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Stereocontrolled *O*-Glycosylation with Palladium-Catalyzed Decarboxylative Allylation

Shaohua Xiang, Jingxi He, Yu Jia Tan, and Xue-Wei Liu*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

Supporting Information

ABSTRACT: The Pd-π-allyl intermediate in an electron-rich glycal system with poor reactivity is employed as an efficient glycosyl donor. Starting from glucal derived carbonate, various *O*-glycosides were formed via a palladium-catalyzed reaction through a tandem decarboxylation, proton abstraction, and nucleophilic addition, in good yields with excellent selectivity. Iterative glycosylation with the same strategy may provide an access to complex oligosaccharides.

INTRODUCTION

The construction of glycosidic bonds with high efficiency and selectivity has been and continues to be a challenging endeavor in carbohydrate chemistry. Enormous progress has been made in the development of new strategies for expeditious glycosidic linkage syntheses to construct glycoconjugates and oligosaccharides due to their common occurrence in many bioactive natural products and their mimetics.[1] Besides the continued interest in traditional glycosyl donors, glycals are becoming increasingly attractive as they can be transformed into 2,3-unsaturated glycosyl derivatives easily by a classic Ferrier rearrangement.[2] Moreover, the core structures can be functionalized readily to a variety of sugar scaffolds.[3] Lewis acid promoted Ferrier rearrangement has demonstrated its capability on syntheses of such glycosides; however, only the α-isomer can be furnished as the major product in most cases, which limits their practical applicability.[4] Therefore, the development of other methods and strategies with impressive yields and selectivities (particularly β-selectivity) remains necessary and imperative.

Compared to traditional methods, the reactions with Pd-π-allyl donors are usually associated with good stereocontrol. Recently, various convenient and efficient methods with metal catalysts toward the syntheses of different glycosidic bonds with excellent selectivity have been reported.[5] However, both the difficulty in formation and the poor reactivity of Pd-π-allyl intermediates in electron-rich glycal systems prove to be an impediment in further development of this methodology.[6] The addition of Et_2Zn activator provided one way to solve this problem, and another solution was employing electron-poor cyclic pyranones as the starting materials.[7,8] However, the employment of a Pd-π-allyl intermediate in an electron-rich glycal system as an efficient glycosyl donor without activator has been only reported by Nguyen's group with phenol type acceptors.[7b] Under this situation, the decarboxylative allylation (DcA), which has been well investigated by many pioneering groups, such as Tunge,[9] Trost,[10] Stoltz,[11] and others,[12] from more active allylic carbonates provided a viable alternative, as demonstrated in our previous studies.[13b] It was found that the driving force, release of CO_2, made formation of Pd-π-allyl species from carbonate substrates faster and more efficient. Moreover, the resultant Pd-π-allyl intermediate can participate in a subsequent intramolecular nucleophilic addition efficiently.[13] We envisioned that this strategy has the potential in the synthesis of other glycosides through an additional proton abstraction step in the presence of another nucleophile (Scheme 1).[14] Herein, we describe our initial results of this palladium-catalyzed intermolecular glycosylation from glucal derived allylic carbonates.

RESULTS AND DISCUSSION

Compound **1**, prepared from 4,6-*para*-methoxybenzylidene-glucal and ethyl chloroformate, was selected as the model substrate in our initial investigation. It was hypothesized that the product of proton transfer in this case, ethanol, can be

Scheme 1. Palladium-Catalyzed *O*-Glycosylation

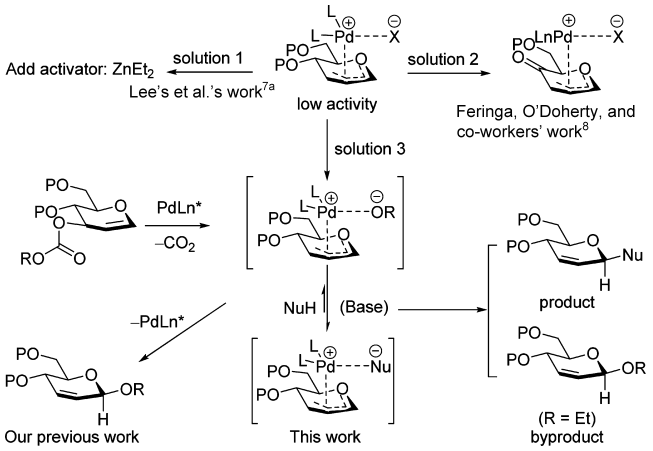

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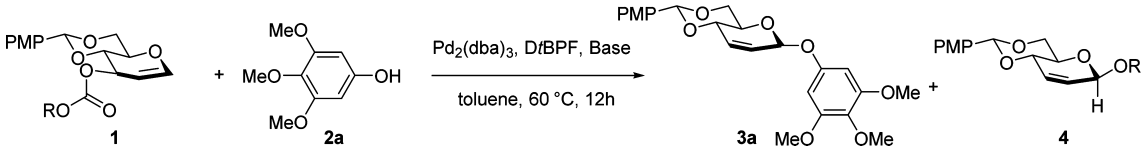
Table 1. Optimization of Reaction Conditions[a]



entry	R	base	base loading	yield of **3** (%)	ratio (α:β)[b]	yield of **4** (%)[c]
1	Et			20	ND	68
2	Et	NaOEt	1.2	69	0:1	21
3	*t*Bu	NaOEt	1.2	55	ND	25
4	Et	K_2CO_3	1.2	79	1:3	
5	Et	Cs_2CO_3	1.2	92	0:1	
6	Et	DBU	1.2	80	0:1	
7	Et	NaH	1.2	23	2:3	
8	Et	Cs_2CO_3	0.1	45	6:1	
9	Et	Cs_2CO_3	0.2	62	5:1	
10	Et	Cs_2CO_3	0.5	90	0:1	
11	**Et**	**Cs_2CO_3**	**2.0**	**93**	**0:1**	
12[d]		Cs_2CO_3	2.0	45	1:1	

[a]Unless otherwise specified, all reactions were carried out with 0.1 mmol of **1**, 0.2 mmol of **2a**, 10% catalyst, and 20% ligand in toluene at 60 °C for 12 h. [b]The ratios were determined by ^{1}H NMR. [c]Isolated yield. [d]At the C-3 position, OCO_2Et group was replaced by OAc.

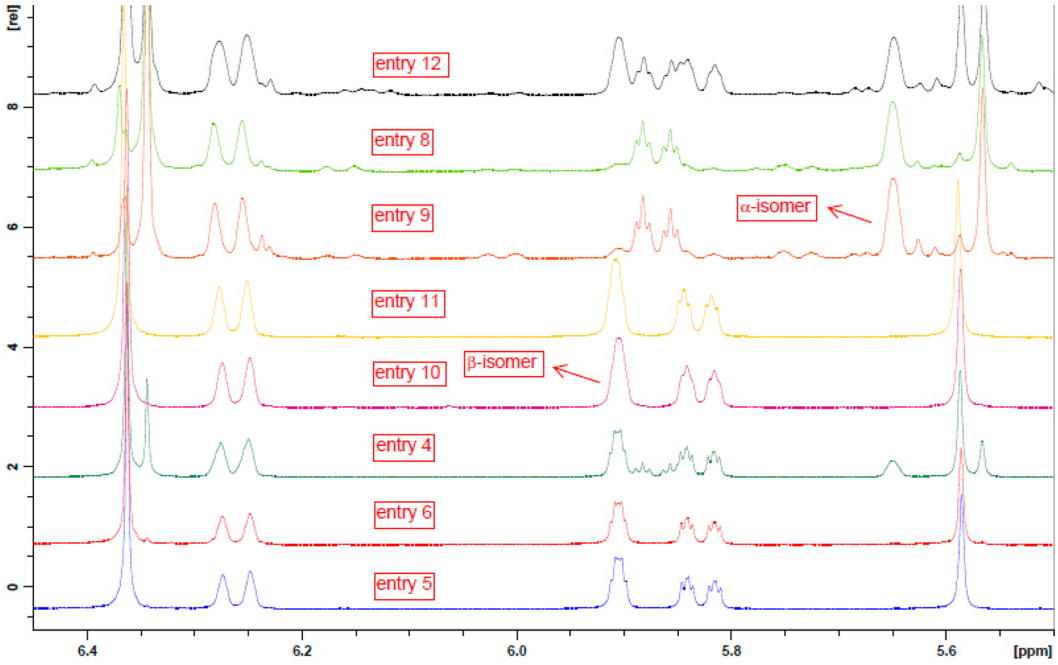


Figure 1. Selectivities confirmed by ^{1}H NMR.

