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Oxidative Heck Reaction of Glycals and Aryl Hydrazines: A Palladium-Catalyzed *C*-Glycosylation

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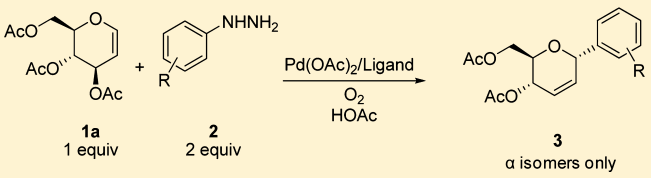
Supporting Information

ABSTRACT: An efficient Heck-type *C*-glycosylation of glycals *via* the C−N bond cleavage of aryl hydrazines has been developed. The flexibility of the reaction was tested by the substrate scope, consisting of glycals from different carbohydrate origins as well as aryl hydrazines with various substituents. Pure α-*C*-glycosides were obtained when (3*R*)-glycals were employed, whereas α,β mixtures were observed with (3*S*)-glycals.



Aryl-*C*-glycosides are a group of compounds possessing aryl groups as the aglycon at the anomeric carbon position. Many synthetic methods have been discovered since the 1980s toward aryl-*C*-glycosides due to their frequent presence in natural products[1] and their important biological functions such as enzyme inhibitors and sugar mimics.[2] Until now, most of the synthetic methods have focused on a transition-metal-catalyzed cross-coupling reaction to construct the glycosidic C−C bond. Earlier strategies comprise using preactivated reagents either on the glycal parts such as iodinated or stannylated glycals[3] or on the aromatic parts such as organometallic reagents.[4] Therefore, problems that often arise from early methods include restricted substrate scopes and high toxicity. In the past decade, Heck reactions were employed for the syntheses of aryl-*C*-glycosides by direct coupling of inactivated glycals and aromatic compounds such as aryl halides,[5] aryl boronic acids,[6] and benzoic acids.[7] Since the reagents in these reactions are moisture-stable and relatively environment-friendly, Heck reaction became one of the most attractive approaches to aryl-*C*-glycosylation. There are two main classes of products generated by Heck-type aryl-*C*-glycosylation. One is the 2,3-deoxy-*C*-glycosides, which is generated *via* β-heteroatom elimination when the glycals are protected by good leaving groups such as an acetyl group. The other is the 2-deoxy-*C*-glycosides, which will undergo β-hydride elimination when the glycals are protected by poor leaving groups such as silyl or benzyl groups.

Recently, C−C bond constructions *via* cleavage of a preactivated C−N bond have attracted considerable attention.[8] Inspired by the versatility of the C−N bond activation, we envisioned that we could further explore the synthetic methods[9] toward aryl-*C*-glycoside by coupling glycals with activated anilines. The general approaches to activate aniline C−N bonds include conversion to diazonium salts or hydrazines. We decided to make hydrazines as the coupling partners of glycals for two main reasons. First, some of the diazonium salts such as diazonium halides are highly explosive and the stable diazonium salts such as diazonium tetrafluoroborates or hexafluorophosphates are prone to decompose upon heating,[10] and heating is usually an indispensible condition for transition-metal-catalyzed coupling reaction. The other reason accouting for our choice is that aryl hydrazines are much more commercially available than aryl diazonium salts. As a result, we herein describe our results for the syntheses of aryl-*C*-glycosides by a palladium-catalyzed cross-coupling reaction of glycals and aryl hydrazines.[11]

Our initial effort was made to achieve the successful coupling of commercially available 3,4,6-tri-*O*-acetyl-D-glucal with phenyl hydrazine. The reaction was carried out by the catalysis of palladium acetate at 40 °C under 1 atm of oxygen (entry 1, Table 1) in dichloroethane. No new compound was detected after 12 h of stirring. Fortunately, increasing the reaction temperature to 80 °C (entry 2, Table 1) with other factors remaining unchanged offered the desired product **3a** in 43% yield as pure α isomer. Several commonly used organic solvents such as chlorobenzene (entries 3−5, Table 1) and acetic acid (entries 5 and 6, Table 1) were tested, and it was proven that higher yield was obtained by using acetic acid as solvent. Addition of 1,10-phenanthroline (entry 6, Table 1) as ligand was found to further enhance the yield. Screening the reaction at different temperatures (entries 7−9, Table 1) revealed that 65 °C was optimal to give the desired product in highest yield (90%) as pure α form.

With these optimized conditions in hand, we first explored the substrate scope of glycals, and the results are summarized in Table 2. Glycals with different protecting groups were tested, and the results show that the desired products were found only when the C-3 protecting groups of glycals are acetyl (**3a**−**3e**) or ethoxycarbonyloxyl (**3f**). Possibly the acetic acid as solvent restricts the reactivity of glycals with other protecting groups.

