Note

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Mild $Cu(OTf)_2$-mediated C-glycosylation with Chelation-Assisted Picolinate as a Leaving Group

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ABSTRACT: C-glycosylation reactions of glycosyl picolinates with allyltrimethylsilane or silyl enol ethers were developed. Picolinate as a chelation-assisted leaving group could be activated by $Cu(OTf)_2$ and avoided the use of harsh Lewis acids. The glycosylations were operated under mild neutral conditions and gave the corresponding C-glycosides in up to 95% yield with moderate to excellent stereoselectivities.

Glycosylation is arguably the most important reaction in carbohydrate chemistry and numerous glycosylation protocols have been developed for the synthesis of glycosides.[1] Compared with O-glycosides, which are susceptible to enzymatic degradation, C-glycosides have attracted widespread attention due to their higher stability to glycosidases and hydrolases.[2] For example, The C-glycoside analogue **1** of KRN7000 showed more effective activity than the corresponding O-glycoside.[3] Glycoconjugate **2** of genistein exhibited higher antiproliferative potential than the parent compound.[4] Various natural products also bear C-glycosidic units, such as (+)-varitriol[5] and (+)-ambruticin S (Figure 1).[6] However, among the diverse glycosylation methods, O-glycosylations occupy a large majority, and C-glycosylations are comparatively less.[2] There have been various reported methods for the formation of C-glycosides, including transition metal catalysis and other catalyst systems,[7] Knoevenagel condensations,[8] and direct nucelophilic substitutions.[9] While these reactions are efficient, they are limited in scope of products and tend to rely on harsh reaction conditions. Considering the C-glycosides as biologically significant molecules, prevalent to many natural products, and hydrolytically stable surrogates of native O-glycosides, it is necessary to develop efficient and stereoselective C-glycosylation methods under mild conditions for satisfying the demands of C-glycoside diversity. Of particular interest is the development of high-yielding and low-cost methods that can be run under mild conditions that are compatible to a variety of functional groups.

Another consideration in the synthesis of C-glycosides are the leaving group. Many leaving groups have been utilized in the past with great successes, such as glycals, glycal halides, thioglycosides, lactols, and acetals.[10] The most common leaving group utilized, however, is the acetyl group and other ester-derivatives, because they are readily available.[11] While the acetyl group has been used effectively as a donor to produce high yields in short time frames, it requires promotion by air-

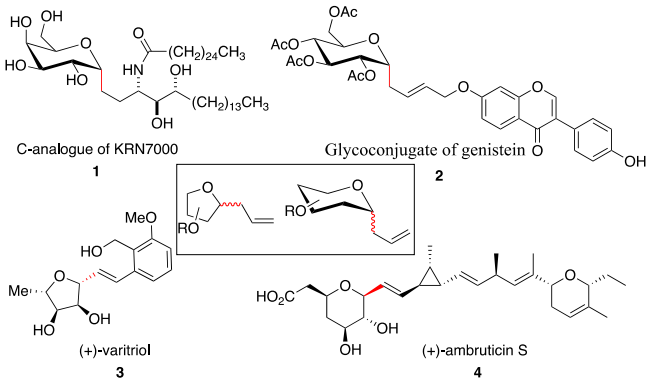
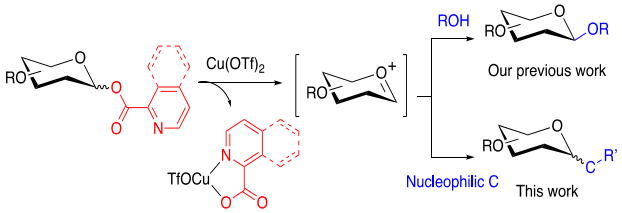


Figure 1. Bioactive and natural C-glycosides.



Scheme 1. Glycosylation with isoquinoline carboxylate or picolinate as a leaving group.

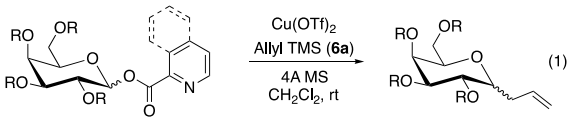
and moisture-sensitive Lewis acids which introduces

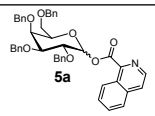
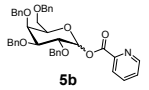
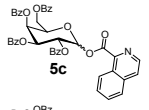
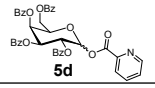
limitations in the reaction scope and feasibility. Therefore, it is highly desirable to have a proper leaving group that does not require these strong acids for activation while maintaining the high yields.

Recently, we developed an efficient mild O-glycosylation method using isoquinoline-1-carboxylate as a leaving group (Scheme 1),[12] which is advantageous over the previously reported picolinate,[13] by minimizing the transesterification byproducts. Using $Cu(OTf)_2$ as a mediator for remote activation,[14] the isoquinoline ester can be removed to give an oxocarbenium ion intermediate, which subsequently leads to O-glycosides with high yields under mild neutral conditions. This chelation-assisted approach shows promise in preliminary application to the synthesis of C-glycosides as the isoquinoline carboxylate and picolinate leaving groups become traceless leaving groups through two-point chelation to the copper ion. Based on these results, we envision that various C-glycosides can also be prepared under mild and neutral conditions using the same type of leaving group, giving advantages over the previous methods that use the acetyl leaving group.

Allylic group is a useful building block and it allows many further transformations due to the versatile terminal olefin functional group. For example, the aforementioned bioactive and natural molecules can be accessed through olefin metathesis of allyl glycosides with the suitable alkenes (Figure 1). The introductions of anomeric allyl saccharides were generally promoted by Lewis acid-activated glycosylations.[15] They usually stereoselectively gave α-allyl glycosides in excellent yield. However, air- and moisture-sensitive Lewis acids, such as $BF_3{\cdot}Et_2O$, TMSOTf, etc. were needed. Recently, the Yu group accomplished C-glycosylation of glycosyl ortho-alkynylbenzoates with allyltrimethylsilane or silyl enol ethers in high yields and stereoselectivities where a milder Lewis acid $Ph_3PAuNTf_2$ was used.[16] Sulfoxide, sulfonates, and hydroxybenzotriazolyl groups were also employed as leaving groups for improving the yields and stereoselectivities.[17] It was also reported that allylation of benzylidene protected glucose and mannose could highly stereoselectively give α- and β-C-glycosides, respectively.[18] Herein, we chose highly nucleophilic and easily functionalized allyl and silyl enol ethers as the glycosyl acceptor, stable picolinates as the donors, and the mild Lewis acid $Cu(OTf)_2$ as the mediator to explore C-glycosylation.

