, 72.09, 70.01, 68.51, 68.33, 31.61, 29.35, 25.82, 22.59, 14.04. HRMS (ESI<sup>+</sup>,  $\text{C}_{40}\text{H}_{44}\text{Cl}_4\text{O}_6\text{Na}$ ): calculated 783.1790, 785.1768, 787.1749, found 783.1800, 785.1765, 787.1760.  $\beta$ -anomer:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.31 – 7.20 (m, 12H), 7.13 (d,  $J$  = 8.4 Hz, 2H), 7.02 (d,  $J$  = 8.4 Hz, 2H), 4.89 (d,  $J$  = 11.4 Hz, 1H), 4.81 (d,  $J$  = 11.4 Hz, 1H), 4.72 – 4.55 (m, 4H), 4.51 – 4.42 (m, 2H), 4.35 (d,  $J$  = 7.8 Hz, 1H), 3.93 (dt,  $J$  = 9.5, 6.5 Hz, 1H), 3.73 – 3.60 (m, 2H), 3.60 – 3.46 (m, 3H), 3.45 – 3.33 (m, 2H), 1.72 – 1.56 (m, 2H), 1.45 – 1.18 (m, 6H), 0.91 – 0.84 (m, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  136.96, 136.91, 136.57, 136.49, 133.56, 133.45, 133.37, 129.31, 129.03, 128.92, 128.84, 128.54, 128.52, 128.50, 128.49, 103.58, 84.48, 82.02, 77.84, 74.70, 74.63, 74.02, 73.74,

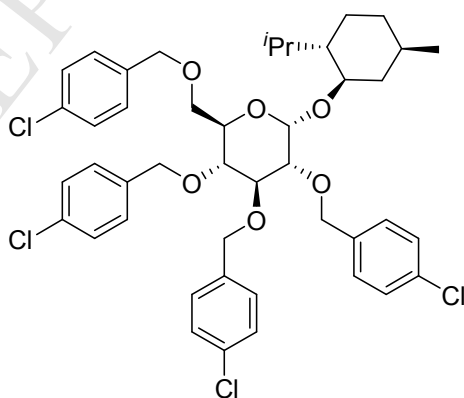
72.69, 70.18, 68.84, 31.61, 29.72, 25.83, 22.59, 14.02. HRMS (ESI+,  $C_{40}H_{44}Cl_4O_6Na$ ): calculated 783.1790, 785.1768, 787.1749, found 783.1815, 785.1765, 787.1738.

### 3b



Prepared in 83% yield.  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.43 – 7.31 (m, 5H), 7.30 – 7.18 (m, 12H), 7.15 (d,  $J$  = 8.4 Hz, 2H), 7.02 (d,  $J$  = 8.2 Hz, 2H), 4.93 – 4.84 (m, 2H), 4.71 (dd,  $J$  = 11.6, 3.0 Hz, 3H), 4.61 – 4.52 (m, 3H), 4.48 (d,  $J$  = 12.1 Hz, 1H), 4.44 – 4.38 (m, 2H), 3.98 (t,  $J$  = 9.3 Hz, 1H), 3.79 (ddd,  $J$  = 10.0, 3.5, 2.0 Hz, 1H), 3.66 (dd,  $J$  = 10.6, 3.5 Hz, 1H), 3.61 – 3.53 (m, 2H), 3.50 (dd,  $J$  = 9.6, 3.6 Hz, 1H).  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  137.15, 136.88, 136.53, 136.41, 136.25, 133.57, 133.55, 133.46, 133.33, 129.17, 129.13, 128.94, 128.80, 128.54, 128.52, 128.44, 128.41, 128.00, 95.19, 81.90, 79.84, 77.54, 74.71, 74.07, 72.65, 72.01, 70.23, 69.12, 68.25. HRMS (ESI+,  $C_{41}H_{38}Cl_4O_6Na$ ): calculated 789.1320, 791.1299, 793.1281, found 789.1318, 791.1260, 793.1290.