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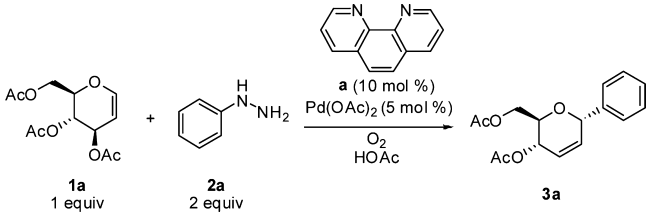
Table 1. Palladium-Catalyzed Ferrier-Type *C*-Glycosylation with 3,4,6-Tri-*O*-acetyl Glucal and Phenyl Hydrazine[a]



entry	ligand	solvent	time (h)	temp (°C)	yield (%)[b]
1		DCE	24	40	
2		DCE	12	80	43
3		PhCl	12	80	40
4		PhCl	8	80	55
5[c]		AcOH/PhCl	8	80	71
6	a	AcOH	6	80	82
7	a	AcOH	6	50	35
8	a	AcOH	6	60	77
9	a	AcOH	6	65	90

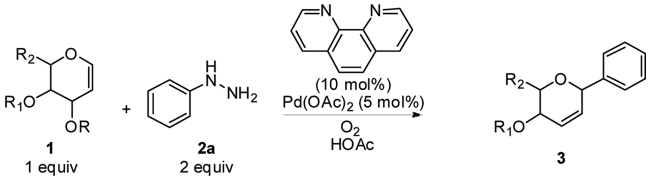
[a]Unless otherwise specified, reactions were carried out with 1 equiv of **1a**, 2 equiv of **2a**, 5% catalyst, 10% ligand, and 1 atm of oxygen. [b]Isolated yield. [c]PhCl/AcOH (v/v) = 1:1.

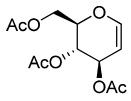
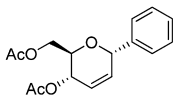
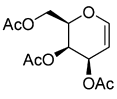
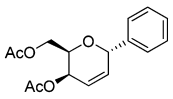
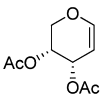
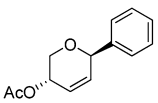
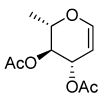
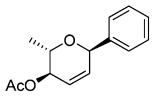
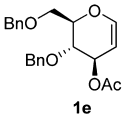
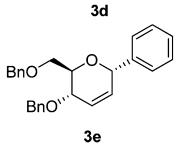
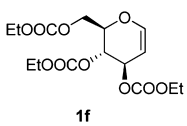
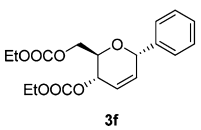
Other leaving groups such as benzoyl, pivaloyl, or *tert*-butoxycarbonyloxy were proven to be inactive under the standard conditions. Subsequently, we moved on to investigate the reactivities of glycals prepared with different carbohydrate origins. Results revealed that glycals prepared from galactose (**3b**), L-6-deoxyglucose (**3d**), and ribose (**3c**) also reacted well with phenyl hydrazine to provide the corresponding *C*-glycosides in moderate to high yields.

Next, 3,4,6-tri-*O*-acetylglucal was treated with various hydrazines of different substituents on different positions (Table 3). Notably, if phenyl hydrazine was replaced with the corresponding hydrochloric salt, no desired product was detected after 48 h. Among all the hydrazines tested, *ortho*-substituted aryl hydrazines were found to have the worst reactivities. Only *o*-chlorophenylhydrazine could offer the corresponding aryl-*C*-glycoside in moderate yield (**3i**). Other *ortho*-substituented aryl hydrazines such as *o*-tolylphenylhydrazine or *o*-bromophenylhydrazine failed to offer any desired product. It is possible that the more sterically hindered bromo or methyl group in the *ortho* position prevents the aryl-palldium complex from approching the glycal, and thus the migratory insertion is inhibited.[12] Moderate to good yields were obtained from various *m*- (**3g**, **3m**) or *p*-phenylhydrazines(**3h**, **3j**, **3k**, **3l**, **3n**). No desired product was detected for aryl hydrazines with strong electron-donating groups, such as methoxyl or ethoxyl, due to the possible decomposition of hydrazine substrates under standard conditions such as 1 atm of oxygen and high temperature. All of the aryl-*C*-glycosides were obtained in pure α selectivity.