Table 1. Optimizing C-glycosylation of galactopyranosyl isoquinoline carboxylate (IQC) and picolinate (Pico) with allyltrimethylsilane.[a]



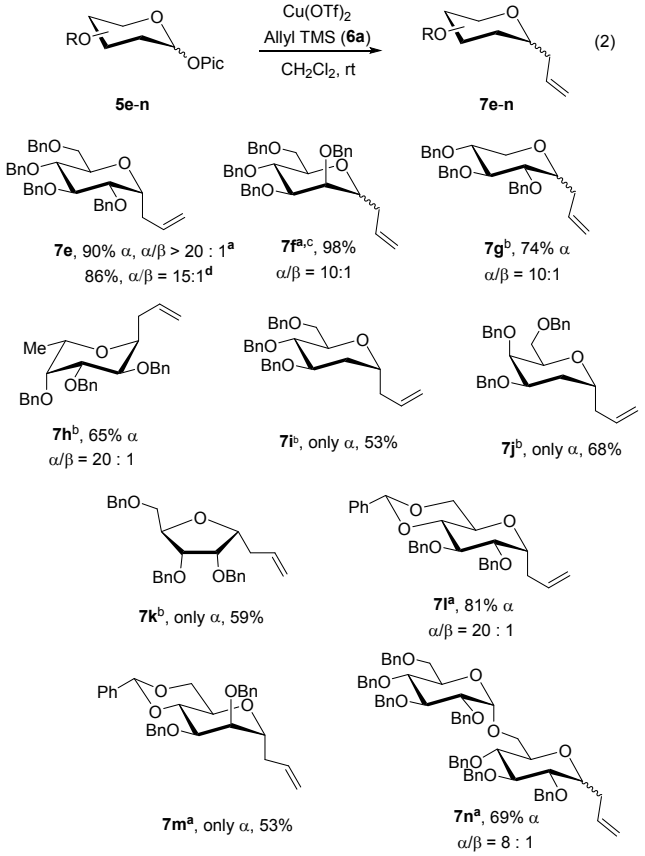
Entry	Donor	Solvent	Yield of **7a** or **7b**[c]
1	 **5a**	CH_2Cl_2	42%
2[b]		CH_2Cl_2	82%
3		CH_2Cl_2	46%
4[b]	 **5b**	CH_2Cl_2	95% (99%)[d]
5		Et_2O	trace
6		CH_3CN	18%
7[b]	 **5c**	CH_2Cl_2	complicated
8[b]	 **5d**	CH_2Cl_2	trace

[a] Conditions: **5** (0.1 mmol), allyl TMS (2.0 eq.), $Cu(OTf)_2$ (1.2 eq.), 4A MS (100 mg), solvent (0.5 mL), rt, Ar, 24 h; [b] allyl TMS (6.0 eq.); [c] Isolated yields; [d] Total yield of α- and β-anomers, α/β > 20:1.

First, benzyl-protected galactosyl isoquinoline carboxylate **5a** and picolinate **5b** were used as the glycosyl donors to optimize the reaction conditions (Table 1). Using $Cu(OTf)_2$ as the mediator and CH_2Cl_2 as the solvent, the reaction of **5a** with allyl TMS gave the corresponding allyl α-C-glycoside **7a** in 42% yield (entry 1). Additionally, trace amounts of allyl β-C-glycoside was observed by TLC analysis. When the amount of allyl TMS was increased to 6.0 equiv, the yield of **7a** was improved to 82% (entry 2). Under the same conditions, we compared the results of the glycosylation of benzyl-protected galactosyl picolinate **5b** with those of **5a**. In our previous work,[12] O-glycosylation of glycosyl isoquinoline carboxylates showed better results than picolinates because the nucleophilic attack of the ester carbonyl group by the alcohol nucleophile in the former was inhibited. We later found that picolinates and isoquinoline carboxylates behaved similarly during the preparation of glycosyl halides, because halides preferentially reacted with the anomeric carbon over the carbonyl ester.[19] In the case of C-glycosylation, picolinate **5b** (entries 3 and 4) is slightly better than isoquinoline carboxylate **5a** (entries 1 and 2). α-C-Glycoside **7a** can be prepared in 95% yield with 6.0 equiv allyl TMS (entry 4). The total yield of α- and β-anomers was 99% and the ratio of α and β anomers was more than 20:1. When the solvent was changed from CH_2Cl_2 to Et_2O or CH_3CN, no more than an 18% yield of allyl α-C-glycoside **7a** was obtained (entries 5 and 6). For Et_2O, little of the starting material was consumed, indicating that the low yield is likely due to solubility issues with $Cu(OTf)_2$. For CH_3CN, it is possible that the oxocarbenium intermediate loses a proton, as will be discussed more with **7o**, as most of the starting material was consumed in the reaction. Disappointingly, the C-glycosylation of disarmed donors **5c** and **5d** did not give the desired allyl C-glycosides. The reaction of perbenzoyl galactosyl isoquinoline carboxylate **5c** with allyl TMS gave a complex mixture and only trace amounts of desired product was observed, while the reaction of less reactive **5d** gave trace amounts of products and most of **5d** was recovered (entries 7 and 8). This may be attributed to the high activation energy

barriers of disarmed saccharides, and the weaker nucleophilicity of allyl TMS compared to O-nucleophiles.[20]