removed with ease from the reaction system at high temperature, inhibiting the formation of byproduct. For the glycosyl acceptor, 3,4,5-trimethoxyphenol was first examined due to its strong nucleophilicity. We initiated our study by treating glucal carbonate **1** with 3,4,5-trimethoxyphenol **2a** under the same conditions established in our previous work on intramolecular *O*-glycosylation.[13b] However, the desired product **3a** was formed in low yield and 68% of byproduct **4** was observed (entry 1, Table 1). Considering the low nucleophilicity of the protonated phenol, sodium ethoxide was added as the base to increase the nucleophilicity. Gratifyingly, the yield of the product **3** increased significantly to 69%. At the same time, the yield of the byproduct decreased to 21%, although sodium ethoxide itself can serve as a nucleophile to increase the potential of byproduct formation (entry 2). A subsequent attempt to inhibit formation of byproduct with a bulky group, tertiary butyl, was, however, futile. Then, the effect of altering the base was examined. It was found that Cs_2CO_3 is most efficient in increasing both the chemical yield and the anomeric selectivity compared to other bases, such as K_2CO_3, DBU, and NaH (entries 4–7). It should be noted that this reaction is very sensitive to not only the chemical properties but also the loading of the base. When less than 0.5 equiv of base was used, the α-isomer was obtained as the major product, while exclusive β-selectivity was afforded with more than 0.5 equiv of base (entries 8–11). The substrate with an *OAc* leaving group on the C-3 position was then investigated, but only an α:β = 1:1 mixture was obtained in 45% yield (entry 12). The ratios of the mixture can be determined by the ^{1}H NMR with ease, and selected results are summarized

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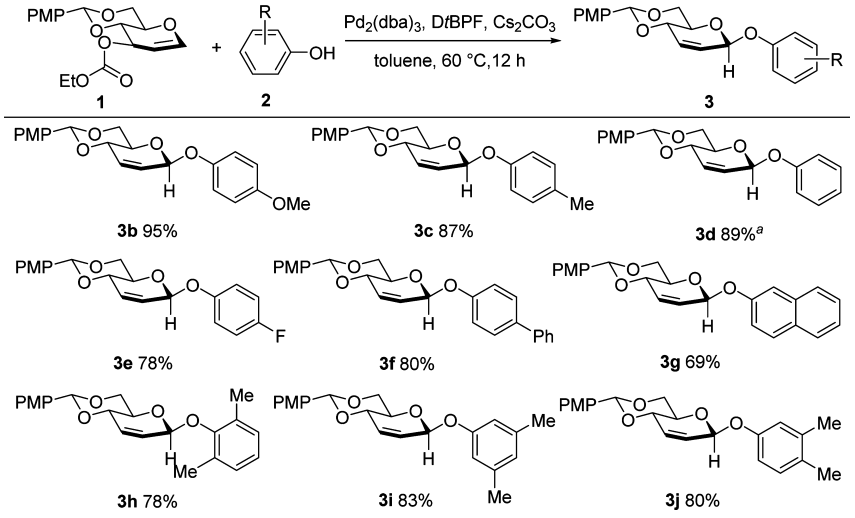
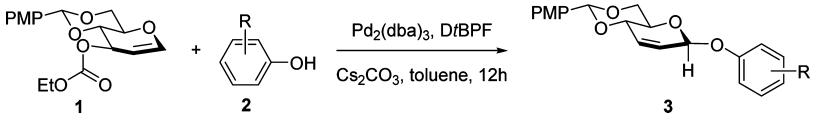
Scheme 2. Substrate Scope of Phenolic *O*-Glycosides[a]



[a]The reaction was conducted at 50 °C.

Table 2. Effects of Substituents on the Phenol and Temperature[a]



entry	R	temperature (°C)	ratio (α:β)[b]	yield of **3** (%)[c]
1	3,4,5-trimethoxy	80	0:1	90
2	3,4,5-trimethoxy	60	0:1	93
3	4-methoxy	70	0:1	95
4	4-methoxy	60	0:1	95
5	4-fluoro	80	1:1	80
6	4-fluoro	60	0:1	78
7	4-phenyl	80	1:1	76
8	4-phenyl	60	0:1	80
9	H	60	1:10	92
10	H	50	0:1	89
11	4-methyl	80	1:1	89
12	4-methyl	70	1:11	90
13	4-methyl	60	0:1	87
14	3,4-dimethyl	80	1:3	75
15	3,4-dimethyl	60	0:1	80
16	3,5-dimethyl	80	1:3	77
17	3,5-dimethyl	60	0:1	83

[a]Unless otherwise specified, all reactions were carried out with 0.1 mmol of compound **1**, 0.2 mmol of compound **2**, 0.2 mmol of Cs_2CO_3, 10% catalyst, and 20% ligand in toluene for 12 h. [b]The ratios were determined by ^{1}H NMR. [c]Isolated yield.

in Figure 1. Hence, our optimized conditions are concluded to be 10% $Pd_2(dba)_3$ as the catalyst, 20% D*t*BPF (1,1′-bis(di-*tert*-butylphosphino)ferrocene) as the ligand, 2.0 equiv of Cs_2CO_3 as the base, and toluene as the solvent at 60 °C for a reaction time of 12 h.

With the optimized conditions in hand, we next turned our attention to exploring the substrate tolerance of this reaction. As detailed in Scheme 2, a more nucleophilic phenol with a strong electron-donating group appended to the aromatic ring gave the desired product in 95% yield (**3b**), while a slightly lower yield was observed with a weaker electron-donating group substituted phenol (**3c**). Under the optimized conditions, unsubstituted phenol afforded the glycoside in good yield with a ratio of α:β = 1:10. The pure product can be furnished by decreasing the temperature to 50 °C, further illustrating the sensitivity of the reaction in terms of temperature (**3d**). This reaction was also tolerant to a fluoro group on the aromatic ring, shown by the generation of compound **3e** in good yield. 4-Phenyl phenol and 2-naphthol were then examined and were observed to give the desired products **3f** and **3g** in moderate to good yields. The different positions of the functionalities on a disubstituted phenol had very little influence on this reaction and gave the *O*-glycosides in good yields (**3h**−**3j**). It is worth noting that only the β-isomer was produced in each reaction.

In the optimization section, we found that the selectivity of the reaction was strongly influenced by the base loading. Besides that, some results also suggested that the electronic

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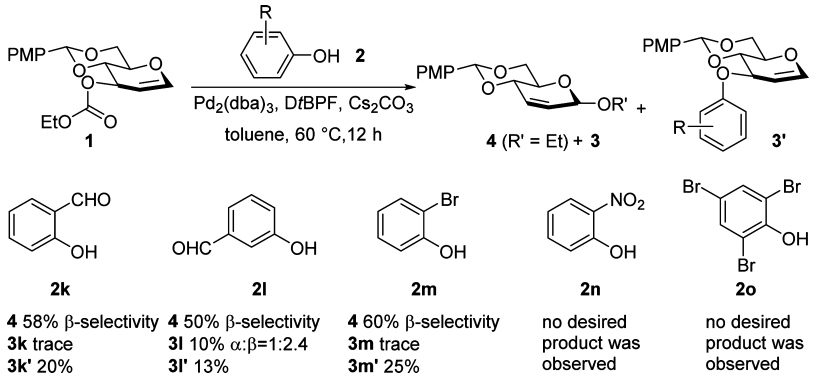
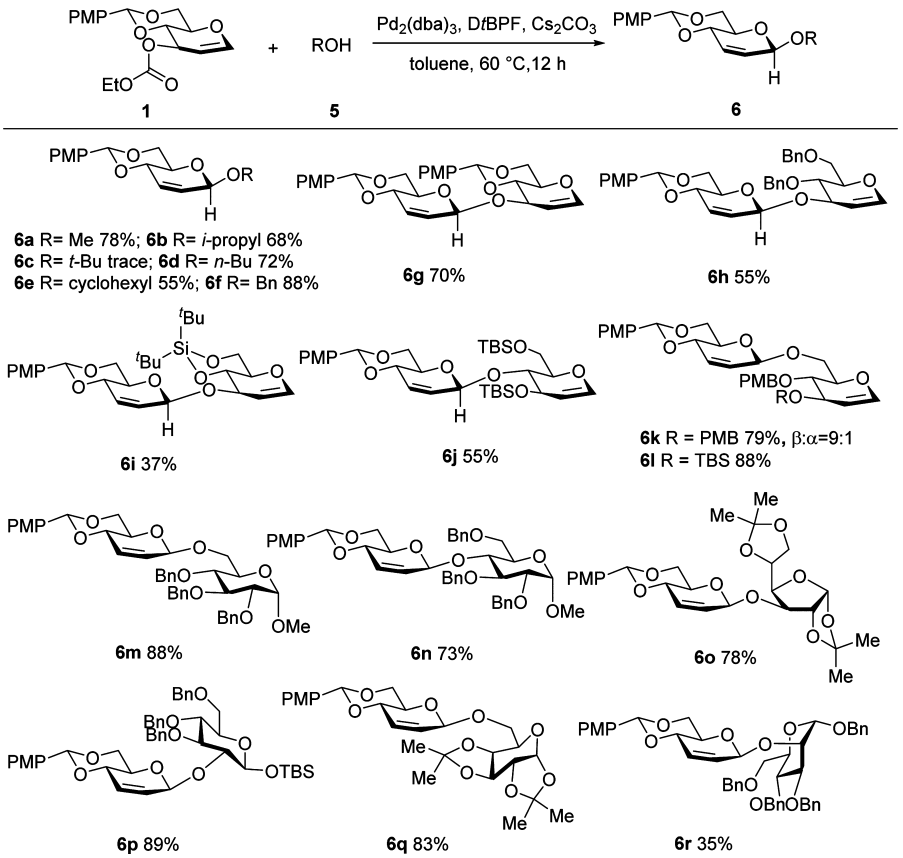
Scheme 3. Effect of Substituents on the Phenol