Although all of the reported transition-metal-catalyzed Heck-type *C*-glycosylation methods showed α selectivity, few reports provided the reason. The stereoselectivity could be attributed to any of the three pre-existing chiral centers on the glycal substrates. In 2009, Ye's group deduced that the stereochemistry of C3 on glycal was the main reason for α selectivity.[5b]Due to the steric hindrance between the bulky palladium species and the protecting group on C3, the palladium species can approach glycals only from the side opposite to the C3 group. Thus, α product was obtained

Table 2. *C*-Glycosylation Coupling Reaction of Glycals and Phenyl Hydrazine[a,b]



entry	glycal	product	yield (%)
1	 1a	 3a	90
2	 1b	 3b	85
3	 1c	 3c	81
4	 1d	 3d	83
5	 1e	 3e	72
6	 1f	 3f	43

[a]Reactions were carried out with 1 equiv of **1a**, 2 equiv of **2a**, 5% catalyst, 10% ligand, and 1 atm of oxygen at 65 °C for 6 h. [b]Isolated yield.

exclusively. To test this hypothesis and prepare β aryl-*C*-glycosides, (3*S*,4*S*,6*R*)-tri-*O*-acetylglycal was synthesized[13] and treated with various hydrazines under standard conditions. The results were summarized in Table 4. Instead of pure α product, a mixture of α and β isomers were obtained, with ratios ranging from 1:1 to 1:0.6. These results suggest that the stereochemistry at C-3 is not the only determining factor for the observed α selectivity.

In conclusion, an efficient Heck-type *C*-glycosylation method with glycals and aryl hydrazines, by C−N bond cleavage, has been developed. The substrate scope includes glycals with protecting groups that function as good leaving groups and various aryl hydrazines. High stereoselectivities were achieved when (3*R*)-glycal substrates were used. On the contrary, α and β mixtures were obtained when (3*S*)-glycals were chosen. To the best of our knowledge, this is the first example for the formation of β aryl-*C*-glycosides *via* Heck-type reaction. Since aryl hydrazines could be prepared by short steps from their corresponding anilines,[14] this protocol presents promising

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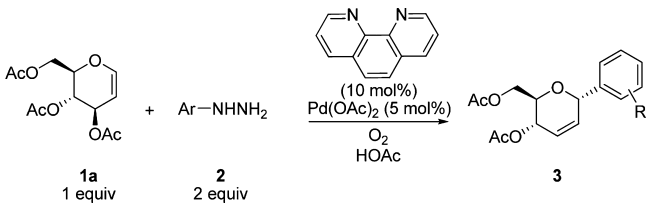
Table 3. *C*-Glycosylation Coupling Reaction of 3,4,6-Tri-*O*-acetylglucal and Various Aryl Hydrazines[a]

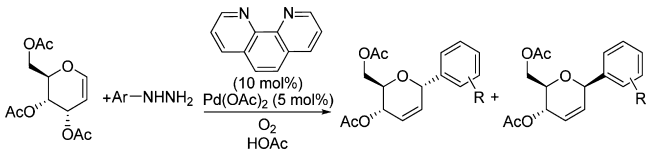


1a, 1 equiv; 2, 2 equiv; 3

entry	R	time (h)	yield (%)[b]
1	3-Me-C_6H_4 (**3g**)	4	80
2	4-Me-C_6H_4 (**3h**)	3	86
3	2-Cl-C_6H_4 (**3i**)	8	43
4	4-Br-C_6H_4 (**3j**)	6	85
5	4-COOMe-C6H4 (**3k**)	10	51
6	4-I-C_6H_4 (**3l**)	2	30
7	3,5-CF_3-C_6H_3 (**3m**)	8	64
8	4-F-C_6H_4 (**3n**)	4	79

[a]Unless otherwise specified, reactions were carried out with 1 equiv of **1a**, 2 equiv of **2**, 5% catalyst, 10% ligand, and 1 atm of oxygen at 65 °C. [b]Isolated yield.

Table 4. *C*-Glycosylation Coupling Reaction of (3*S*,4*S*,6*R*)-Tri-*O*-acetylglycal and Various Aryl Hydrazines[a]



4, 1 equiv; 2, 2 equiv; alpha isomer; beta isomer

entry	R	time (h)	yield (%)[b]	α:β
1	Ph (**3o**)	6	79	1:1
2	4-F-C_6H_4(**3p**)	4	75	1:0.81
3	4-Br-C_6H_4 (**3q**)	6	83	1:0.6
4	3-Me-C_6H_4(**3r**)	4	74	1:0.87

[a]Unless otherwise specified, reactions were carried out with 1 equiv of **4**, 2 equiv of **2**, 5% catalyst, 10% ligand, and 1 atm of oxygen at 65 °C. [b]Isolated yield.

applications to the syntheses of aryl-*C*-glycosides containing natural products.