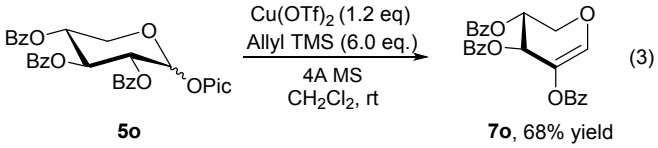
Considering the slightly better performance of the picolinate donor for C-glycosylation and the lower price of picolinic acid than that of isoquinoline carboxylic acid, glycosyl picolinates were selected as donors for testing the scope of the $Cu(OTf)_2$-mediated C-glycosylation (Scheme 2). Most of the armed monosaccharides and disaccharides demonstrated expected reactivity and the corresponding allyl C-glycosides were obtained in moderate to excellent yields. The reaction of perbenzyl glucosyl picolinate **5e** with allyl TMS gave an excellent result and produced the corresponding allyl C-glucoside α-**7e** in 90% yield. A small amount of β anomer was also collected and the ratio of α and β anomers was more than 20:1. Similar results were obtained when the reaction was scaled up to 1 mmol, which afforded **7e** in 86% yield with a 15:1 α/β ratio. Using perbenzyl mannosyl picolinate **5f** as the donor, the reaction gave **7f** in 98% total yield with the α/β ratio of 10:1. The allylation of xylosyl picolinate **5g** led to the allyl C-glycoside α-**7g** in 74% yield and the ratio of α and β anomers was also 10:1. C-glycosylation of Bn-protected L-fucosyl picolinate **5h** similarly gave α-allyl product **7h** in 65% yield with a α/β ratio of 20:1.



Scheme 2. $Cu(OTf)_2$-mediated C-Glycosylation with allyl TMS as an acceptor. [a)] Condition A: **5** (0.1 mmol), allyl TMS (6.0 equiv), $Cu(OTf)_2$ (1.2 equiv), 4A MS (100 mg), CH_2Cl_2 (0.5 mL), rt, Ar, 16 h; [b)] Condition B: **5** (0.1 mmol), allyl TMS (6.0 equiv), $Cu(OTf)_2$ (1.2 equiv), CH_2Cl_2 (0.5 mL), rt, Ar, 16 h, toluene was used as azeotrope to remove water; [c)] The yield is the combined of α and β; [d)] 1 mmol reaction scale.

Using the present allylation protocol, allyl 2-deoxy glycosides were successfully prepared. The allylation of **5i** and **5j** exclusively gave α anomers **7i** and **7j** in 53% and 68% yields, respectively. Exclusive allyl C-glycoside α-**7k** was obtained in 59% yield for the perbenzyl ribosyl picolinate **5k** substrate. For these perbenzyl monosaccharide substrates, the allylation showed high α selectivity, which could be well explained through the conformational preferences of the oxocarbenium ion intermediate, as well as consideration of steric effects that developed in the transition states for nucleophilic attack.[20] C-glycosylation with benzylidene protected glucosyl picolinate **5l** and mannosyl picolinate **5m** donors were also tested. Allyl C-glycosides α-**7l** and α-**7m** were acquired in 81% and 53% yields, respectively. The stereoselectivities of these two reactions were coherent with the allylation of thioglycosides reported in the literature.[18] The ratio of 20:1 for **7l** and exclusive α for **7m** were obtained. C-glycosylation of disaccharide donor **5n** was also explored, giving the corresponding allyl C-glycoside α-**7n** in 69% yield with a α/β ratio of 8:1.

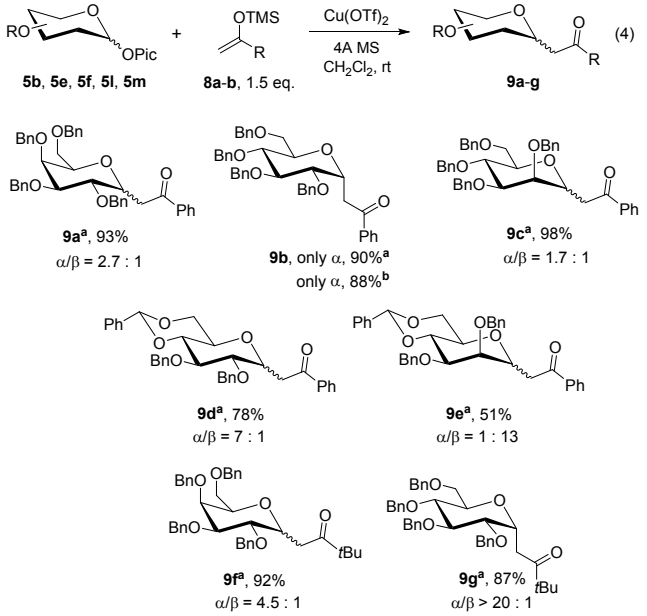
Using $Cu(OTf)_2$ as the mediator and CH_2Cl_2 as the solvent, the reactions of several more disarmed glycosyl donors with allyl TMS were investigated. Disappointingly, no desired allyl C-glycosides were obtained. The reaction of acetyl- or pivaloyl glucosyl picolinate with allyl TMS showed most of the starting material remained after the reaction. Hydrolysis products were collected for perbenzoyl ribosyl and perbenzoyl fucosyl picolinate substrates. The reaction of perbenzoyl-protected xylosyl picolinate **5o** gave a glycal product **7o** in 68% yield without the desired C-glycoside found (Scheme 3).



Scheme 3. Reaction of disarmed saccharide with allyl TMS.

Silyl enol ethers are highly versatile coupling reagents for constructing C-C bonds.[21] C-glycosylations of picolinate donors with nucleophilic silyl enol ethers were therefore explored (Scheme 4). Aromatic silyl enol ether **8a** and aliphatic silyl enol ether **8b** were used as acceptors to investigate the reactivity and selectivity of the glycosylations. Generally, C-glycosylations with silyl enol ethers showed less stereoselectivities than those with allyl TMS as the acceptor. With 1.2 equiv $Cu(OTf)_2$ as the promoter, the reaction of perbenzyl galactopyranosyl donor **5b** with 1-styrenyloxytrimethylsilane **8a** (1.5 equiv) produced the corresponding C-glycoside **9a** in 93% total yield with the stereoselectivity of 2.7:1. Exclusive α C-glycoside **9b** was obtained in 90% yield for the glycosylation of glucosyl donor **5e**. Again, the scalability of the reaction was demonstrated by performing the same reaction on 1 mmol scale, with **9b** isolated in 88% yield as a single anomer. Mannosyl C-glycoside **9c** was prepared as a 1.7:1 mixture of anomers in 98% total yield. The reactions of benzylidene-protected glucosyl donor **5l** and mannosyl donor **5m** with **8a** gave similar results to the previous allylations, but showed lower stereoselectivities. The

glycosylations of **5l** and **5m** led to the corresponding C-glycosides **9d** and **9e** in 78% and 51% total yields with α/β



Scheme 4. $Cu(OTf)_2$-mediated C-Glycosylation with silyl enol ether as an acceptor. [a] Reaction conditions: **5** (0.1 mmol), silyl enol ether (1.5 equiv), $Cu(OTf)_2$ (1.2 equiv), 4A MS (100 mg), CH_2Cl_2 (0.5 mL), rt, Ar, 16 h. The yield is the combined of α and β; [b] 1 mmol reaction scale.

ratios of 7:1 and 1:13, respectively. The C-glycosylations with 1-*tert*-butylvinyloxytrimethylsilane **8b** provided the corresponding 2-carbonyl C-glycosides **9f** and **9g** in 92% and 87% yield with α/β ratios of 4.5:1 and >20:1, respectively, which were similar to the results of acceptor **8a**.