Scheme 4. Substrate Scope of Aliphatic *O*-Glycosides[a]



[a]The reaction was conducted with **5a**−**5f** (1.0 mmol) or **5g**−**5r** (0.2 mmol) as the acceptor.

nature of the substituents on the phenol and the reaction temperature are also important in controlling the stereoselectivities of this reaction. From the results detailed in Table 2, it is apparent that a lower reaction temperature always results in higher selectivity. The good selectivity generally observed with electron-rich phenol can be retained at higher temperatures, but electron-deficient phenol substrates can only afford good selectivity at lower temperatures, such as 60 °C. Little variation in yield is observed when the reaction temperature is above 60 °C.

Interestingly, the regioselectivity of the reaction could also be affected by a glycosyl acceptor when electron-deficient phenol was employed. For instance, when substrates **2k**, **2l**, and **2m** with an electron-withdrawing group were treated under the optimized reaction conditions, the byproduct **4** from ethoxide addition was observed as the major product (Scheme 3). At the same time, only a trace amount of desired products **3k** and **3m** was detected and compound **3l** was isolated in 10% yield as inseparable mixtures with a ratio of α:β = 1:2.4, which could be determined by ^{1}H NMR. Noteworthy, the C-3 position addition products **3′** were also isolated with yields of 18, 13, and 20%, respectively.[15] The difference in regioselectivity (C-1 or C-3) could be explained by the hard and soft acids and bases (HSAB) principle.[16] Further investigations revealed that, in reactions involving phenols with strong electron-withdrawing groups, such as 2-nitro phenol (**2n**) or 2,4,6-tribromo phenol (**2o**), no desired product was observed.

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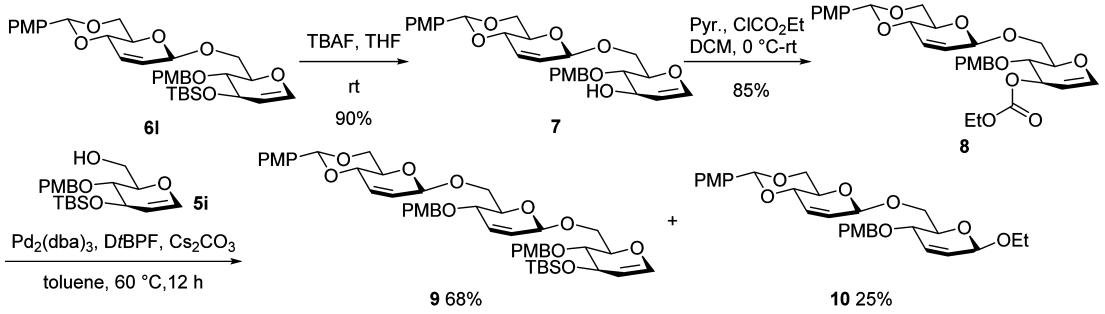
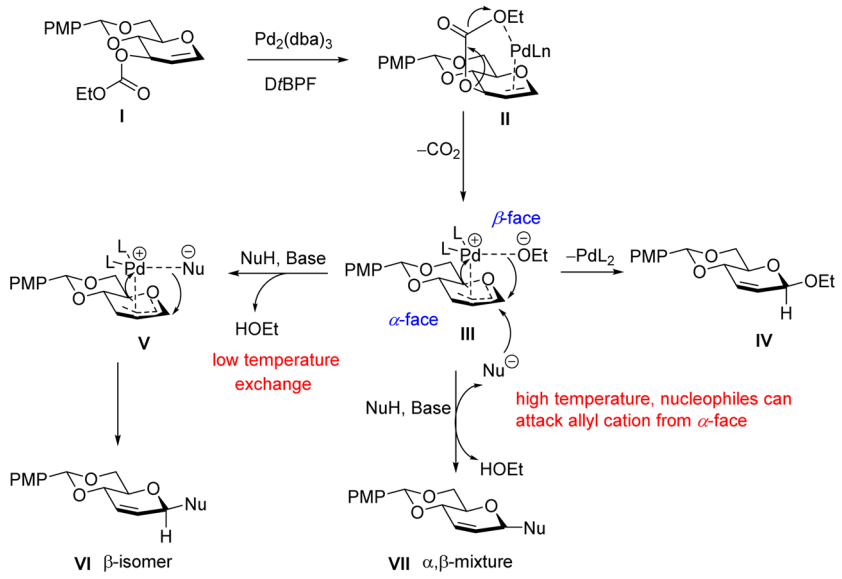
Scheme 5. Preparation of the Trisaccharide 9



Scheme 6. Plausible Mechanism



Having confirmed the efficiency of this reaction in syntheses of phenolic *O*-glycosides, we next focused on its extension toward aliphatic *O*-glycosides and attempted the synthesis of disaccharides and oligosaccharides. The aliphatic alcohols were first investigated and the results shown in Scheme 4 demonstrated that the reaction proceeds efficiently under the optimized conditions (**6a**–**6f**) with the exception of sterically hindered tertiary butanol (**6c**). It should be noted that 10 equiv of alcohol was used in each reaction. Next, glucal with a free hydroxyl group at different positions was employed. Notably, the reaction with 3-OH glucals as the substrates proceeded smoothly to form the desired glycosides, which cannot be generated by intramolecular glycosylation (**6g**–**6i**). The bulky glycosyl acceptor with a free hydroxyl group in the 4-position gave the desired product with a much lower yield (**6j**). The 6-OH glucal substrates afforded the desired products in good yields (**6k**–**6l**), albeit with a ratio of α:β = 1:10 when PMB was selected as the protecting group. Glucose type acceptors were then examined, and gratifyingly, good to excellent yields with excellent β-selectivity were observed (**6m**–**6p**). Galactose and mannose type glycosides can also be prepared under this set of conditions, with yields of 83% and 35%, respectively (**6q**–**6r**).

Encouraged by the above results, we next explored the synthetic utility of this approach by the synthesis of trisaccharide **9**. As detailed in Scheme 5, starting from the first glycosylation product **6l**, intermediate **7** was obtained by a deprotection in the presence of TBAF. In a parallel synthesis, disaccharide carbonate **8** was prepared according to the standard procedure for preparation of carbonates. Thereafter, **8** was treated under the optimized conditions with compound **5i** as the glycosyl acceptor for the second glycosylation. Fortunately, the desired product **9** was provided in 68% yield with exclusive β-selectivity. The ease of access of trisaccharide **9** demonstrates the potential of this methodology in the synthesis of more complex oligosaccharides.