EXPERIMENTAL SECTION

General Procedure of Pd-Catalyzed Cross-Coupling of Glycals and Aryl Hydrazines. To a round-bottom flask containing the solution of glycal (1 equiv), palladium(II) diacetate (5% mol), and 1,10-phenantroline (10% mol) in acetic acid (2.5 mL/mmol) at 65 °C was added dropwise phenyl hydrazine (1.5 equiv) in acetic acid (5 mL/mmol). The mixture was allowed to stir at 65 °C for the indicated time in Tables 1, 2, and 3. Then the mixture was diluted with ethyl acetate (20 mL/mmol), filtered, and washed with water (5 mL/mmol) and brine (5 mL/mmol). The organic layer was evaporated, and the residue was purified by flash column chromatography to afford the product.

((2*R*,3*S*,6*S*)-3-Acetoxy-6-phenyl-3,6-dihydro-2*H*-pyran-2-yl)-methyl Acetate (3a). Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (6:1 to 4:1) to give a colorless oil, 52 mg, 90% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.07 (s, 3H), 2.09 (s, 3H), 3.83−3.97 (m, 1H), 4.09 (dd, J = 3.1, 12.0 Hz, 1H), 4.25 (dd, J = 5.9, 12 Hz, 1H), 5.29−5.33 (m, 2H), 5.97−6.01 (m, 1H), 6.19 (ddd, J = 1.5, 3.0, 10.4 Hz, 1H), 7.32−7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 20.8, 21.1, 62.9, 65.0, 69.3, 73.7, 125.0, 127.9, 128.3, 128.5, 131.5, 138.8, 170.5, 170.9; $[\alpha]_D^{20}$ = 13.9 (c 2.00, $CHCl_3$); HRMS (ESI) calcd for $C_{16}H_{18}O_5Na$ [M + Na]$^+$313.1052, found 313.1053.

((2*R*,3*R*,6*S*)-3-Acetoxy-6-phenyl-3,6-dihydro-2*H*-pyran-2-yl)-methyl Acetate (3b). Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (6:1 to 4:1) to give a pale yellow oil, 49 mg, 85% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.99 (s, 3H), 2.11 (s, 3H), 3.92−3.95 (m, 1H), 4.14−4.23 (m, 2H), 5.11 (dd, J = 2.6, 5.1 Hz, 1H), 5.39−5.41 (m, 1H), 6.20 (ddd, J = 2.1, 5.2, 10.2 Hz, 1H), 6.41 (ddd, J = 0.5, 3.6, 10.2 Hz, 1H), 7.30−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 20.7, 20.9, 62.8, 63.8, 68.3, 73.8, 123.5, 127.8, 128.2, 128.5, 133.3, 138.3, 170.6, 170.6; $[\alpha]_D^{20}$ = −371.1 (c 3.00, $CHCl_3$); HRMS (ESI) calcd for $C_{16}H_{18}O_5Na$ [M + Na]$^+$313.1052, found 313.1060.

(3*S*,6*R*)-6-Phenyl-3,6-dihydro-2*H*-pyran-3-yl Acetate (3c). Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (10:1 to 8:1) to give a yellow oil, 35 mg, 81% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.11 (s, 3H), 3.69 (dd, J = 5.2, 11.9 Hz, 1H), 4.04 (dd, J = 4.4, 11.9 Hz, 1H), 5.21 (t, J = 2.1, 1H), 5.22−5.29 (m, 1H), 6.03−6.07 (m, 1H), 6.16 (ddd, J = 1.2, 2.6, 10.4 Hz, 1H), 7.30−7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 21.1, 64.7, 64.7, 75.1, 124.5, 127.8, 128.3, 128.6, 133.3, 139.1, 170.7; $[\alpha]_D^{20}$ = 170.0 (c 3.00, $CHCl_3$); HRMS (ESI) calcd for $C_{13}H_{14}O_3Na$ [M + Na]$^+$ 241.0841, found 241.0842.

(2*S*,3*R*,6*R*)-2-Methyl-6-phenyl-3,6-dihydro-2*H*-pyran-3-yl Acetate (3d). Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (8:1) to give a bright yellow oil, 38 mg, 83% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (d, J = 6.44 Hz, 3H), 2.10 (s, 3H), 3.87 (t, J = 6.3 Hz, 1H), 5.05 (m, 1H), 5.23 (q, J = 2.2 Hz, 1H), 5.95 (ddd, J = 2.1, 3.2, 10.3 Hz, 1H), 6.13 (ddd, J = 1.4, 2.8, 10.3 Hz, 1H), 7.30 − 7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 17.3, 21.2, 68.0, 69.8, 72.8, 124.2, 127.9, 128.1, 128.5, 132.2, 139.6, 170.8; $[\alpha]_D^{20}$ = −34.8 (c 1.50, $CHCl_3$); HRMS (ESI) calcd for $C_{14}H_{16}O_3Na$ [M + Na]$^+$ 255.0997, found 255.0989.