In conclusion, both picolinates and isoquinoline carboxylates are convenient leaving groups for glycosylations, but the former is more suitable for C-glycosylations. With $Cu(OTf)_2$ as a mediator, C-glycosylations of stable glycosyl picolinate donors with allyltrimethylsilane or silyl enol ethers were explored. The allylations of various armed glycosyl picolinates offered the corresponding C-glycosides in up to 95% yield with excellent stereoselectivities. The reactions abided by the oxocarbenium ion intermediate mechanism reported previously.[18,20] Disarmed saccharides could not produce the desired allyl C-glycosides due to low reactivity. The glycosylations of armed glycosyl picolinates with silyl enol ethers exhibited good reactivities but moderate stereoselectivities, except for the reaction of perbenzyl glucosyl picolinate which exclusively gave α-C-glycoside.

An added benefit of the method reported here over those previously reported is the use of a relatively cheap copper salt. This decrease in cost while maintaining relatively good yields, increases the synthetic efficacy. The use of a picolinate ester as the glycosyl donor brings added benefits, as they are easily prepared from commercially available picolinic acid and can be cleaved under mostly neutral conditions. Picolinic acid is also much cheaper than reagents involved for the formation of many other glycosyl donors including the tested isoquinoline-1-carboxylic acid. The above results show that the stable picolinate group could be a good glycosyl donor to efficiently synthesize useful C-glycosides under mild reaction conditions.

EXPERIMENTAL SECTION

All reactions in non-aqueous media were conducted under a positive pressure of dry argon in glassware that had been dried in oven prior to use unless noted otherwise. Anhydrous solutions of reaction mixtures were transferred via an oven dried syringe or cannula. All solvents were dried prior to use unless noted otherwise. Starting materials were azeotroped with dry toluene three times the day before use. Thin layer chromatography was performed using precoated silica gel plates. Flash column chromatography was performed with silica gel (40-63 μm). Infrared spectra (IR) were obtained on a Bruker Equinox 55 Spectrophotometer. ^1H and ^{13}C nuclear magnetic resonance spectra (NMR) were obtained on a Varian Unity-Inova 400 MHz or 500 MHz recorded in ppm (δ) downfield of TMS (δ = 0) in $CDCl_3$ unless noted otherwise. Signal splitting patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), or multiplet (m), with coupling constants (J) in hertz. High resolution mass spectra (HRMS) were performed by Analytical Instrument Center at the School of Pharmacy or Department of Chemistry on an Electron Spray Injection (ESI) mass spectrometer.

General procedure for the synthesis of silyl enol ether. Silyl enol ether **8a**[22] and **8b**[23] were prepared and characterized according to the literature methods and their spectra were in accordance with the literature.

Synthesis and characterization of isoquinoline and picolinic glycosyl donors. All isoquinoline and picolinic glycosyl donors not otherwise specified below were prepared and characterized in accordance with previous literature.[19]

5a: 2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl isoquinoline-1-carboxylate. To an oven-dried flask was added commercially available 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranose (1.00 mmol, 540.7 mg), DMAP (0.20 mmol, 24.4 mg), 1-isoquinolinecarboxylic acid (ISQ-COOH) (1.30 mmol, 225.2 mg), EDCI (2.00 mmol, 383.3 mg) and dry DCM (5.0 mL) under Ar. The reaction was stirred at RT and monitored by TLC. After the reaction was completed (~12 h), the solvent was removed under vacuum and the residue was purified by flash column chromatography (eluent: Hex:EA=5:1, V/V) to afford **5a** (white solid, 650.0 mg, 94% yield). M.P.: 100-102 °C. Optical rotation: $[\alpha]_D^{21}$ = +7.32 (c 0.205, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, *J* = 8.7 Hz, 1H), 8.63 (d, *J* = 5.5 Hz, 1H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.82 (d, *J* = 5.5 Hz, 1H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.32 (m, 17H), 7.19-7.08 (m, 3H), 5.99 (d, *J* = 8.0 Hz, 1H), 5.03-4.93 (m, 2H), 4.86 (d, *J* = 10.9 Hz, 1H), 4.78 (s, 2H), 4.62 (d, *J* = 11.4 Hz, 1H), 4.47 (q, *J* = 11.8 Hz, 2H), 4.21 (t, *J* = 8.9 Hz, 1H), 4.04 (d, *J* = 2.8 Hz, 1H), 3.86 (t, *J* = 6.6 Hz, 1H), 3.78-3.58 (m, 3H). $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$) δ 164.6, 148.2, 141.8, 138.6, 138.4, 138.3, 137.8, 136.8, 130.5, 128.7, 128.4, 128.4, 128.2, 128.1, 128.1, 128.0, 127.8, 127.7, 127.6, 127.5, 127.4, 127.1, 126.8, 126.3, 124.1, 95.8, 82.3, 78.1, 77.2, 75.3, 74.8, 74.5, 73.6, 72.9, 68.1. HRMS (ESI) for $C_{44}H_{41}NO_7$ (M+H), 696.2956 (Calc.), found 696.2951. IR (neat): ν 1743, 1454, 1366, 1215, 1099, 1028, 745, 698, 997.