On the basis of the results obtained and precedent work on palladium-catalyzed reactions,[13,14] we henceforth propose a plausible mechanism involved in this intermolecular glycosylation. As a traditional palladium-catalyzed decarboxylative allylation reaction, starting from glucal carbonate compound **I**, the palladium intermediate **III** is first generated by coordination from the β-face and a subsequent decarboxylative reaction (Scheme 6). In the absence of other nucleophiles, the intramolecular product **IV** is then obtained through an elimination of the Pd species. In the presence of an external nucleophile, the reaction is intercepted by a proton transfer between the ethoxide anion and the added nucleophile, yielding Pd intermediate **V**. Thereafter, the desired β-product **VI** is obtained with the elimination of the Pd species. Nevertheless, besides the proton transfer, a nucleophile addition to the allyl cation from the α-face, which can furnish the α-product, can take place simultaneously at high temperature. Under such conditions, a mixture of α- and β-product **VII** is thus observed.

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CONCLUSION

In summary, we have reported a palladium-catalyzed intermolecular glycosylation based on a decarboxylative reaction. Various nucleophiles were tested in this reaction, and the desired phenolic *O*-glycosides, aliphatic *O*-glycosides, and disaccharides were formed in moderate to good yields with excellent selectivity. The results also illustrate the sensitivity of the reaction to the nature and loading of the base, reaction temperature, and electronic nature of the substrates. In addition, this method provides a practical and concise method to synthesize some glycosides that cannot be prepared by the intramolecular glycosylation. Moreover, by replacing the complex carbonate substrates with readily available glucal derivatives, preparation of complex carbonate substrates and isolation of the related glycosides are more facile and expeditious. The efficiency and practical applicability were further proven by the iterative synthesis of a trisaccharide. Further application of this methodology for the synthesis of complex oligosaccharides is currently being explored in our laboratory.

EXPERIMENTAL SECTION

General Procedure for Preparing Phenolic *O*-Glycosides. To a mixture of D*t*BPF (0.02 mmol), $Pd_2(dba)_3$ (0.01 mmol), carbonate **1** (0.1 mmol), phenol **2** (0.2 mmol), and Cs_2CO_3 (0.2 mmol) was added toluene (2 mL) under an atmosphere of argon. After stirring at 60 °C for 12 h, the solvent was removed under reduced pressure to give a crude product that was further purified by column chromatography to afford the desired phenolic *O*-glycosides **3** with 69−95% yields.

*(4aR,6S,8aS)-2-(4-Methoxyphenyl)-6-(3,4,5-trimethoxyphenoxy)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (**3a**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), phenol **2a** (36.8 mg, 0.2 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography (EA:Hexane = 1:2) to afford phenolic *O*-glycoside **3a** (40.0 mg, 93%) as a white solid. mp 153−155 °C; $[\alpha]_D^{23}$ = +15.0 (*c* = 1.0 in $CHCl_3$); IR (neat) ν: 3016, 2303, 1695, 1616, 1477, 1415, 1215, 1088 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41−7.44 (m, 2H), 6.86−6.93 (m, 2H), 6.36 (s, 2H), 6.26 (d, *J* = 10.3 Hz, 1H), 5.89−5.92 (m, 1H), 5.83 (ddd, J_1 = 10.3 Hz, J_2 = 2.4 Hz, J_3 = 1.8 Hz, 1H), 5.59 (s, 1H), 4.39−4.44 (m, 1H), 4.26−4.34 (m, 1H), 3.79−3.94 (m, 14H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 153.6, 153.1, 133.9, 132.3, 129.6, 127.5, 126.9, 113.7, 102.1, 97.2, 95.1, 74.6, 71.0, 68.9, 60.9, 56.1, 55.3 ppm; HRMS (ESI) calcd. for $C_{23}H_{26}O_8Na$ [M + Na]: 453.1525, found: 453.1522.

*(4aR,6S,8aS)-6-(4-Methoxyphenoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (**3b**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), phenol **2b** (24.8 mg, 0.2 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography (EA:Hexane = 1:4) to afford phenolic *O*-glycoside **3b** (35.1 mg, 95%) as a white solid. mp 140−142 °C; $[\alpha]_D^{23}$ = +31.2 (*c* = 1.0 in $CHCl_3$); IR (neat) ν: 3018, 2308, 1694, 1620, 1523, 1479, 1411, 1085, 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.7 Hz, 2H), 7.01−7.07 (m, 2H), 6.87−6.93 (m, 2H), 6.80−6.86 (m, 2H), 6.23 (d, *J* = 10.5 Hz, 1H), 5.80−5.86 (m, 2H), 5.58 (s, 1H), 4.37−4.42 (m, 1H), 4.28−4.34 (m, 1H), 3.83−3.94 (m, 2H), 3.80 (s, 3H), 3.77 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 155.3, 150.7, 132.0, 129.7, 127.5, 127.3, 118.4, 114.5, 113.7, 102.1, 97.8, 74.7, 70.9, 69.0, 55.6, 55.3 ppm; HRMS (ESI) calcd. for $C_{21}H_{22}O_6Na$ [M + Na]: 393.1350, found: 393.1350.

*(4aR,6S,8aS)-2-(4-Methoxyphenyl)-6-(p-tolyloxy)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (**3c**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), phenol **2c** (21.6 mg, 0.2 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography (EA:Hexane = 1:6) to afford the desired phenolic *O*-glycoside **3c** (30.8 mg, 87%) as a white solid. mp 154−156 °C; $[\alpha]_D^{23}$ = +26.6 (*c* = 1.0 in $CHCl_3$); IR (neat) ν: 3019, 1520, 1474, 1423, 1215, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40−7.45 (m, 2H), 7.07−7.11 (m, 2H), 6.96−7.01 (m, 2H), 6.87−6.92 (m, 2H), 6.23 (d, *J* = 10.3 Hz, 1H), 5.88−5.91 (m, 1H), 5.82 (ddd, J_1 = 10.3 Hz, J_2 = 2.5 Hz, J_3 = 1.7 Hz, 1H), 5.57 (s, 1H), 4.38−4.42 (m, 1H), 4.25−4.35 (m, 1H), 3.82−3.92 (m, 2H), 3.79 (s, 3H), 2.30 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 154.6, 132.1, 132.0, 129.9, 129.7, 127.5, 127.3, 116.8 113.7, 102.0, 97.0, 74.7, 70.9, 69.0, 55.3, 20.6 ppm; HRMS (ESI) calcd. for $C_{21}H_{22}O_5Na$ [M + Na]: 377.1365, found: 377.1359.

*(4aR,6S,8aS)-2-(4-Methoxyphenyl)-6-phenoxy-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (**3d**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), phenol **2d** (18.8 mg, 0.2 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography (EA:Hexane = 1:6) to afford the desired phenolic *O*-glycoside **3d** (30.3 mg, 89%) as a white solid.[13b]

*(4aR,6S,8aS)-6-(4-Fluorophenoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (**3e**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), phenol **2e** (22.4 mg, 0.2 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography (EA:Hexane = 1:6) to afford the desired phenolic *O*-glycoside **3e** (27.9 mg, 78%) as a white solid.[13b]

*(4aR,6S,8aS)-6-(Biphenyl-4-yloxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (**3f**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), phenol **2f** (34.0 mg, 0.2 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography (EA:Hexane = 1:6) to afford the desired phenolic *O*-glycoside **3f** (33.3 mg, 80%) as a white solid.[13b]

*(4aR,6S,8aS)-2-(4-Methoxyphenyl)-6-(naphthalen-2-yloxy)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (**3g**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), phenol **2g** (28.8 mg, 0.2 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography (EA:Hexane = 1:6) to afford the desired phenolic *O*-glycoside **3g** (26.9 mg, 69%) as a white solid.[13b]

*(4aR,6S,8aS)-6-(2,6-Dimethylphenoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (**3h**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), phenol **2h** (24.4 mg, 0.2 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography (EA:Hexane = 1:6) to afford the desired phenolic *O*-glycoside **3h** (28.7 mg, 78%) as a white solid.[13b]

*(4aR,6S,8aS)-6-(3,5-Dimethylphenoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (**3i**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), phenol **2i** (24.4 mg, 0.2 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography (EA:Hexane = 1:6) to afford the desired phenolic *O*-glycoside **3i** (30.5 mg, 83%) as a white solid.[13b]

*(4aR,6S,8aS)-6-(3,4-Dimethylphenoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (**3j**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), phenol **2j** (24.4 mg, 0.2 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography (EA:Hexane = 1:6) to afford the desired phenolic *O*-glycoside **3j** (29.4 mg, 80%) as a white solid. mp

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107−109 °C; $[\alpha]_D^{23}$ = +29.9 (*c* = 1.0 in $CHCl_3$); IR (neat) ν: 3022, 1614, 1517, 1476, 1423, 1382, 1217, 1126, 1088, 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40−7.45 (m, 2H), 7.01−7.06 (m, 1H), 6.81−6.93 (m, 4H), 6.23 (d, *J* = 10.3 Hz, 1H), 5.88−5.93 (m, 1H), 5.79−5.86 (m, 1H), 5.58 (s, 1H), 4.38−4.43 (m, 1H), 4.26−4.35 (m, 1H), 3.83−3.93 (m, 2H), 3.80 (s, 3H), 2.24 (s, 3H), 2.20 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 154.9, 137.8, 131.9, 130.8, 130.3, 129.8, 127.5, 127.4, 118.4, 114.1 113.7, 102.1, 97.1, 74.8, 71.0, 69.0, 55.3, 20.0, 18.9 ppm; HRMS (ESI) calcd. for $C_{22}H_{24}O_5Na$ [M + Na]: 391.1521, found: 391.1517.

