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Stereoselective Synthesis of *C*-2-Methylene and *C*-2-Methyl α- and β-*C*-Glycosides from 2-*C*-Branched Glycals: Formal Total Synthesis of (–)-Brevisamide

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The stereoselective synthesis of deoxy *C*-glycoside derivatives that have a methylene or methyl group at *C*-2 position was investigated by employing the Claisen rearrangement of 2-vinyloxy methyldeoxy-glycals as the synthetic precursors. The method proceeded with high diastereoselectivity to afford *C*-2-methylene α-*C*-glycosides. Complementary to this protocol, a Zn^{II}-mediated anomerization of the α-*C*-glycosides to give the corresponding β-*C*-glycosides was also used to obtain diastereomerically pure *C*-2-methylene β-*C*-glycosides. The generality of the reaction was fully evaluated, and the developed method was successfully applied to the formal stereoselective total synthesis of (–)-brevisamide, a monocyclic ether alkaloid that was isolated from *Karenia brevis* (red tide dinoflagellate).

Introduction

Many microorganisms produce *C*-branched-*C*-glycoside derived natural products that exhibit extremely high bioactivity.[1] Very often these compounds are produced as a line of defense against their predators. Among them, *C*-glycosides that have a methyl or methylene group at the *C*-2 position frequently exist as a subunit of these highly bioactive natural products.[2] For example, brevenal, brevetoxin, eribulin, gambieric acids, halichondrins, (+)-lasonolide, phorboxazoles, spliceostatins, and spongistatins (see Figure 1) contain a deoxy *C*-2-methyl/*C*-2-methylene-*C*-glycopyranoside subunit.[2] In general, most of the chemical syntheses of these scaffolds involve an achiral starting material to assemble the carbon-branched *C*-glycoside unit. Although highly abundant carbohydrates could be the closest chiral pool starting materials to synthesize these complex architectures, the stereoselective incorporation of a carbon branch

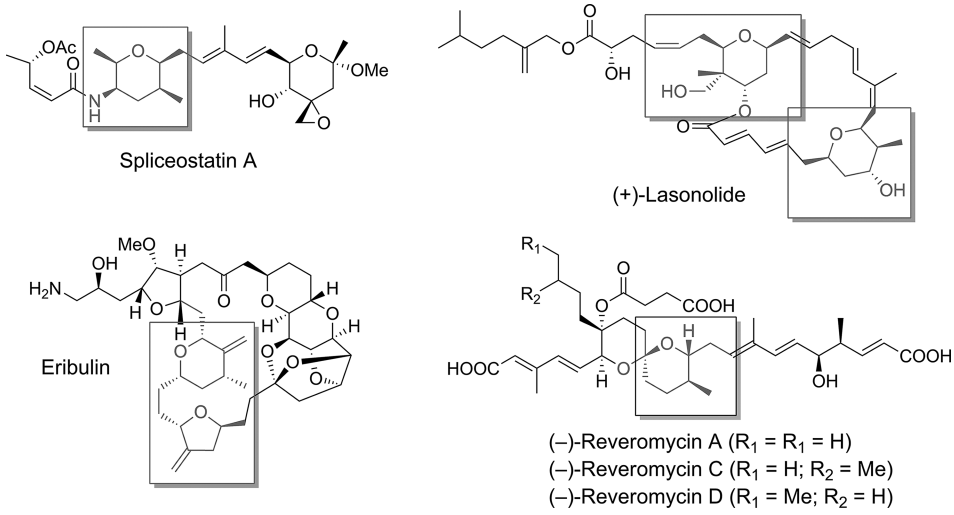

Figure 1. Some natural products that have *C*-2-methylene/*C*-2-methyl *C*-glycoside subunits.

at the *C*-2,[3] *C*-3,[4] or *C*-4[5] position of a *C*-glycoside is particularly difficult.[6] Several methods have been reported for the synthesis of normal *C*-glycosides,[7] but general protocols to synthesize carbon-branched *C*-glycosides are very scarce.[2–5]

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One of the common approaches for the stereoselective formation of *C*-glycosides employs the Claisen or Ireland–Claisen rearrangement[8] of glucal-derived ally vinyl ethers.[9] This reaction was extensively studied by using 3-*O*-vinyl glycal derivatives to obtain *C*-glycosides of 2,3-glycals.[10] In continuation of our investigations towards the synthesis of *C*-branched sugars,[11] we recently reported the Claisen rearrangement of 2-vinyloxymethyl glycal derivatives to provide access to the construction of *C*-2-methylene and *C*-2-methyl *C*-glycosides in a stereoselective fashion.[12] This protocol, however, provides access to the synthesis of *C*-2-branched α-*C*-glycosides as the major products. Herein, we report our further investigations of 2-vinyloxymethyl glycals that are derived from deoxy-sugars as well as the conversion of *C*-2-methylene α-*C*-glycosides into the corresponding β-*C*-glycosides. Furthermore, we also report the application of the developed method towards the formal stereoselective total synthesis of (–)-brevisamide.