5j: 3,4,6-Tri-*O*-benzyl-2-deoxy-D-galactopyranosyl picolinate. To an oven-dried flask was added commercially available 3,4,6-tri-*O*-benzyl-2-deoxy- D-galactopyranose (1.00

mmol, 434.5 mg), DMAP (0.20 mmol, 24.4 mg), picolinate acid (1.30 mmol, 160.0 mg), EDCI (2.00 mmol, 383.3 mg) and dry DCM (5.0 mL) under Ar. The reaction was stirred at RT and monitored by TLC. After the reaction was completed (~12 h), the solvent was removed under vacuum and the residue was purified by flash column chromatography (eluent: Hex:EA=2:1, V/V) to afford **5j** (α:β=2.3:1, colorless syrup, 420.0 mg, 80% yield). Reported as mixture of anomers, ratio identified through ^{1}H NMR spectroscopy. Optical rotation: $[\alpha]_D^{21}$ = +35.3 (c 0.575, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 – 8.74 (m, 2H), 8.13 (d, *J* = 7.8 Hz, 1H), 7.98 (d, *J* = 7.9 Hz, 1H), 7.84 – 7.77 (m, 2H), 7.45 (m, 2H), 7.39 – 7.21 (m, 30H), 6.58 (d, *J* = 3.2 Hz, 1H), 5.98 (dd, *J* = 10.1, 2.4 Hz, 1H), 5.01 – 4.92 (m, 2H), 4.72 – 4.58 (m, 6H), 4.54 – 4.37 (m, 4H), 4.23 – 4.05 (m, 4H), 3.93 (d, *J* = 2.4 Hz, 2H), 3.81 – 3.52 (m, 4H), 2.61 – 2.37 (m, 2H), 2.31 – 2.16 (m, 2H). ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$) δ 163.5, 163.1, 150.2, 150.1, 147.9, 147.3, 138.8, 138.7, 138.2, 138.1, 137.9, 137.9, 137.0, 137.0, 129.8, 129.7, 129.7, 128.5, 128.5, 128.5, 128.4, 128.4, 128.4, 128.4, 128.3, 128.2, 128.2, 128.1, 128.0, 128.0, 128.0, 127.9, 127.9, 127.8, 127.8, 127.8, 127.7, 127.6, 127.6, 127.5, 127.4, 127.2, 127.1, 125.7, 125.3, 94.6, 93.8, 75.0, 74.5, 74.5, 74.0, 73.6, 73.6, 72.8, 72.6, 71.6, 70.5, 70.5, 68.8, 68.6, 31.5, 30.2. HRMS (ESI) for $C_{33}H_{33}NO_6$ (M+Na), 562.2200 (Calc.), found 562.2201. IR (neat): ν 1727, 1644, 1585, 1496, 1454, 1438, 1361, 1304, 1279, 1245, 1201, 1146, 1097, 1044, 1026, 992, 891, 844, 817, 745, 696, 665.

5k: 2,3,5-Tri-*O*-benzyl-D-ribofuranosyl picolinate. To an oven-dried flask was added commercially available 2,3,5-tri-*O*-benzyl-D-ribofuranose (1.00 mmol, 420.5 mg), DMAP (0.20 mmol, 24.4 mg), picolinate acid (1.30 mmol, 160.0 mg), EDCI (2.00 mmol, 383.3 mg) and dry DCM (5.0 mL) under Ar. The reaction was stirred at RT and monitored by TLC. After the reaction was completed (~12 h), the solvent was removed under vacuum and the residue was purified by flash column chromatography (eluent: Hex:EA=5:1, V/V) to afford **5k** (α:β=2.2:1, light yellow syrup, 430.0 mg, 82% yield). Reported as mixture of anomers, ratio identified through ^{1}H NMR spectroscopy. Optical rotation: $[\alpha]_D^{21}$ = +30.9 (c 1.14, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.86 – 8.69 (m, 2H), 8.06 (dd, *J* = 29.2, 7.7 Hz, 2H), 7.84 (m, 2H), 7.64 (td, *J* = 7.7, 1.8 Hz, 2H), 7.55 – 7.23 (m, 30H), 6.55 (s, 1H), 6.38 (d, *J* = 7.3 Hz, 1H), 5.02 – 4.84 (m, 2H), 4.83 – 4.43 (m, 8H), 4.41 – 4.31 (m, 2H), 4.26 – 4.07 (m, 2H), 3.92 (dd, *J* = 11.1, 4.6 Hz, 1H), 3.83 (dd, *J* = 11.1, 3.1 Hz, 1H), 3.77 – 3.62 (m, 3H). ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$, TMS) δ 163.7, 163.7, 163.4, 150.1, 150.0, 147.6, 147.5, 139.1, 138.7, 138.2, 138.1, 138.0, 137.9, 137.6, 137.6, 137.4, 136.9, 136.9, 136.9, 128.5, 128.5, 128.5, 128.4, 128.3, 128.3, 128.2, 128.2, 128.0, 127.9, 127.9, 127.9, 127.8, 127.8, 127.7, 127.7, 127.6, 127.6, 127.5, 127.5, 127.4, 127.1, 127.0, 126.8, 126.4, 125.5, 125.4, 100.5, 94.0, 89.9, 81.9, 78.7, 75.2, 74.7, 74.5, 74.5, 74.2, 73.8, 73.3, 72.5, 72.2, 71.6, 71.2, 69.6, 63.2, 58.9. HRMS (ESI) for $C_{32}H_{31}NO_6$ (M+Na), 548.2044 (Calc.), found 548.2040. IR (neat): ν 1736, 1585, 1496, 1454, 1361, 1305, 1284, 1244, 1216, 1071, 1027, 995, 925, 821, 745, 696, 666.