General Procedure for Preparing Compounds 3k′, 3l′, and 3m′. To a mixture of D*t*BPF (0.02 mmol), $Pd_2(dba)_3$ (0.01 mmol), carbonate **1** (0.1 mmol), phenol **2** (0.2 mmol), and Cs_2CO_3 (0.2 mmol) was added toluene (2 mL) under an atmosphere of argon. After stirring at 60 °C for 12 h, the solvent was removed under reduced pressure to give a crude product that was further purified by column chromatography to afford compound **3′** with 13−25% yields. For these three substrates, compound **4** was obtained as the major product and compound **3** was observed as a mixture.

*2-((4aR,8R,8aS)-2-(4-Methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-8-yloxy)phenol (**3k′**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), phenol **2k** (24.4 mg, 0.2 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography (EA:Hexane = 1:6) to afford compound **3k′** (7.4 mg, 20%) as a white solid. mp 122−124 °C; $[\alpha]_D^{23}$ = −123.5 (*c* = 0.35 in $CHCl_3$); IR (neat) ν: 3018, 1603, 1519, 1474, 1415, 1212, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (dd, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 1H), 7.47−7.55 (m, 1H), 7.33−7.40 (m, 2H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.05 (t, *J* = 7.4 Hz, 1H), 6.87 (dd, J_1 = 9.6 Hz, J_2 = 2.8 Hz, 2H), 6.46 (dd, J_1 = 6.2 Hz, J_2 = 1.2 Hz, 1H), 5.62 (s, 1H), 5.16−5.22 (m, 1H), 4.92 (dd, J_1 = 6.2 Hz, J_2 = 1.8 Hz, 1H), 4.43 (dd, J_1 = 10.6 Hz, J_2 = 5.1 Hz, 1H), 4.23 (dd, J_1 = 10.3 Hz, J_2 = 7.5 Hz, 1H), 4.06 (dt, J_1 = 10.2 Hz, J_2 = 5.1 Hz, 1H), 3.90 (t, *J* = 10.4 Hz, 1H), 3.79 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.8, 160.5, 160.2, 145.8, 135.7, 129.3, 128.4, 127.3, 126.0, 121.5, 115.1, 113.6, 101.5, 99.8, 78.1, 73.6, 68.9, 68.2, 55.3 ppm; HRMS (ESI) calcd. for $C_{21}H_{21}O_6$ [M + H]: 369.1338, found: 369.1337.

*3-((4aR,8R,8aS)-2-(4-Methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-8-yloxy)phenol (**3l′**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), phenol **2l** (24.4 mg, 0.2 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography (EA:Hexane = 1:6) to afford compound **3l′** (4.8 mg, 13%) as a white solid. mp 129−131 °C; $[\alpha]_D^{23}$ = −33.2 (*c* = 0.30 in $CHCl_3$); IR (neat) ν: 3020, 1602, 1517, 1477, 1416, 1214, 1125 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50−7.54 (m, 1H), 7.35−7.50 (m, 4H), 7.22−7.26 (m, 1H), 6.83−6.89 (m, 2H), 6.42−6.47 (m, 1H), 5.61 (s, 1H), 5.13−5.19 (m, 1H), 4.89 (dd, J_1 = 6.2 Hz, J_2 = 1.6 Hz, 1H), 4.41 (dd, J_1 = 10.6 Hz, J_2 = 5.1 Hz, 1H), 4.17 (dd, J_1 = 10.3 Hz, J_2 = 7.5 Hz, 1H), 4.06 (dt, J_1 = 10.2 Hz, J_2 = 5.1 Hz, 1H), 3.89 (t, *J* = 10.4 Hz, 1H), 3.79 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.9, 160.2, 158.4, 145.5, 137.8, 130.1, 129.4, 127.4, 123.6, 123.2, 115.2, 113.6, 101.5, 100.0, 78.2, 72.7, 68.9, 68.2, 55.3 ppm; HRMS (ESI) calcd. for $C_{21}H_{21}O_6$ [M + H]: 369.1338, found: 369.1342.

*(4aR,8R,8aS)-8-(2-Bromophenoxy)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxine (**3m′**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), phenol **2m** (34.6 mg, 0.2 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography (EA:Hexane = 1:6) to afford compound **3m′** (10.5 mg, 25%) as a white solid. mp 92−94 °C; $[\alpha]_D^{23}$ = −60.8 (*c* = 0.75 in $CHCl_3$); IR (neat) ν: 3023, 1603, 1514, 1216, 1179, 1133, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.53 (dd, J_1 = 7.9 Hz, J_2 = 1.4 Hz, 1H), 7.31−7.39 (m, 2H), 7.18−7.25 (m, 1H), 7.09−7.15 (m, 1H), 6.82−6.91 (m, 3H), 6.40−6.46 (m, 1H), 5.62 (s, 1H), 5.02−5.09 (m, 1H), 4.95 (dd, J_1 = 6.2 Hz, J_2 = 1.8 Hz, 1H), 4.40 (dd, J_1 = 10.4 Hz, J_2 = 5.0 Hz, 1H), 4.27 (dd, J_1 = 10.2 Hz, J_2 = 7.5 Hz, 1H), 4.00 (dt, J_1 = 10.2 Hz, J_2 = 5.1 Hz, 1H), 3.88 (t, *J* = 10.4 Hz, 1H), 3.79 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.0, 155.0, 145.3, 133.4, 129.5, 128.3, 127.3, 123.0, 117.4, 114.0, 113.5, 101.2, 100.7, 78.5, 75.0, 68.9, 68.2, 55.3 ppm; HRMS (ESI) calcd. for $C_{20}H_{20}O_5Br$ [M + H]: 419.0494, found: 419.0493.

General Procedure for Preparing Aliphatic *O*-Glycosides. To a mixture of D*t*BPF (0.02 mmol), $Pd_2(dba)_3$ (0.01 mmol), carbonate **1** (0.1 mmol), alcohol **5** (**5a**−**5f**, 1.0 mmol), and Cs_2CO_3 (0.2 mmol) was added toluene (2 mL) under an atmosphere of argon. After stirring at 60 °C for 12 h, the solvent was removed under reduced pressure to give a crude product that was further purified by column chromatography to afford the desired aliphatic *O*-glycosides **6a**−**6f** with 55−88% yields.

*(4aR,6R,8aS)-6-Methoxy-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (**6a**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), methanol **5a** (32.0 mg, 1.0 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography (EA:Hexane = 1:6) to afford the desired aliphatic *O*-glycoside **6a** (21.7 mg, 78%) as a white solid.[13b]

*(4aR,6R,8aS)-6-Isopropoxy-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (**6b**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), isopropanol **5b** (60.1 mg, 1.0 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography (EA:Hexane = 1:6) to afford the desired aliphatic *O*-glycoside **6b** (20.8 mg, 68%) as a white solid. mp 83−85 °C; $[\alpha]_D^{23}$ = +36.6 (*c* = 1.0 in $CHCl_3$); IR (neat) ν: 3016, 1614, 1595, 1518, 1462, 1219, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39−7.45 (m, 2H), 6.86−6.91 (m, 2H), 6.09 (d, *J* = 10.3 Hz, 1H), 5.62−5.69 (m, 1H), 5.60 (s, 1H), 5.37−5.41 (m, 1H), 4.30−4.36 (m, 1H), 4.26 (dd, J_1 = 10.2 Hz, J_2 = 4.5 Hz, 1H), 4.03 (septet, *J* = 6.2 Hz, 1H), 3.86 (t, *J* = 10.3 Hz, 1H), 3.80 (s, 3H), 3.70−3.77 (m, 1H), 1.26 (d, *J* = 6.2 Hz, 3H), 1.21 (d, *J* = 6.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 130.8, 129.9, 129.1, 127.5, 113.7, 102.0, 97.3, 75.0, 71.0, 70.5, 69.1, 55.3, 23.6, 22.1 ppm; HRMS (ESI) calcd. for $C_{17}H_{22}O_5Na$ [M + Na]: 329.1365, found: 329.1368.