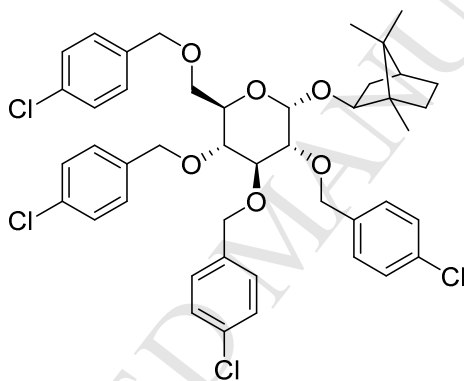
### 3c



Prepared in 72% yield.  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.29 – 7.20 (m, 12H), 7.16 (d,  $J$  = 8.2 Hz, 2H), 7.01 (d,  $J$  = 8.4 Hz, 2H), 5.02 (d,  $J$  = 3.6 Hz, 1H), 4.86 (d,  $J$  = 11.4 Hz, 1H), 4.73 – 4.68 (m,

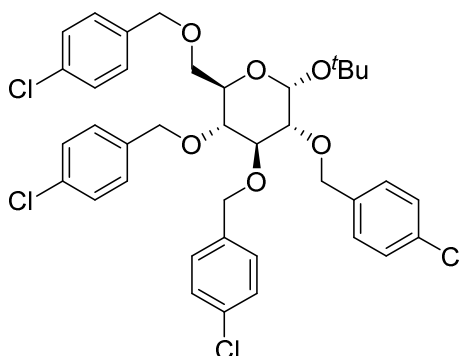
2H), 4.65 – 4.56 (m, 3H), 4.39 (dd,  $J = 11.7, 7.7$  Hz, 2H), 3.99 – 3.90 (m, 2H), 3.70 (dd,  $J = 10.5, 3.7$  Hz, 1H), 3.61 – 3.52 (m, 2H), 3.48 (dd,  $J = 9.7, 3.5$  Hz, 1H), 3.33 (td,  $J = 10.6, 4.3$  Hz, 1H), 2.36 (pd,  $J = 6.9, 2.4$  Hz, 1H), 2.16 – 2.08 (m, 1H), 1.66 – 1.58 (m, 2H), 1.41 – 1.22 (m, 3H), 1.08 – 0.90 (m, 2H), 0.85 (t,  $J = 6.4$  Hz, 6H), 0.69 (d,  $J = 6.9$  Hz, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  137.21, 136.68, 136.64, 136.41, 133.52, 133.47, 133.35, 133.30, 129.15, 128.91, 128.80, 128.72, 128.52, 128.48, 128.44, 98.44, 81.72, 81.49, 80.61, 78.01, 75.27, 74.50, 74.05, 72.67, 72.19, 70.21, 68.64, 48.71, 43.04, 34.22, 31.70, 24.68, 22.98, 22.28, 21.07, 16.09. HRMS (ESI+,  $\text{C}_{44}\text{H}_{50}\text{Cl}_4\text{O}_6\text{Na}$ ): calculated 837.2259, 839.2239, 841.2222, found 837.2247, 839.2239, 841.2240.