5n: 2,3,4-Tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-D-glucopyranosyl picolinate. To an oven-dried flask was added commercially available 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-D-glucopyranose (1.00 mmol, 973.2 mg), DMAP (0.20 mmol, 24.4 mg), picolinate acid (1.30 mmol, 160.0 mg), EDCI (2.00 mmol, 383.3 mg) and dry DCM (5.0 mL) under Ar. The reaction was stirred at RT and monitored by TLC. After the reaction was completed (~12 h), the solvent was removed under vacuum and the residue was purified by flash column chromatography (eluent: Hex:EA=5:1, V/V) to afford **5n** (α:β=1.4:1, colorless syrup, 260.0 mg, 78% yield). Reported as mixture of anomers, ratio identified through ^{1}H NMR spectroscopy. Optical rotation: $[\alpha]_D^{21}$ = +52.5 (c 1.01, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 – 8.68 (m, 2H), 8.12 (d, *J* = 7.8 Hz, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.78 (td, *J* = 7.8, 1.7 Hz, 1H), 7.69 (td, *J* = 7.8, 1.7 Hz, 1H), 7.47 – 7.34 (m, 2H), 7.37 – 7.04 (m, 70H), 6.70 (d, *J* = 3.6 Hz, 1H), 6.04 (d, *J* = 6.9 Hz, 1H), 5.78 (d, *J* = 3.5 Hz, 1H), 5.67 (d, *J* = 3.6 Hz, 1H), 5.06 (d, *J* = 11.7 Hz, 1H), 4.96 – 4.78 (m, 12H), 4.71 (d, *J* = 11.3 Hz, 2H), 4.66 – 4.42 (m, 12H), 4.32 – 4.16 (m, 8H), 4.03 – 3.75 (m, 8H), 3.74 – 3.64 (m, 2H), 3.59 – 3.49 (m, 2H), 3.47 – 3.34 (m, 3H). ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$) δ 163.7, 163.6, 150.3, 150.2, 147.7, 147.4, 138.9, 138.9, 138.7, 138.5, 138.4, 138.3, 138.2, 138.1, 138.0, 138.0, 137.9, 137.5, 137.0, 128.5, 128.5, 128.5, 128.4, 128.4, 128.3, 128.3, 128.2, 128.2, 128.1, 128.1, 128.0, 1278.0, 127.9, 127.9, 127.8, 127.8, 127.8, 127.7, 127.7, 127.6, 127.6, 127.5, 127.4, 127.3, 127.3, 126.9, 126.8, 125.7, 125.6, 97.1, 97.1, 95.2, 91.3, 84.9, 82.1, 81.8, 80.7, 79.6, 79.5, 79.4, 77.8, 75.7, 75.2, 75.1, 74.8, 74.5, 74.2, 73.6, 73.6, 73.5, 73.5, 73.4, 73.4, 73.3, 73.1, 72.8, 71.9, 71.2, 71.2, 68.9, 68.6, 68.3. HRMS (ESI) for $C_{67}H_{67}NO_{12}$ (M+Na), 1100.4561 (Calc.), found 1100.4561. IR (neat): ν 1738, 1585, 1496, 1454, 1362, 1303, 1289, 1244, 1214, 1152, 1069, 1041, 1027, 914, 849, 819, 744, 735, 696, 665.

General procedure for the synthesis of C-glycosides with allyl TMS. **Condition A**: Picolinic ester (0.10 mmol), $Cu(OTf)_2$ (1.2 eq, dried under vacuum overnight), and 4Å MS (about 100.0 mg, dried with hot gun under vacuum for 15 min) were added to a vial. Then the vial was refilled with Argon. CH_2Cl_2 (0.5 mL) and allyl TMS (6.0 equiv) were added with syringes under Argon. The vial was capped and stirred at rt for 12-30 h until TLC analysis showed the picolinate was completely converted, usually 16 h. The mixture was purified through a silica gel column chromatography (Hexane/Ethyl acetate = 10:1) to give the corresponding C-glycosides. **Condition B**: Picolinic ester (0.10 mmol) and toluene (0.30 mL, as the azeotrope to remove water) were added to 3 mL vial. The mixture was stirred under vacuum to remove toluene and the operation was repeated 3 times for removing water as much as possible. Then dried $Cu(OTf)_2$ (1.2 equiv) was added to the vial and the vial was refilled with Argon. CH_2Cl_2 (0.5 mL) and allyl TMS (6.0 equiv) were added with syringes under Argon. The vial was capped and stirred at rt for 12-30 h until TLC analysis showed the picolinate was completely converted, usually 16 h. The mixture was purified through a silica gel column chromatography (Hexane/Ethyl acetate = 10:1) to give the corresponding C-glycosides.

7a: 3-(Tetra-*O*-benzyl-α-D-galactopyranosyl)-prop-1-ene. Condition A was used to synthesize compound **7a**. Crude product purified via flash column chromatography (eluent: Hex:EA=10:1, V/V) to afford **7a** (α, colorless oil, 53.0 mg, 95% yield; β, colorless oil, 2.5 mg, 4% yield). Spectral data are in accordance with the literature.[24]

7e: 3-(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)-prop-1-ene. Condition A was used to synthesize compound **7e**. Crude product purified via flash column chromatography

(eluent: Hex:EA=10:1, V/V) to afford **7e** (α, colorless oil, 51.0 mg, 90% yield; β, colorless oil, 2.0 mg, 4% yield). Spectral data are in accordance with the literature.[25] The one mmol scale reaction was performed following the same procedure. Picolinic ester **5e** (645.8 mg, 1.00 mmol), $Cu(OTf)_2$ (434.0 mg, 1.20 mmol), and activated 4Å MS (600.0 mg) were added to a 25 mL round bottom flask. Then the flask was refilled with Argon. CH_2Cl_2 (3.0 mL) and allyl TMS (685.6 mg, 6.00 mmol) were added with syringes under Argon. The reaction mixture was stirred at rt for 17 h before it was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. Flash column chromatography (eluent: Hex:EA=10:1, V/V) afford **7e** as a colorless oil (484.6 mg, 86% yield, α:β=15:1).

7f: 3-(2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl)-prop-1-ene. Condition A was used to synthesize compound **7f**. Crude product purified via flash column chromatography (eluent: Hex:EA=10:1, V/V) to afford **7f** (α:β=10:1, colorless oil, 55.0 mg, 98% total yield). Spectral data are in accordance with the literature.[25]

7g: 3-(2,3,4-Tri-*O*-benzyl-D-xylopyranosyl)-prop-1-ene. Condition B was used to synthesize compound **7g**. Crude product purified via flash column chromatography (eluent: Hex:EA=10:1, V/V) to afford **7g** (α, colorless oil, 33.0 mg, 74% yield; α:β=10:1). The α isomer: Optical rotation: $[\alpha]_D^{21}$ = +12.6 (c 0.170, $CHCl_3$)**.** ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.41 – 7.27 (m, 15H), 5.77 (ddt, J = 17.1, 10.2, 6.9 Hz, 1H), 5.13 – 4.99 (m, 2H), 4.65 (d, J = 11.9 Hz, 1H), 4.59 (d, J = 7.7 Hz, 4H), 4.51 (d, J = 11.8 Hz, 1H), 3.83 – 3.67 (m, 4H), 3.42 (dd, J = 5.3, 3.7 Hz, 2H), 2.60 – 2.48 (m, 1H), 2.36 (m, 1H). $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$, TMS) δ 138.3, 138.3, 135.0, 128.4, 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 127.7, 116.9, 77.2, 76.4, 75.2, 74.9, 74.8, 73.4, 72.6, 72.1, 64.5, 33.0, 29.7. HRMS (ESI) for $C_{29}H_{32}O_4$ (M+Na), 467.2193 (Calc.), found 467.2187. IR (neat): ν 1496, 1454, 1421, 1395, 1361, 1325, 1301, 1280, 1253, 1209, 1087, 1027, 1003, 992, 973, 935, 912, 873, 848, 828, 807, 796, 751, 737, 697, 679.