*(4aR,6R,8aS)-6-Butoxy-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (**6d**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), *n*-butanol **5d** (74.1 mg, 1.0 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography (EA:Hexane = 1:6) to afford the desired aliphatic *O*-glycoside **6d** (23.0 mg, 72%) as a white solid. mp 76−78 °C; $[\alpha]_D^{23}$ = +43.4 (*c* = 1.0 in $CHCl_3$); IR (neat) ν: 3017, 1614, 1517, 1422, 1248 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39−7.44 (m, 2H), 6.86−6.92 (m, 2H), 6.12 (d, *J* = 10.3 Hz, 1H), 5.65−5.72 (m, 1H), 5.59 (s, 1H), 5.31−5.35 (m, 1H), 4.24−4.34 (m, 2H), 3.70−3.89 (m, 6H), 3.48−3.57 (m, 1H), 1.57−1.65 (m, 2H), 1.33−1.45 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 131.1, 129.8, 128.5, 127.5, 113.7, 102.0, 98.6, 75.0, 70.4, 69.0, 68.0, 55.2, 31.7, 19.2, 13.8 ppm; HRMS (ESI) calcd. for $C_{18}H_{25}O_5$ [M + H]: 321.1702, found: 321.1689.

*(4aR,6R,8aS)-6-(Cyclohexyloxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (**6e**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), cyclohexanol **5e** (100.2 mg, 1.0 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography (EA:Hexane = 1:6) to afford the desired aliphatic *O*-glycoside **6e** (19.0 mg, 55%) as a white solid. mp 108−110 °C; $[\alpha]_D^{23}$ = +33.7 (*c* = 1.0 in $CHCl_3$); IR (neat) ν: 3016, 1616, 1252, 1085, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39−7.44 (m, 2H), 6.86−6.91 (m, 2H), 6.09 (d, *J* = 10.3 Hz, 1H), 5.63−5.70 (m, 1H), 5.56 (s, 1H), 5.41−5.46 (m, 1H), 4.31−4.37 (m,

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1H), 4.26 (dd, J_1 = 10.2 Hz, J_2 = 4.5 Hz, 1H), 3.64−3.90 (m, 6H), 1.87−2.01 (m, 2H), 1.69−1.80 (m, 2H), 1.13−1.46 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 130.7, 129.9, 129.3, 127.5, 113.7, 102.0, 97.1, 76.7, 75.1, 70.5, 69.1, 55.3, 33.7, 32.2, 25.5, 24.3, 24.1 ppm; HRMS (ESI) calcd. for $C_{20}H_{27}O_5$ [M + H]: 347.1858, found: 347.1865.

*(4aR,6R,8aS)-6-(Benzyloxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (**6f**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), benzyl alcohol **5f** (108.1 mg, 1.0 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography (EA:Hexane = 1:6) to afford the desired aliphatic *O*-glycoside **6f** (31.1 mg, 88%) as a white solid.[13b]

General Procedure for Preparing Disaccharides. To a mixture of D*t*BPF (0.02 mmol), $Pd_2(dba)_3$ (0.01 mmol), carbonate **1** (0.1 mmol), alcohol **5** (**5g**−**5r**, 0.2 mmol), and Cs_2CO_3 (0.2 mmol) was added toluene (2 mL) under an atmosphere of argon. After stirring at 60 °C for 12 h, the solvent was removed under reduced pressure to give a crude product that was further purified by column chromatography to afford the desired disaccharides **6g**−**6r** with 35−89% yields.

*(4aR,8R,8aS)-2-(4-Methoxyphenyl)-8-((4aR,6R,8aS)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yloxy)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxine (**6g**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), compound **5g** (52.8 mg, 0.2 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography (EA:Hexane = 1:3) to afford the desired disaccharide **6g** (35.7 mg, 70%) as a white solid.[13b]

*(4aR,6R,8aS)-6-((2R,3S,4R)-3-(Benzyloxy)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran-4-yloxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxide (**6h**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), compound **5h** (65.3 mg, 0.2 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography (EA:Hexane = 1:4) to afford the desired disaccharide **6h** (31.5 mg, 55%) as a white solid. mp 94−96 °C; $[\alpha]_D^{23}$ = +54.6 (c = 0.7 in $CHCl_3$); IR (neat) ν: 3016, 2303, 1614, 1596, 1523, 1466, 1218 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26−7.43 (m, 12H), 6.86−6.92 (m, 2H), 6.41−6.46 (m, 2H), 6.12 (d, J = 10.3 Hz, 1H), 5.60 (ddd, J_1 = 10.3 Hz, J_2 = 2.4 Hz, J_3 = 1.5 Hz, 1H), 5.48−5.53 (m, 2H), 4.83−4.91 (m, 2H), 4.55−4.66 (m, 3H), 4.45−4.51 (m, 1H), 4.18−4.26 (m, 2H), 4.08−4.15 (m, 1H), 3.85 (dd, J_1 = 7.9 Hz, J_2 = 5.8 Hz, 1H), 3.69−3.82 (m, 7H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 144.9, 138.3, 138.0, 131.5, 129.8, 128.4(2C), 128.3, 127.9, 127.7, 127.6, 127.5, 113.7, 102.0, 99.8, 96.9, 75.0, 74.2, 73.4, 72.8, 70.6, 69.0, 68.5 ppm; HRMS (ESI) calcd. for $C_{34}H_{36}O_8Na$ [M + Na]: 595.2308, found: 595.2331.

*(4aR,8R,8aS)-2,2-Di-tert-butyl-8-((4aR,6R,8aS)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yloxy)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3,2]dioxasiline (**6i**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), compound **5i** (57.3 mg, 0.2 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography (EA:Hexane = 1:20) to afford the desired disaccharide **6i** (19.7 mg, 37%) as a colorless oil. $[\alpha]_D^{23}$ = +57.4 (c = 0.44 in $CHCl_3$); IR (neat) ν: 3016, 1655, 1608, 1523, 1258 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.45 (m, 2H), 6.86−6.92 (m, 2H), 6.27 (dd, J_1 = 6.0 Hz, J_2 = 1.4 Hz, 1H), 6.16 (d, J = 10.3 Hz, 1H), 5.71−5.78 (m, 1H), 5.65−5.70 (m, 1H), 5.58 (s, 1H), 4.78 (dd, J_1 = 6.0 Hz, J_2 = 2.0 Hz, 1H), 4.25−4.36 (m, 3H), 4.16 (dd, J_1 = 10.3 Hz, J_2 = 4.9 Hz, 1H), 4.09 (dd, J_1 = 10.3 Hz, J_2 = 7.3 Hz, 1H), 3.97 (t, J = 10.3 Hz, 1H), 3.72−3.88 (m, 6H), 1.08 (s, 9H), 1.00 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 144.0, 131.4, 129.8, 129.3, 127.5, 113.7, 103.4, 102.0, 97.9, 75.0, 74.9, 74.0, 73.1, 71.0, 69.1, 65.8, 55.3, 27.4, 26.9, 22.7, 19.9 ppm; HRMS (ESI) calcd. for $C_{28}H_{40}O_8NaSi$ [M + Na]: 555.2390, found: 555.2380.