### 3d

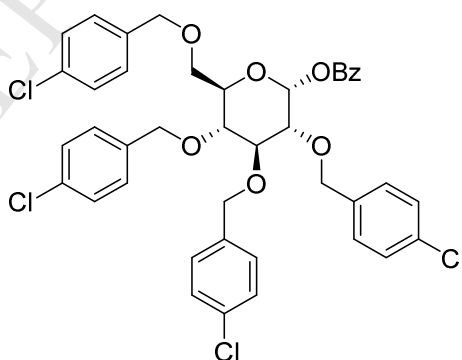


Prepared in 76% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{cdcl}_3$ )  $\delta$  7.30 – 7.21 (m, 12H), 7.18 (d,  $J = 8.4$  Hz, 2H), 7.02 (d,  $J = 8.4$  Hz, 2H), 4.94 (d,  $J = 3.6$  Hz, 1H), 4.87 (d,  $J = 11.4$  Hz, 1H), 4.71 (dd,  $J = 11.3, 1.8$  Hz, 2H), 4.66 – 4.53 (m, 3H), 4.40 (d,  $J = 11.9$  Hz, 2H), 3.94 (t,  $J = 9.3$  Hz, 1H), 3.85 (ddd,  $J = 10.1, 3.6, 2.0$  Hz, 1H), 3.80 (ddd,  $J = 10.0, 3.6, 1.8$  Hz, 1H), 3.71 (dd,  $J = 10.5, 3.5$  Hz, 1H), 3.62 – 3.54 (m, 2H), 3.49 (dd,  $J = 9.6, 3.6$  Hz, 1H), 2.18 (dddd,  $J = 13.3, 9.9, 4.8, 3.2$  Hz, 1H), 2.09 (ddd,  $J = 15.1, 10.0, 4.4$  Hz, 1H), 1.71 (td,  $J = 11.2, 10.4, 6.1$  Hz, 1H), 1.62 (t,  $J = 4.5$  Hz, 1H), 1.27 – 1.20 (m, 3H), 1.11 (dd,  $J = 13.4, 3.4$  Hz, 1H), 0.89 (s, 3H), 0.85 (s, 6H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  137.30, 136.74, 136.56, 136.41, 133.57, 133.52, 133.44, 133.28, 129.14, 129.00, 128.92, 128.91, 128.57, 128.53, 128.51, 128.49, 98.38, 85.68, 81.79, 80.51, 77.84, 74.55, 74.21, 72.67, 71.70, 70.45, 68.55, 49.64, 47.42, 45.08, 36.92, 28.32, 26.73, 19.69, 18.80, 13.92. HRMS (ESI+,  $\text{C}_{44}\text{H}_{48}\text{Cl}_4\text{O}_6\text{Na}$ ): calculated 835.2103, 837.2082, 839.2065, found 835.2119, 837.2073, 839.2104.



**3e**

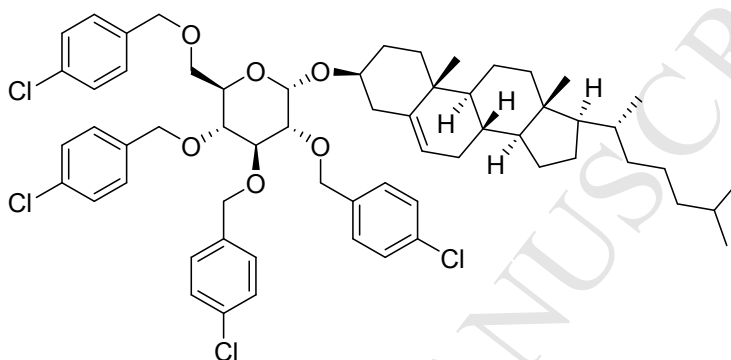
Prepared in 73% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.30 – 7.21 (m, 12H), 7.18 (d,  $J$  = 8.3 Hz, 2H), 7.01 (d,  $J$  = 8.3 Hz, 2H), 5.15 (d,  $J$  = 3.6 Hz, 1H), 4.87 (d,  $J$  = 11.4 Hz, 1H), 4.70 (dd,  $J$  = 11.3, 2.2 Hz, 2H), 4.64 – 4.57 (m, 3H), 4.39 (dd,  $J$  = 11.6, 5.2 Hz, 2H), 3.96 – 3.90 (m, 2H), 3.70 (dd,  $J$  = 10.5, 3.4 Hz, 1H), 3.62 – 3.53 (m, 2H), 3.47 (dd,  $J$  = 9.7, 3.6 Hz, 1H), 1.26 (s, 9H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  137.34, 136.67, 136.62, 136.41, 133.60, 133.50, 133.27, 129.34, 129.22, 129.14, 129.03, 128.86, 128.84, 128.69, 128.60, 128.57, 128.54, 128.51, 128.50, 128.34, 91.20, 86.41, 81.89, 80.11, 78.04, 75.41, 74.52, 74.10, 72.67, 72.02, 69.59, 68.62, 28.62. HRMS (ESI+,  $\text{C}_{38}\text{H}_{40}\text{Cl}_4\text{O}_6\text{Na}$ ): calculated 755.1476, 757.1454, 759.1435, found 755.1470, 757.1459, 759.1436.