7h: 3-(2,3,4-Tri-*O*-benzyl-α-L-fucopyranosyl)-prop-1-ene. Condition B was used to synthesize compound **7h**. Crude product purified via flash column chromatography (eluent: Hex:EA=10:1, V/V) to afford **7h** (α, colorless oil, 30.0 mg, 65% yield; α:β=20:1). Spectral data are in accordance with the literature.[26]

7i: 3-(3,4,6-Tri-*O*-benzyl-2-deoxy-D-glucopyranosyl)-prop-1-ene. Condition B was used to synthesize compound **7i**. Crude product purified via flash column chromatography (eluent: CH_2Cl_2:Acetone=50:1, V/V) to afford **7i** (only α, colorless oil, 24.0 mg, 53% yield). Spectral data are in accordance with the literature.[27]

7j: 3-(3,4,6-Tri-*O*-benzyl-2-deoxy-α-D-galactopyranosyl)-prop-1-ene. Condition B was used to synthesize compound **7j**. Crude product purified via flash column chromatography (eluent: Hex:EA=10:1, V/V) to afford **7j** (only α, colorless oil, 31.0 mg, 68% yield). Spectral data are in accordance with the literature.[16]

7k: 3-(2,3,5-Tri-*O*-benzyl-α-D-ribofuranosyl)-prop-1-ene. Condition B was used to synthesize compound **7k**. Crude product purified via flash column chromatography (eluent: Hex:EA=10:1, V/V) to afford **7k** (only α, colorless oil, 26.0 mg, 59% yield). Spectral data are in accordance with the literature.[28]

7l: 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-1-deoxy-1-allyl-D-glucopyranose. Condition A was used to synthesize compound **7l**. Crude product purified via flash column chromatography (eluent: Hex:EA=10:1, V/V) to afford **7l** (α, white solid, 38.0 mg, 81% yield; α:β=20:1). Spectral data are in accordance with the literature.[18a]

7m: 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-1-deoxy-1-allyl-α-D-mannopyranose. Condition A was used to synthesize compound **7m**. Crude product purified via flash column chromatography (eluent: Hex:EA=10:1, V/V) to afford **7m** (only α, colorless oil, 25.0 mg, 53% yield). Spectral data are in accordance with the literature.[18a]

7n: 2,3,4-Tris-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-1-deoxy-1-allyl-D-glucopyranose. Condition A was used to synthesize compound **7n**. Crude product purified via flash column chromatography (eluent: Hex:EA=10:1, V/V) to afford **7n** (α, colorless oil, 60.0 mg, 69% yield; α:β=8:1, 0.09 mmol scale). The α isomer: Optical rotation: $[\alpha]_D^{21}$ = +41.2 (c 0.425, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.14 (m, 33H), 7.10 (dd, *J* = 6.9, 2.7 Hz, 2H), 5.88 – 5.73 (m, 1H), 5.57 (d, *J* = 3.6 Hz, 1H), 5.20 – 5.00 (m, 2H), 4.87 (dd, *J* = 11.3, 8.2 Hz, 2H), 4.80 – 4.71 (m, 3H), 4.64 – 4.39 (m, 8H), 4.28 (d, *J* = 12.2 Hz, 1H), 4.10 (dt, *J* = 10.3, 4.8 Hz, 1H), 4.02 (t, *J* = 8.3 Hz, 1H), 3.95 – 3.86 (m, 2H), 3.82 – 3.72 (m, 4H), 3.69 – 3.61 (m, 2H), 3.55 – 3.47 (m, 2H), 3.40 (dd, *J* = 10.8, 2.0 Hz, 1H), 2.61 – 2.49 (m, 1H), 2.49 – 2.39 (m, 1H). $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$) δ 138.8, 138.8, 138.5, 138.5, 138.1, 138.1, 138.0, 134.8, 128.4, 128.4, 128.3, 128.3, 128.3, 128.2, 128.1, 127.9, 127.87, 127.85, 127.8, 127.8, 127.7, 127.7, 127.6, 127.5, 127.4, 127.3, 127.3, 126.9, 117.0, 96.9, 82.0, 81.4, 79.6, 79.5, 77.8, 75.5, 75.0, 73.6, 73.5, 73.4, 73.2, 73.0, 72.7, 71.2, 71.0, 69.6, 68.2, 30.7. HRMS (ESI) for $C_{64}H_{68}O_{10}$ (M+Na), 1019.4705 (Calc.), found 1019.4681. IR (neat): ν 1497, 1454, 1360, 1215, 1074, 1027, 916, 745, 697, 666.

7o: 1,5-Anhydro-2,3,4-tri-*O*-benzoyl-D-threo-pent-1-enitol. Condition A was used to synthesize compound **7o**. Crude product purified via flash column chromatography (eluent: Hex:EA=10:1, V/V) to afford **7o** (white solid, 30.0 mg, 68% yield). Spectral data are in accordance with the literature.[29]

General procedure for the synthesis of C-glycosides with silyl enol ethers. Picolinic ester (0.10 mmol), $Cu(OTf)_2$ (1.2 eq, dried under vacuum overnight), and 4Å MS (about 100.0 mg, dried with hot gun under vacuum for 15 min) were added to a vial. Then the vial was refilled with Argon. CH_2Cl_2 (0.5 mL) and silyl enol ether (1.5 equiv) were added with syringes under Argon. The vial was capped and stirred at rt for 12-30 h until TLC analysis showed the picolinate was completely converted, usually 16 h. The mixture was purified through a silica gel column chromatography (Hexane/Ethyl acetate=10:1) to give the corresponding C-glycosides.