(2*R*,3*R*,6*S*)-3-(Benzyloxy)-2-((benzyloxy)methyl)-6-phenyl-3,6-dihydro-2*H*-pyran (3e). Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (10:1 to 6:1) to give a colorless oil, 56 mg, 72% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.60−3.67 (m, 1H), 3.68−3.72 (m, 2H), 4.18−4.21 (m, 2H), 4.45−4.51 (m, 2H), 4.58−4.64 (m, 2H), 5.32 (d, J = 1.5 Hz, 1H), 6.08−6.16 (m, 2H), 7.25−7.37 (m, 13H), 7.43−7.46 (m, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 69.2, 70.2, 70.7, 71.2, 73.3, 74.1, 77.2, 127.2, 127.6, 127.8, 127.9, 128.0, 128.1, 128.3, 128.4, 128.4, 129.6, 138.2, 139.6; $[\alpha]_D^{20}$ = 22.8 (c 1.20, $CHCl_3$); HRMS (ESI) calcd for $C_{26}H_{26}O_3Na$ [M + Na]$^+$ 409.1780, found 409.1779.

((2*R*,3*S*,6*S*)-6-Phenyl-2-((ethoxycarbonyloxy)methyl)-3,6-dihydro-2*H*-pyran-3-yl)methyl Ethyl Carbonate (3f). Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (4:1 to 3:1) to give a brown oil, 30 mg, 43% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27−1.34 (m, 6H), 3.87−3.91 (m, 1H), 4.15−4.28 (m, 5H), 4.30−4.33 (m, 1H), 5.21 (dd, J = 1.9, 7.6 Hz, 1H), 5.33 (d, J = 2.4 Hz, 1H), 6.06 (dt, J = 2.2, 10.4 Hz, 1H), 6.20 (ddd, J = 1.6, 3.1, 10.4 Hz, 1H), 7.32−7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 14.1, 14.1, 64.1, 64.3, 66.0, 68.1, 68.5, 73.7, 77.0, 124.4, 127.9, 128.1, 128.3, 128.4, 131.7, 138.3, 154.4, 154.9; $[\alpha]_D^{20}$ = 19.8 (c 0.80, $CHCl_3$); HRMS (ESI) calcd for $C_{18}H_{22}O_7Na$ [M + Na]$^+$ 373.1263, found 373.1263.

((2*R*,3*S*,6*S*)-3-Acetoxy-6-(*m*-tolyl)-3,6-dihydro-2*H*-pyran-2-yl)methyl Acetate (3g). Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (6:1 to 4:1) to give a colorless oil, 49 mg, 80% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.08 (s, 3H), 2.09 (s, 3H), 2.37 (s, 3H), 3.84−3.88 (m, 1H), 4.10 (dd, J = 3.1, 12.0 Hz, 1H), 4.27 (dd, J = 5.9, 12 Hz, 1H), 5.29−5.32 (m, 2H), 5.96−6.00 (m, 1H), 6.17−6.20 (m, 1H), 7.13−7.25 (m, 4H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 20.8, 21.1, 21.5, 62.9, 65.0, 69.3, 73.7, 124.9, 124.9, 128.4, 128.6, 129.0, 131.6, 138.2, 138.8, 170.5, 170.9; $[\alpha]_D^{20}$ = 19.5 (c 1.50, $CHCl_3$); HRMS (ESI) calcd for $C_{17}H_{20}O_5Na$ [M + Na]$^+$ 327.1208, found 327.1204.

((2*R*,3*S*,6*S*)-3-Acetoxy-6-(*p*-tolyl)-3,6-dihydro-2*H*-pyran-2-yl)methyl Acetate (3h). Following the general procedure, the crude

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product was purified over a silica gel column using a hexane/EtOAc system (6:1 to 4:1) to give a pale yellow oil, 52 mg, 86% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.07 (s, 3H), 2.08 (s, 3H), 2.36 (s, 3H), 3.80−3.84 (m, 1H), 4.08 (dd, J = 3.1, 12.0 Hz, 1H), 4.26 (dd, J = 5.7, 12.0 Hz, 1H), 5.30−5.33 (m, 2H), 5.98 (dt, J = 2.1, 10.3 Hz, 1H), 6.17 (ddd, J = 1.4, 2.9, 10.4 Hz, 1H), 7.18 (m, 2H), 7.28 (m, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 20.8, 21.1, 21.2, 62.9, 65.1, 69.0, 73.7, 125.0, 128.0, 129.2, 131.6, 135.8, 138.1, 170.5, 170.9; $[\alpha]_D^{20}$ = 5.2 (c 1.50, $CHCl_3$); HRMS (ESI) calcd for $C_{17}H_{20}O_5Na$ $[M + Na]^+$ 327.1208, found 327.1198.