Results and Discussion

To obtain deoxysugar-derived 2-vinyloxymethyl glucal **4**, 3-deoxy-4,6-di-*O*-benzyl-D-glucal (**1**)[13] was formylated[14] by using *N*,*N*-dimethylformamide (DMF) and $POCl_3$ to give 3-deoxy-2-formyl-4,6-di-*O*-benzyl-D-glucal (**2**),[15] which upon reduction by treatment with $NaBH_4$ in EtOH provided 3-deoxy-2-hydroxymethyl-4,6-di-*O*-benzyl-D-glucal (**3**).[16] Vinylation of **3** by using catalytic mercuric acetate in ethyl vinyl ether provided the required 3-deoxy-2-vinyloxymethyl-4,6-di-*O*-benzyl-D-glucal (**4**) in 60% yield. Upon heating at 180 °C for 6 h in a sealed tube, compound **4** smoothly underwent a Claisen rearrangement and provided a mixture of 3-deoxy-*C*-2-methylene *C*-glycosides **5α** and **5β** in a 66:34 ratio.[17] However, chromatography on a silica gel column provided an inseparable mixture of **5α** and **5β** in a 66:34 ratio in 35% yield along with the ring-opened α,β-unsaturated aldehyde derivative **6** in 50% yield.[18] Interestingly, the direct reduction of the crude mixture obtained from the Claisen rearrangement with $NaBH_4$/EtOH at –10 °C produced the corresponding alcohols **7α** and **7β** in a 66:34 ratio in good yield, and no product from the reduction of **6** was observed (see Scheme 1). The two anomers **7α** and **7β** were easily separated by silica gel column chromatography.

The stereochemistry at the anomeric position was determined by 2D NOESY experiments. In the case of α-*C*-glycoside **7α**, a strong NOE correlation was observed between the axial CH_2 (C-7 protons) and the axial C-5 proton (1,3-diaxial interaction). On the other hand, for β-*C*-glycoside **7β**, an NOE correlation was observed between the three axial hydrogen atoms present at C-1, C-3 and C-5 (see Figure 2).[19]

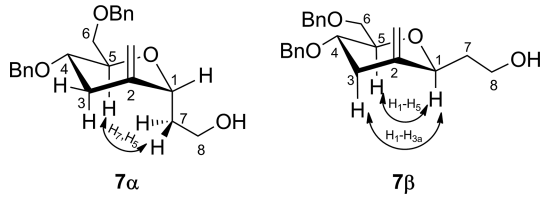
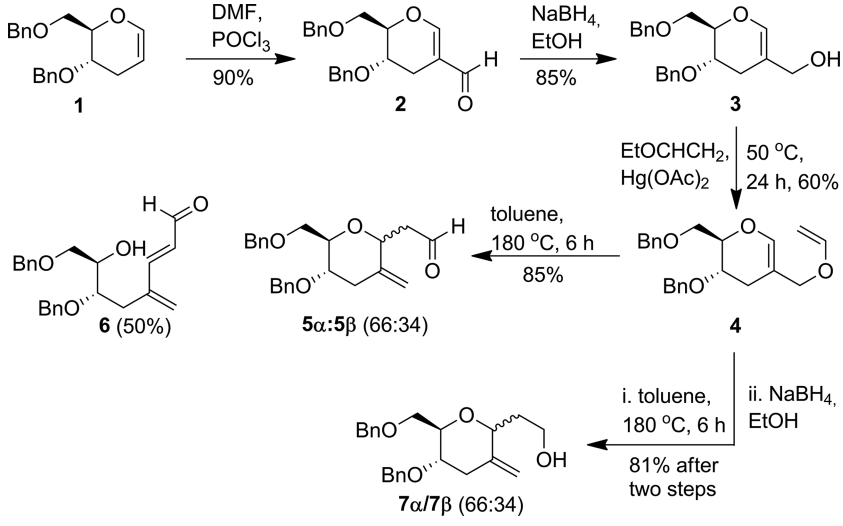