9a: 1-(2,3,4,6-Tetra-*O*-benzyl-D-galactopyranosyl)-acetophenone. Crude product purified via flash column chromatography (eluent: Hex:EA=10:1, V/V) to afford **9a** (α:β=2.7:1, colorless oil, 60.0 mg, 93% total yield). Spectral data are in accordance with the literature.[30]

9b: 1-(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)-acetophenone. Crude product purified via flash column chromatography (eluent: Hex:EA=10:1, V/V) to afford **9b** (only α, white solid, 58.0 mg, 90% yield). Spectral data are in accordance with the literature.[16] The 1.0 mmol scale reaction was performed following the same procedure. Picolinic ester **5e** (645.8 mg, 1.00 mmol), $Cu(OTf)_2$ (434.0 mg, 1.20 mmol), and activated 4Å MS (600.0 mg) were added to a 25 mL round bottom flask. Then the flask was refilled with Argon. CH_2Cl_2 (5.0 mL) and silyl enol ether **8a** (288.5 mg, 1.50 mmol) were added with syringes under Argon. The reaction mixture was stirred at rt for 7 h before it was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. Flash column chromatography (eluent: Hex:EA=10:1, V/V) afford **9b** as a white solid (567.9 mg, 88% yield, only α).

9c: 1-(2,3,4,6-Tetra-*O*-benzyl-D-mannopyranosyl)-acetophenone. Crude product purified via flash column chromatography (eluent: Hex:EA=10:1, V/V) to afford 9c (α:β=1.7:1, colorless oil, 63.0 mg, 98% total yield). A small portion of the anomers was separated. The α isomer: Optical rotation: $[\alpha]_D^{21}$ = +5.26 (c 0.570, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.1 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.37 – 7.17 (m, 20H), 4.78 – 4.71 (m, 1H), 4.65 (dd, *J* = 11.5, 1.5 Hz, 1H), 4.61 – 4.39 (m, 7H), 3.91 – 3.84 (m, 2H), 3.84 – 3.76 (m, 3H), 3.76 – 3.72 (m, 1H), 3.21 (td, *J* = 6.5, 1.5 Hz, 2H). ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$) δ 197.6, 138.4, 138.2, 138.1, 138.1, 137.0, 133.1, 128.6, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 127.8, 127.8, 127.7, 127.5, 76.0, 75.3, 74.6, 73.5, 73.4, 71.9, 71.2, 69.1, 68.8, 39.8. HRMS (ESI) for $C_{42}H_{42}O_6$ (M+Na), 665.2874 (Calc.), found 665.2857. IR (neat): ν 1682, 1598, 1496, 1453, 1362, 1216, 1093, 1026, 913, 863, 846, 814, 746, 696, 666.

9d: 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-1-(2-oxo-2-phenylethyl)-D-glucopyranose. Crude product purified via flash column chromatography (eluent: Hex:EA=10:1, V/V) to afford **9d** (α:β=7:1, colorless oil, 43.0 mg, 78% total yield). Spectral data are in accordance with the literature.[18b]

9e: 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-1-deoxy-1-(2-oxo-2-phenylethyl)-D-mannopyranose. Crude product purified via flash column chromatography (eluent: Hex:EA=10:1, V/V) to afford **9e** (α:β=1:13, colorless oil, 28.0 mg, 51% total yield). Spectral data are in accordance with the literature.[18b]

9f: 3,3-Dimethyl-1-(2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl)-butan-2-one. Crude product purified via flash column chromatography (eluent: Hex:EA=10:1, V/V) to afford **9f** (α:β=4.5:1, colorless oil, 57.0 mg, 92% total yield). Reported as mixture of anomers, ratio identified through ^{1}H NMR spectroscopy. Optical rotation: $[\alpha]_D^{21}$ = +16.1 (c 0.410, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.15 (m, 40H), 4.94 (dd, *J* = 17.3, 11.6 Hz, 2H), 4.77 – 4.72 (m, 1H), 4.69 – 4.60 (m, 7H), 4.58 – 4.35 (m, 8H), 4.08 – 4.00 (m, 2H), 3.98 (dd, *J* = 4.3, 2.8 Hz, 1H), 3.92 – 3.83 (m, 2H), 3.81 (dd, 1H), 3.74 – 3.64 (m, 4H), 3.61– 3.44 (m, 2H), 2.85 – 2.63 (m, 3H), 2.56 (dd, *J* = 16.8, 2.2 Hz, 1H), 1.07 (s, 9H), 1.03 (s, 9H). ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$) δ 213.2, 213.1, 138.8, 138.5, 138.5, 138.4, 138.3, 138.1, 138.0, 128.4, 128.4, 128.4, 128.3, 128.2, 128.2, 128.1, 127.9, 127.8, 127.8, 127.7, 127.7, 127.6, 127.5, 85.0, 77.6, 77.2, 76.9, 76.2, 75.7, 75.6, 74.9, 74.7, 74.0, 73.8, 73.4, 73.3, 73.2, 72.8, 72.7, 72.2, 68.7, 67.3, 67.2, 44.2, 44.1, 39.0, 35.8, 29.7, 26.3, 26.1. HRMS (ESI) for $C_{40}H_{46}O_6$ (M+Na), 645.3187 (Calc.), found 645.3173. IR (neat): ν 1704, 1496, 1454, 1367, 1216, 1092, 1028, 911, 746, 696, 667.

9g: 3,3-Dimethyl-1-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-butan-2-one. Crude product purified via flash column chromatography (eluent: Hex:EA=10:1, V/V) to afford **9g**[15b] (α:β > 20:1, white solid, 54.0 mg, 87% yield). Spectral data are in accordance with the literature.[31]

ASSOCIATED CONTENT

Supporting Information.
This material is available free of charge via the Internet at http://pubs.acs.org

Copies of ^{1}H NMR data
Copies of ^{13}C{^{1}H}NMR data

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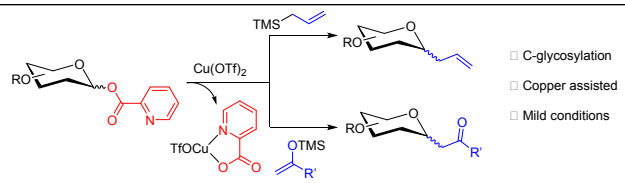
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