((2*R*,3*S*,6*S*)-3-Acetoxy-6-(2-chlorophenyl)-3,6-dihydro-2*H*-pyran-2-yl)methyl Acetate (3i). Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (6:1 to 4:1) to give a pale yellow oil, 28 mg, 43% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.06 (s, 3H), 2.11 (s, 3H), 3.95−3.99 (m, 1H), 4.10 (dd, J = 3.7, 12.0 Hz, 1H), 4.34 (dd, J = 6.6, 12 Hz, 1H), 5.23−5.26 (m, 1H), 5.71 (dd, J = 2.2, 2.2 Hz, 1H), 6.04 (ddd, J = 2.0, 3.1, 10.4 Hz, 1H), 6.12 (dd, J = 1.2, 2.6, 10.4 Hz, 1H), 7.27−7.30 (m, 2H), 7.30−7.42 (m, 1H), 7.47 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 20.8, 21.1, 62.5, 64.8, 70.2, 77.2, 124.7, 126.7, 129.3, 129.6, 130.0, 131.4, 134.2, 135.9, 170.5, 170.9; $[\alpha]_D^{20}$ = 16.8 (c 1.50, $CHCl_3$); HRMS (ESI) calcd for $C_{16}H_{17}O_5ClNa$ $[M + Na]^+$ 347.0662, found 347.0669.

((2*R*,3*S*,6*S*)-3-Acetoxy-6-(4-bromophenyl)-3,6-dihydro-2*H*-pyran-2-yl)methyl Acetate (3j). Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (4:1) to give a colorless oil, 62 mg, 85% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.07 (s, 3H), 2.08 (s, 3H), 3.77−3.81 (m, 1H), 4.08 (dd, J = 3.0, 12.0 Hz, 1H), 4.25 (dd, J = 6.0, 12.0 Hz, 1H), 5.27−5.29 (m, 2H), 5.97−6.00 (m, 1H), 6.12−6.16 (m, 1H), 7.26−7.29 (m, 2H), 7.48−7.51 (m, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 20.8, 21.1, 62.8, 64.9, 69.4, 73.0, 122.4, 125.5, 129.6, 130.9, 131.7, 137.9, 170.4, 170.8; $[\alpha]_D^{20}$ = −22.0 (c 3.00, $CHCl_3$); HRMS (ESI) calcd for $C_{16}H_{17}O_5BrNa$ $[M + Na]^+$ 391.0157, found 391.0155.

Methyl-4-((2*S*,5*S*,6*R*)-5-acetoxy-6-(acetoxymethyl)-5,6-dihydro-2*H*-pyran-2-yl)benzoate (3k). Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (4:1 to 3:1) to give a yellow oil, 35 mg, 51% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.08 (s, 3H), 2.10 (s, 3H), 3.80−3.84 (m, 1H), 3.92 (S, 3H), 4.11 (dd, J = 3.0, 12.0 Hz, 1H), 4.20−4.28 (m, 1H), 5.28−5.30 (m, 1H), 5.36 (s, 1H), 5.98−6.02 (m, 1H), 6.17−6.21 (m, 1H), 7.48 (d, J = 8.2 Hz, 2H), 8.04 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 20.8, 21.0, 52.1, 62.7, 64.8, 69.7, 73.1, 125.4, 127.5, 129.8, 129.9, 130.8, 144.0, 166.7, 170.4, 170.7; $[\alpha]_D^{20}$ = −6.0 (c 2.00, $CHCl_3$); HRMS (ESI) calcd for $C_{18}H_{20}O_7Na$ $[M + Na]^+$ 371.1107, found 371.1111.

((2*R*,3*S*,6*S*)-3-Acetoxy-6-(4-iodophenyl)-3,6-dihydro-2*H*-pyran-2-yl)methyl Acetate (3l). Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (4:1) to give a dark brown oil, 25 mg, 30% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.08 (s, 3H), 2.09 (s, 3H), 3.78−3.82 (m, 1H), 4.09 (dd, J = 3.1, 12.0 Hz, 1H), 4.26 (dd, J = 6.0, 12.0 Hz, 1H), 5.26−5.31 (m, 2H), 5.98−6.01 (m, 1H), 6.13−6.16 (m, 2H), 7.16 (d, J = 8.2 Hz, 2H), 7.72 (dd, J = 1.8, 6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 20.9, 21.1, 62.9, 64.9, 69.5, 73.2, 94.1, 125.5, 129.8, 130.9, 137.7, 138.7, 170.5, 170.9; $[\alpha]_D^{20}$ = 1.4 (c 1.00, $CHCl_3$); HRMS (ESI) calcd for $C_{16}H_{17}O_5INa$ $[M + Na]^+$ 439.0018, found 439.0014.