*tert-Butyl(((2R,3R,4S)-4-(tert-butyldimethylsilyloxy)-3-((4aR,6S,8aS)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano-[3,2-d][1,3]dioxin-6-yloxy)-3,4-dihydro-2H-pyran-2-yl)methoxy)-dimethylsilane (**6j**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), compound **5j** (74.9 mg, 0.2 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography (EA:Hexane = 1:20) to afford the desired disaccharide **6j** (34.1 mg, 55%) as a colorless oil. $[\alpha]_D^{23}$ = +20.0 (c = 1.0 in $CHCl_3$); IR (neat) ν: 3015, 1650, 1614, 1522, 1254, 1082 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.44 (m, 2H), 6.86−6.91 (m, 2H), 6.32 (dd, J_1 = 6.2 Hz, J_2 = 0.7 Hz, 1H), 6.10 (d, J = 10.3 Hz, 1H), 5.73 (ddd, J_1 = 10.3 Hz, J_2 = 2.4 Hz, J_3 = 1.3 Hz, 1H), 5.54−5.58 (m, 2H), 4.70 (dd, J_1 = 6.1 Hz, J_2 = 3.5 Hz, 1H), 4.28−4.34 (m, 1H), 4.19−4.28 (m, 2H), 3.91−4.04 (m, 3H), 3.78−3.88 (m, 5H), 3.72 (ddd, J_1 = 10.3 Hz, J_2 = 8.4 Hz, J_3 = 4.6 Hz, 1H), 0.87−0.94 (m, 18H), 0.09−0.13 (m, 6H), 0.05−0.09 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 143.3, 131.1, 129.8, 128.4, 127.5, 113.7, 102.5, 102.0, 98.4, 78.0, 75.0, 74.8, 70.7, 69.0, 66.5, 61.5, 55.3, 25.9, 25.8, 18.3, 18.1, −4.6(2C), −5.2, −5.3 ppm; HRMS (ESI) calcd. for $C_{32}H_{52}O_8NaSi_2$ [M + Na]: 643.3098, found: 643.3106.

*(4aR,6R,8aS)-6-(((2R,3S,4R)-3,4-Bis(4-methoxybenzyloxy)-3,4-dihydro-2H-pyran-2-yl)methoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxide (**6k**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), compound **5k** (77.3 mg, 0.2 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography (EA:Hexane = 1:4) to afford the desired disaccharide **6k** (49.9 mg, 79%, α:β = 1:9) as a yellow solid.[13b]

*(4aR,6R,8aS)-6-(((2R,3S,4R)-4-(tert-Butyldimethylsilyloxy)-3-(4-methoxybenzyloxy)-3,4-dihydro-2H-pyran-2-yl)methoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (**6l**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), compound **5l** (76.1 mg, 0.2 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography (EA:Hexane = 1:5) to afford the desired disaccharide **6l** (55.1 mg, 88%) as a colorless oil.[13b]

*(4aR,6R,8aS)-2-(4-Methoxyphenyl)-6-(((2R,3R,4S,5R,6S)-3,4,5-tris-(benzyloxy)-6-methoxytetrahydro-2H-pyran-2-yl)methoxy)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (**6m**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), compound **5m** (92.9 mg, 0.2 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography (EA:Hexane = 1:2) to afford the desired disaccharide **6m** (62.5 mg, 88%) as a white solid.[13b]

*(4aR,6S,8aS)-6-((2R,3R,4S,5R,6S)-4,5-Bis(benzyloxy)-2-(benzyloxymethyl)-6-methoxytetrahydro-2H-pyran-3-yloxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (**6n**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), compound **5n** (92.9 mg, 0.2 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography (EA:Hexane = 1:2) to afford the desired disaccharide **6n** (51.8 mg, 73%) as a colorless oil.[13b]

*(4aR,6S,8aS)-6-((3aR,5R,6S,6aR)-5-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yloxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (**6o**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), compound **5o** (52.1 mg, 0.2 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography

(EA:Hexane = 1:3) to afford the desired disaccharide **6o** (39.5 mg, 78%) as a colorless oil.[13b]

*((2S,3R,4S,5R,6R)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-3-((4aR,6S,8aS)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano-[3,2-d][1,3]dioxin-6-yloxy)tetrahydro-2H-pyran-2-yloxy)(tert-butyl)-dimethylsilane (**6p**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), compound **5p** (113.0 mg, 0.2 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography (EA:Hexane = 1:4) to afford the desired disaccharide **6p** (72.1 mg, 89%) as a colorless oil. $[\alpha]_D^{23}$ = +28.7 (*c* = 1.0 in $CHCl_3$); IR (neat) ν: 3016, 1650, 1614, 1520, 1252, 1214 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.17−7.43 (m, 17H), 6.85−6.91 (m, 2H), 6.03 (d, *J* = 10.3 Hz, 1H), 5.68−5.75 (m, 1H), 5.60−5.66 (m, 1H), 5.53 (s, 1H), 4.77−4.88 (m, 3H), 4.51−4.65 (m, 4H), 4.25−4.32 (m, 1H), 4.21 (dd, J_1 = 10.2 Hz, J_2 = 4.5 Hz, 1H), 3.75−3.85 (m, 4H), 3.53−3.73 (m, 6H), 3.40−3.49 (m, 1H), 0.95 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 138.3, 138.2, 138.0, 130.4, 129.8, 128.4(2C), 128.3, 127.9, 127.8, 127.7(2C), 127.5, 127.4(2C), 113.6, 101.9, 99.6, 97.0 84.6, 81.2, 78.2, 75.7, 74.9, 73.4, 70.8, 68.9(2C), 55.2, 25.7, 18.1, −4.1, −5.3 ppm; HRMS (ESI) calcd. for $C_{47}H_{58}O_{10}NaSi$ [M + Na]: 833.3697, found: 833.3661.

*(3aR,5R,5aS,8aS,8bR)-5-(((4aR,6R,8aS)-2-(4-Methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yloxy)methyl)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4′,5′-d]pyran (**6q**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), compound **5q** (52.1 mg, 0.2 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography (EA:Hexane = 1:3) to afford the desired disaccharide **6q** (42.0 mg, 83%) as a colorless oil.[13b]

*(4aR,6S,8aS)-2-(4-Methoxyphenyl)-6-((2S,3S,4S,5R,6R)-2,4,5-tris-(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-3-yloxy)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (**6r**).* Following the general procedure, the reaction with D*t*BPF (9.5 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), carbonate **1** (33.6 mg, 0.1 mmol), compound **5r** (108.1 mg, 0.2 mmol), and Cs_2CO_3 (65.2 mg, 0.2 mmol) in toluene (2 mL) at 60 °C for 12 h gave a crude product that was further purified by column chromatography (EA:Hexane = 1:3) to afford the desired disaccharide **6r** (27.5 mg, 35%) as a colorless oil. $[\alpha]_D^{23}$ = +77.3 (*c* = 1.0 in $CHCl_3$); IR (neat) ν: 3014, 1649, 1612, 1523, 1251, 1079 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.23−7.43 (m, 20H), 7.14−7.19 (m, 2H), 6.86−6.92 (m, 2H), 6.13 (d, *J* = 10.3 Hz, 1H), 5.63−5.69 (m, 1H), 5.52−5.57 (m, 1H), 5.45 (s, 1H), 5.01−5.06 (m, 1H), 4.88 (d, *J* = 10.8 Hz, 1H), 4.69−4.76 (m, 2H), 4.61−4.69 (m, 2H), 4.46−4.58 (m, 3H), 4.05−4.16 (m, 3H), 3.93−3.99 (m, 1H), 3.87−3.93 (m, 1H), 3.70−3.87 (m, 6H), 3.60−3.69 (m, 1H), 3.47 (t, *J* = 10.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 138.4(2C), 138.3, 137.4, 132.2, 129.8, 128.4, 128.3(3C), 128.1, 127.9, 127.8, 127.6(2C), 127.5, 113.7, 101.9, 97.7(2C), 78.7, 75.1, 74.8, 73.4, 72.1, 71.8, 71.6, 70.6, 69.2, 68.7(2C), 55.3 ppm; HRMS (ESI) calcd. for $C_{48}H_{50}O_{10}Na$ [M + Na]: 809.3302, found: 809.3300.