**3f**

Prepared in 73% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.07 – 8.04 (m, 2H), 7.64 – 7.59 (m, 1H), 7.51 – 7.46 (m, 2H), 7.30 – 7.18 (m, 14H), 7.04 (d,  $J$  = 8.4 Hz, 2H), 6.61 (d,  $J$  = 3.4 Hz, 1H), 4.88 (d,  $J$  = 11.3 Hz, 1H), 4.78 – 4.68 (m, 3H), 4.57 (d,  $J$  = 12.0 Hz, 2H), 4.48 (d,  $J$  = 11.1 Hz,

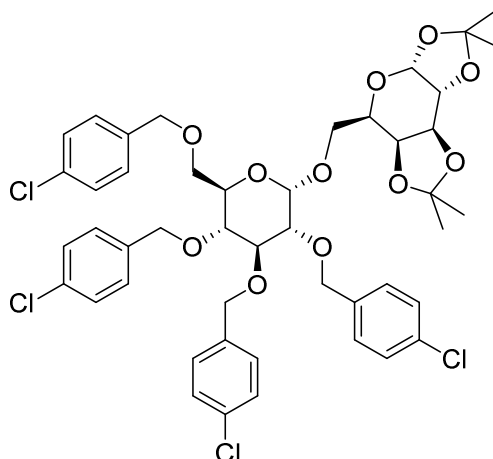
1H), 4.42 (d,  $J = 12.4$  Hz, 1H), 4.02 – 3.92 (m, 2H), 3.78 – 3.69 (m, 4H), 3.62 (dd,  $J = 10.9$ , 2.0 Hz, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  164.83, 136.89, 135.95, 133.77, 133.75, 133.64, 133.59, 133.48, 129.91, 129.30, 129.21, 129.06, 128.95, 128.83, 128.64, 128.61, 128.59, 128.58, 128.57, 128.56, 90.36, 81.53, 79.10, 74.69, 74.45, 73.07, 72.81, 72.18, 68.08, 29.70. HRMS (ESI+,  $\text{C}_{41}\text{H}_{36}\text{Cl}_4\text{O}_7\text{Na}$ ): calculated 803.1113, 805.1091, 807.1074, found 803.1118, 805.1094, 807.1047.

### 3g



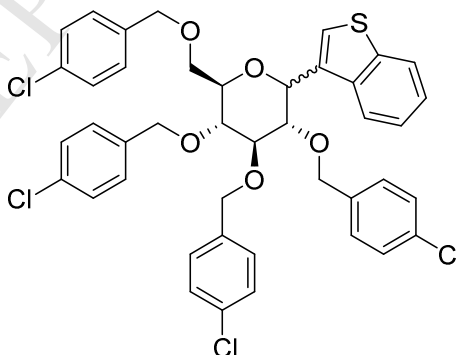
Prepared in 63% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32 – 7.17 (m, 14H), 7.02 (d,  $J = 8.4$  Hz, 2H), 5.26 (dd,  $J = 5.0$ , 2.4 Hz, 1H), 4.97 (d,  $J = 3.7$  Hz, 1H), 4.89 (d,  $J = 11.4$  Hz, 1H), 4.74 – 4.67 (m, 2H), 4.66 – 4.54 (m, 3H), 4.43 – 4.34 (m, 2H), 3.93 (t,  $J = 9.3$  Hz, 1H), 3.85 (ddd,  $J = 10.2$ , 3.7, 2.1 Hz, 1H), 3.69 (dd,  $J = 10.6$ , 3.7 Hz, 1H), 3.60 (dd,  $J = 10.6$ , 2.1 Hz, 1H), 3.55 (dd,  $J = 10.1$ , 8.9 Hz, 1H), 3.51 – 3.42 (m, 2H), 2.47 – 2.34 (m, 1H), 2.27 (ddd,  $J = 13.4$ , 5.0, 2.1 Hz, 1H), 1.99 (ddt,  $J = 30.4$ , 12.8, 3.5 Hz, 2H), 1.91 – 1.79 (m, 3H), 1.63 – 1.02 (m, 18H), 1.03 – 0.78 (m, 15H), 0.68 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  140.64, 137.30, 136.59, 136.58, 136.36, 133.72, 133.51, 133.32, 129.28, 129.15, 128.87, 128.86, 128.60, 128.54, 128.53, 128.51, 121.89, 94.51, 81.93, 79.99, 77.85, 74.64, 74.11, 72.65, 71.99, 70.02, 68.64, 56.77, 56.18, 50.14, 42.34, 39.93, 39.78, 39.52, 37.09, 36.77, 36.20, 35.78, 31.92, 31.89, 29.69, 28.22, 28.01, 27.64, 24.29, 23.83, 22.80, 22.55, 21.07, 19.37, 18.72, 11.86. HRMS (ESI+,  $\text{C}_{61}\text{H}_{76}\text{Cl}_4\text{O}_6\text{Na}$ ): calculated 1067.4293, 1069.4280, 1070.4304, found 1067.4281, 1069.4283, 1070.4281.