((2*R*,3*S*,6*S*)-3-Acetoxy-6-(3,5-bis(trifluoromethyl)phenyl)-3,6-dihydro-2*H*-pyran-2-yl)methyl Acetate (3m). Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (6:1 to 4:1) to give a colorless oil, 54 mg, 64% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.10 (s, 3H), 2.11 (s, 3H), 3.81−3.86 (m, 1H), 4.16 (dd, J = 2.9, 12.0 Hz, 1H), 4.28 (dd, J = 7.4, 12.0 Hz, 1H), 5.25−5.28 (m, 1H), 5.42 (d, J = 1.84 Hz, 1H), 6.08 (ddd, J = 2.2, 2.8, 10.4 Hz, 1H), 6.26 (ddd, J = 1.5, 3.1, 10.4 Hz, 1H), 7.85 (s, 1H), 7.90 (s, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 20.6, 21.0, 29.9, 62.9, 64.7, 70.4, 72.0, 122.0, 126.3, 127.4, 129.9, 131.8, 132.1, 170.4, 170.8; $[\alpha]_D^{20}$ = 24.4 (c 0.80, $CHCl_3$); HRMS (ESI) calcd for $C_{18}H_{16}O_5F_6Na$ $[M + Na]^+$ 449.0800, found 449.0811.

((2*R*,3*S*,6*S*)-3-Acetoxy-6-(4-fluorophenyl)-3,6-dihydro-2*H*-pyran-2-yl)methyl Acetate (3n). Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (6:1 to 4:1) to give a colorless oil, 48 mg, 79% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.06 (s, 3H), 2.09 (s, 3H), 3.79−3.83 (m, 1H), 4.08 (dd, J = 3.1, 12.0 Hz, 1H), 4.26 (dd, J = 6.0, 12.0 Hz, 1H), 5.28−5.30 (m, 2H), 5.98−6.01 (m, 1H), 6.19 (m,1H), 7.04−7.08 (m, 2H), 7.36−7.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 20.8, 21.1, 62.8, 64.9, 69.3, 73.0, 115.3, 115.5, 125.2, 129.7, 129.8, 131.3, 134.6, 134.7, 161.4, 163.9, 170.5, 170.8; $[\alpha]_D^{20}$ = 15.8 (c 2.50, $CHCl_3$); HRMS (ESI) calcd for $C_{16}H_{17}O_5FNa$ $[M + Na]^+$ 331.0960, found 331.0958.

((2*R*,3*S*,6*S*)-3-Acetoxy-6-phenyl-3,6-dihydro-2*H*-pyran-2-yl)-methyl Acetate and ((2*R*,3*S*,6*R*)-3-Acetoxy-6-phenyl-3,6-dihydro-2*H*-pyran-2-yl)methyl Acetate (3o). Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (6:1 to 4:1) to give a yellow oil, 46 mg, 79% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.07−2.09 (m, 9H), 2.11 (s, 3H), 3.83−3.87 (m, 1H), 3.92−3.96 (m, 1H), 4.10 (dd, J = 3.1, 12.0 Hz, 1H), 4.18−4.30 (m, 3H), 5.21−5.22 (m, 1H), 5.30−5.34 (m, 2H), 5.40−5.44 (m, 1H), 5.83 (dt, J = 2.1, 10.3 Hz, 1H), 5.91−6.18 (m, 1H), 7.31−7.42 (m, 10H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 20.8, 20.9, 21.1, 62.9, 63.8, 65.0, 65.5, 69.3, 73.7, 74.8, 77.2, 77.6, 124.9, 125.0, 127.2, 127.9, 128.3, 128.4, 128.5, 128.7, 131.5, 132.8, 138.8, 139.8, 170.4, 170.5, 170.9, 171.0; HRMS (ESI) calcd for $C_{16}H_{18}O_5Na$ $[M + Na]^+$ 313.1052, found 313.1053.