Preparation of Trisaccharide 9. *(2R,3S,4R)-3-(4-Methoxybenzyloxy)-2-(((4aR,6R,8aS)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yloxy)methyl)-3,4-dihydro-2H-pyran-4-ol (**7**).* Compound **6l** (0.5 mmol) was dissolved in THF (10 mL) under an atmosphere of N_2, and the solution was cooled to 0 °C. After stirring at 0 °C for 10 min, TBAF (1.0 M solution in THF, 0.7 mL) was added over a duration of 5 min. The mixture was then allowed to warm to room temperature. After stirring for overnight, the solvent was removed under reduced pressure to give a crude product that was further purified by column chromatography (EA:Hexane = 1:2) to afford compound **7** (230.6 mg, 90%) as a colorless oil. $[\alpha]_D^{23}$ = +57.5 (*c* = 1.0 in $CHCl_3$); IR (neat) ν: 3020, 1652, 1616, 1521, 1244, 1215 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39−7.45 (m, 2H), 7.27−7.33 (m, 2H), 6.86−6.94 (m, 4H), 6.37 (dd, J_1 = 6.0 Hz, J_2 = 1.4 Hz, 1H), 6.13−6.21 (m, 1H), 5.70 (ddd, J_1 = 10.3 Hz, J_2 = 2.4 Hz, J_3 = 1.5 Hz, 1H), 5.55 (s, 1H), 5.40−5.46 (m, 1H), 4.68−4.79 (m, 3H), 4.22−4.39 (m, 3H), 4.09 (dd, J_1 = 10.8 Hz, J_2 = 2.3 Hz, 1H), 3.97 (ddd, J_1 = 9.3 Hz, J_2 = 4.5 Hz, J_3 = 2.3 Hz, 1H), 3.78−3.90 (m, 8H), 3.70−3.78 (m, 1H), 3.61 (dd, J_1 = 9.4 Hz, J_2 = 6.6 Hz, 1H), 1.76−1.84 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 159.4, 144.4, 132.0, 130.3, 129.7, 129.6, 127.8, 127.5, 114.0, 113.7, 102.9, 102.0, 98.6, 76.5, 76.4, 74.8, 73.4, 70.6, 69.5, 68.9, 65.5, 55.3 ppm; HRMS (ESI) calcd. for $C_{28}H_{32}O_9Na$ [M + Na]: 535.1944, found: 535.1943.

*Ethyl(2R,3S,4R)-3-(4-methoxybenzyloxy)-2-(((4aR,6R,8aS)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yloxy)methyl)-3,4-dihydro-2H-pyran-4-yl Carbonate (**8**).* To a solution of compound **7** (0.2 mmol) in DCM (5 mL) was added pyridine (1.0 mmol) at 0 °C. Then, ethyl chloroformate (0.8 mmol) was added slowly. The mixture was allowed to warm to room temperature and stir overnight. After the reaction was completed, the solvent was removed under reduced pressure. The residue was purified by column chromatography (EA:Hexane = 1:4) on silica gel to provide compound **8** (99.4 mg, 85%) as a colorless oil. $[\alpha]_D^{23}$ = +43.3 (*c* = 1.0 in $CHCl_3$); IR (neat) ν: 3022, 1649, 1616, 1522, 1417, 1243, 1128 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40−7.48 (m, 2H), 7.26−7.34 (m, 2H), 6.87−6.95 (m, 4H), 6.47 (dd, J_1 = 6.1 Hz, J_2 = 0.8 Hz, 1H), 6.15−6.22 (m, 1H), 5.66−5.74 (m, 1H), 5.57 (s, 1H), 5.38−5.44 (m, 1H), 5.27−5.35 (m, 1H), 4.87 (dd, J_1 = 6.1 Hz, J_2 = 3.0 Hz, 1H), 4.70−4.78 (m, 1H), 4.60−4.68 (m, 1H), 4.20−4.34 (m, 4H), 4.10−4.15 (m, 1H), 4.04 (dd, J_1 = 10.9 Hz, J_2 = 2.7 Hz, 1H), 3.79−3.94 (m, 9H), 3.71−3.79 (m, 1H), 1.35 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 159.3, 154.6, 145.9, 131.9, 129.8, 129.7, 129.4, 127.7, 127.4, 113.8, 113.6, 101.9, 98.6, 98.5, 76.3, 74.8, 74.2, 73.0, 72.6, 70.5, 68.9, 65.0, 64.0, 55.2, 14.2 ppm; HRMS (ESI) calcd. for $C_{31}H_{36}O_{11}Na$ [M + Na]: 607.2155, found: 607.2148.

*tert-Butyl((2R,3R,4R)-3-(4-methoxybenzyloxy)-2-(((2R,5S,6R)-5-(4-methoxybenzyloxy)-6-(((4aR,6R,8aS)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yloxy)methyl)-5,6-dihydro-2H-pyran-2-yloxy)methyl)-3,4-dihydro-2H-pyran-4-yloxy)-dimethylsilane (**9**).* To a mixture of D*t*BPF (0.02 mmol), $Pd_2(dba)_3$ (0.01 mmol), carbonate **8** (0.1 mmol), compound **5i** (0.2 mmol), and Cs_2CO_3 (0.2 mmol) was added toluene (2 mL) under an atmosphere of argon. After stirring at 60 °C for 12 h, the solvent was removed under reduced pressure to give a crude product that was further purified by column chromatography (EA:CH_2Cl_2 = 1:10) to afford the desired trisaccharide **9** (59.5 mg, 68%) as a colorless oil. $[\alpha]_D^{23}$ = +49.3 (*c* = 1.0 in $CHCl_3$); IR (neat) ν: 3025, 1652, 1616, 1517, 1130 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38−7.45 (m, 2H), 7.21−7.29 (m, 4H), 6.83−6.92 (m, 6H), 6.30 (dd, J_1 = 6.2 Hz, J_2 = 0.8 Hz, 1H), 6.06−6.13 (m, 1H), 5.96−6.06 (m, 1H), 5.80−5.89 (m, 1H), 5.59−5.67 (m, 1H), 5.52 (s, 1H), 5.29−5.34 (m, 1H), 5.07−5.15 (m, 1H), 4.72−4.80 (m, 1H), 4.64 (dd, J_1 = 6.1 Hz, J_2 = 2.7 Hz, 1H), 4.47−4.62 (m, 3H), 4.29−4.35 (m, 1H), 4.19−4.26 (m, 2H), 4.01−4.09 (m, 2H), 3.88−4.00 (m, 3H), 3.64−3.82 (m, 13H), 3.55−3.61 (m, 1H), 0.91 (s, 9H), 0.10 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 159.3(2C), 143.2, 131.4, 130.2, 130.1, 129.8, 129.5(2C), 128.7, 128.4, 128.2, 127.5, 113.9, 113.8, 113.7, 103.5, 102.0, 98.7, 96.0, 76.4, 76.3, 75.0, 74.9, 73.5, 70.5, 70.4, 69.0, 68.9, 68.8, 67.4, 66.5, 55.3, 55.2, 25.8, 17.9, −4.4, −4.6 ppm; HRMS (ESI) calcd. for $C_{48}H_{62}O_{13}Si$ [M + Na]: 897.3857, found: 897.3862.

*(4aR,6R,8aS)-6-(((2R,3S,6R)-6-Ethoxy-3-(4-methoxybenzyloxy)-3,6-dihydro-2H-pyran-2-yl)methoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (Byproduct **10**).* From the synthesis of trisaccharide **9**, byproduct compound **10** (13.5 mg, 25%) was purified by column chromatography (EA:CH_2Cl_2 = 1:10) as a colorless oil. $[\alpha]_D^{23}$ = +66.4 (*c* = 1.0 in $CHCl_3$); IR (neat) ν: 3023, 1650, 1615, 1517, 1416, 1220, 1132 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38−7.46 (m, 2H), 7.21−7.29 (m, 2H), 6.83−6.94 (m, 4H), 6.09−6.16 (m, 1H), 5.92−6.05 (m, 1H), 5.79−5.87 (m, 1H), 5.67 (ddd, J_1 = 10.3 Hz, J_2 = 2.4 Hz, J_3 = 1.5 Hz, 1H), 5.54 (s, 1H), 5.35−5.41 (m, 1H), 5.07−5.15 (m, 1H), 4.53−4.59 (m, 1H), 4.46−4.53 (m, 1H), 4.21−4.30 (m, 2H), 3.87−4.00 (m, 4H), 3.67−3.86 (m, 9H), 3.51−3.62 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 159.4, 131.5, 130.0, 129.8, 129.5, 129.1, 128.4, 128.2, 127.5, 113.8, 113.7, 102.0, 98.8, 95.9, 75.1, 75.0, 70.6, 70.5, 69.1, 69.0, 67.4, 63.7, 55.3, 15.1 ppm; HRMS (ESI) calcd. for $C_{30}H_{36}O_9Na$ [M + Na]: 563.2257, found: 563.2257.

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■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: xuewei@ntu.edu.sg (X.-W.L.).

Notes

The authors declare no competing financial interest.

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