### 3h



Prepared in 63% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29 – 7.21 (m, 12H), 7.17 (d,  $J$  = 8.2 Hz, 2H), 7.01 (d,  $J$  = 8.2 Hz, 2H), 5.52 (d,  $J$  = 5.0 Hz, 1H), 4.99 (d,  $J$  = 3.6 Hz, 1H), 4.86 (d,  $J$  = 11.4 Hz, 1H), 4.72 – 4.66 (m, 3H), 4.62 – 4.54 (m, 3H), 4.40 (dd,  $J$  = 11.8, 3.2 Hz, 2H), 4.35 – 4.28 (m, 2H), 4.03 (td,  $J$  = 6.8, 1.8 Hz, 1H), 3.92 (t,  $J$  = 9.3 Hz, 1H), 3.84 – 3.77 (m, 2H), 3.74 – 3.67 (m, 2H), 3.63 – 3.56 (m, 2H), 3.54 – 3.49 (m, 1H), 1.52 (s, 3H), 1.44 (s, 3H), 1.33 (s, 3H), 1.30 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  137.26, 136.68, 136.36, 133.53, 133.43, 133.30, 129.18, 129.04, 128.92, 128.77, 128.54, 128.50, 128.48, 109.30, 108.59, 81.72, 79.84, 77.50, 74.61, 73.94, 72.66, 71.40, 70.92, 70.67, 70.58, 70.09, 68.36, 66.24, 65.64, 26.14, 26.06, 24.92, 24.66. HRMS (ESI+,  $\text{C}_{46}\text{H}_{50}\text{Cl}_4\text{O}_{11}\text{Na}$ ): calculated 941.2005, 943.1985, 945.1970, found 941.2009, 943.1934, 945.1954.

#### Compound D



Found in all reactions. NMR spectra closely resembles similar compound reported by Yu group.[38]  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.83 (d, 1H), 7.73 (d, 1H), 7.40 – 7.27 (m, 9H), 7.17 (d,  $J$  = 8.4 Hz, 2H), 7.12 – 7.04 (m, 4H), 6.87 – 6.82 (m, 2H), 4.86 – 4.77 (m, 2H), 4.74 (d,  $J$  = 11.1 Hz, 1H), 4.68 – 4.57 (m, 4H), 4.53 (d,  $J$  = 12.4 Hz, 1H), 4.41 (d,  $J$  = 10.9 Hz, 1H), 4.08 (d,  $J$  =

10.8 Hz, 1H), 3.81 – 3.70 (m, 4H), 3.62 – 3.54 (m, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  142.22, 139.63, 139.07, 136.85, 136.74, 136.45, 135.93, 133.64, 133.53, 133.46, 133.38, 129.35, 129.03, 129.02, 128.92, 128.80, 128.69, 128.61, 128.60, 128.55, 128.51, 128.34, 128.24, 124.52, 124.44, 123.57, 122.88, 122.51, 86.41, 83.69, 79.61, 78.09, 77.98, 74.68, 74.22, 74.18, 72.79, 68.73.

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- Gold-catalyzed glucosylation reaction using an o-ethynylphenyl thioglucoside donor
- Mostly  $S_N2$  with good nucleophilic alcohols
- *p*-Chlorobenzyl used as protecting group to retard  $S_N1$  process