((2*R*,3*S*,6*S*)-3-Acetoxy-6-(4-fluorophenyl)-3,6-dihydro-2*H*-pyran-2-yl)methyl Acetate and ((2*R*,3*S*,6*R*)-3-Acetoxy-6-(4-fluorophenyl)-3,6-dihydro-2*H*-pyran-2-yl)methyl Acetate (3p). Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (6:1 to 4:1) to give a colorless oil, 46 mg, 75% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.07 (s, 3.56H), 2.08 (s, 3.15H), 2.09 (s, 3.63H), 2.11 (s, 2.89H), 3.79−3.83 (m, 1.24H), 3.91−3.95 (m, 1H), 4.08 (dd, J = 3.1, 12.0 Hz, 1.28H), 4.19 (dd, J = 5.9, 12.1 Hz, 1H), 4.24−4.29 (m, 2.27H), 5.20 (s, 1H), 5.20−5.30 (m, 2.45H), 5.39−5.42 (m, 1H), 5.82−5.90 (m, 2H), 5.98−6.02 (m, 1.24H), 6.13−6.16 (m, 1.25H), 7.02−7.08 (m, 4.47H), 7.29−7.33 (m, 2H), 7.37 − 7.38 (m, 2.45H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 20.8, 20.9, 21.1, 62.8, 63.7, 64.9, 65.3, 69.3, 73.0, 74.9, 76.9, 77.2, 115.3, 115.4, 115.5, 115.7, 125.2, 129.0, 129.1, 129.7, 129.8, 131.3, 132.5, 134.7, 134.7, 135.7, 135.7, 161.4, 161.5, 163.9, 163.9, 170.4, 170.5, 170.8, 171.0; HRMS (ESI) calcd for $C_{16}H_{17}O_5FNa$ $[M + Na]^+$ 331.0958, found 331.0956.

((2*R*,3*S*,6*S*)-3-Acetoxy-6-(4-bromophenyl)-3,6-dihydro-2*H*-pyran-2-yl)methyl Acetate and ((2*R*,3*S*,6*R*)-3-Acetoxy-6-(4-bromophenyl)-3,6-dihydro-2*H*-pyran-2-yl)methyl Acetate (3q). Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (4:1 to 3:1) to give a yellow oil, 61 mg, 83% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.08 (s, 3H), 2.08 (s, 1.68H), 2.09 (s, 3H), 2.11 (s, 1.77H), 3.78−3.82 (m, 1H), 3.91−3.94 (m, 0.64H), 4.09 (dd, J = 3.1, 12.0 Hz, 1H), 4.17−4.24 (m, 0.67H), 4.25−4.30 (m, 1.66H), 5.18 (s, 0.87H), 5.18 (s, 0.60H), 5.28−5.31 (m, 2H), 5.38−5.41 (m, 0.61H), 5.84−5.86 (m, 1.22H), 6.00 (dt, J = 2.1, 10.4 Hz, 1H), 6.13 −6.16 (m, 1H), 7.20−7.24 (m, 1.25H), 7.26−7.30 (m, 2H), 7.47−7.52 (m, 3.2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 20.8, 20.9, 21.1, 62.8, 63.6, 64.9, 65.3, 69.4, 73.0, 74.8, 76.9, 77.2, 122.3, 122.4, 125.4, 125.5, 128.9, 129.6, 130.9, 131.7, 131.8, 132.0, 132.2, 137.9, 138.8, 170.4, 170.4, 170.8, 171.0; HRMS (ESI) calcd for $C_{16}H_{17}O_5BrNa$ $[M + Na]^+$ 391.0157, found 391.0156.

((2*R*,3*S*,6*S*)-3-Acetoxy-6-(*m*-tolyl)-3,6-dihydro-2*H*-pyran-2-yl)methyl Acetate and ((2*R*,3*S*,6*R*)-3-Acetoxy-6-(*m*-tolyl)-3,6-dihydro-2*H*-pyran-2-yl)methyl Acetate (3r). Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (6:1 to 4:1) to give a pale yellow oil, 45 mg, 84% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.08 (s, 5.35H), 2.09 (s, 3H), 2.11 (s, 2.59H), 2.35 (s, 2.62H), 2.37 (s, 3H), 3.84−3.88 (m, 1H), 3.91−3.95 (m, 0.87H), 4.10 (dd, J = 3.1, 12.0 Hz, 1H), 4.20 (dd, J = 6.0, 12.1 Hz, 0.88H), 4.25−4.29 (m, 2H), 5.18 (s, 0.87H), 5.18−5.32 (m, 2H), 5.41−5.44 (m, 0.87H), 5.82 (dt, J = 2.1, 10.3 Hz, 0.87H), 5.93 (dt, J = 1.6, 10.2 Hz, 1H), 6.19 (m, 1H), 7.11−7.23 (m, 6.72H), 7.24−6.29 (m, 0.87H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 20.8, 20.9, 21.1, 21.4, 21.5, 62.9, 63.8, 65.1, 65.5, 69.3, 73.7, 74.8, 77.2, 77.7, 124.4, 124.8, 124.9, 124.9, 128.0, 128.4, 128.6, 128.6, 129.0, 129.2, 131.6, 132.9, 138.2, 138.4, 138.8, 139.7, 170.4, 170.5,

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170.9, 171.0; HRMS (ESI) calcd for $C_{17}H_{20}O_5Na$ $[M + Na]^+$ 327.1208, found 327.1204.

■ ASSOCIATED CONTENT

Supporting Information

General experimental conditions; general synthesis of compound **4**; spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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