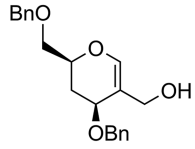
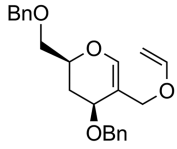
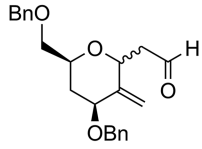
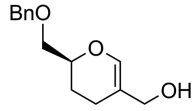
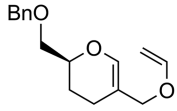
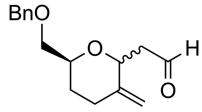
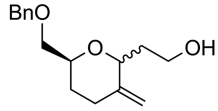
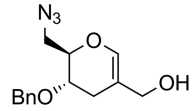
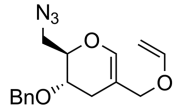
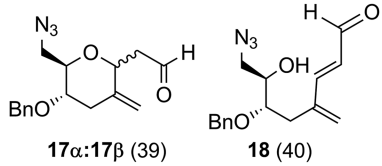
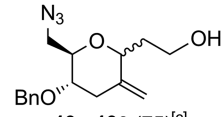
Figure 2. Assignment of the stereochemistry of C-2-methylene α- and β-C-glycosides.

Encouraged by this result, we further applied this method to other deoxy-2-vinyloxymethyl glycal derivatives. Thus, 4-deoxy-2-hydroxymethyl-3,6-di-*O*-benzyl-D-glucal (**8**) underwent a vinylation reaction to give the corresponding vinyl ether **9**. The Claisen rearrangement of **9** provided 4-deoxy-*C*-2-methylene *C*-glycosides **10α** and **10β** in 90:10 ratio (see Table 1, Entry 1). Similarly, 2,3-dideoxy vinyl ether **12**, which was derived from 2-hydroxymethyl glycal **11**, underwent a Claisen rearrangement to provide *C*-2-methylene-*C*-glycosides **13α** and **13β** in good yield in a ratio of 83:17 (see Table 1, Entry 2). The direct treatment of the crude mixture of aldehydes **13α** and **13β** with $NaBH_4$ provided *C*-2-methylene *C*-glycosides **14α** and **14β** in a ratio of 83:17 (see Table 1, Entry 3). Vinyl ether **16**, which was



Scheme 1. Synthesis of 3-deoxy *C*-2-methylene *C*-glycoside derivative.

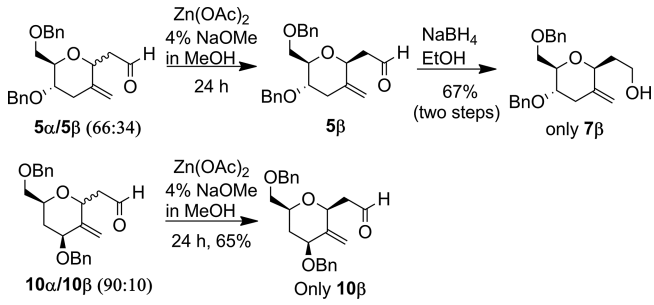
Table 1. Synthesis of deoxysugar-derived *C*-2-methylene *C*-glycosides.

Entry	2-Hydroxymethyl glycal derivative	Vinyl ether [%][a]	*C*-2 Methylene *C*-glycoside [%][a]	α/β Ratio
1	 **8** (85)	 **9** (74)	 **10**α:**10**β (65)	90:10
2	 **11** (80)	 **12** (65)	 **13**α:**13**β (75)[b]	83:17
3	**11**	**12**	 **14**α:**14**β (69)[c]	83:17
4	 **15** (87)	 **16** (66)	 **17**α:**17**β (39) **18** (40)	72:28
5	**15**	**16**	 **19**α:**19**β (75)[c]	72:28

[a] Yield refers to pure, isolated products. [b] Obtained as an inseparable mixture. [c] The vinyl ether was subjected to Claisen rearrangement, and the obtained crude product was directly reduced with $NaBH_4$/EtOH.

prepared by the vinylation of azido alcohol **15**, underwent a Claisen rearrangement followed by column chromatography to provide a mixture of *C*-2-methylene *C*-glycosides **17α** and **17β** in a 72:28 ratio along with the corresponding ring-opened α,β-unsaturated aldehyde derivative **18** (see Table 1, Entry 4). Conversely, the direct reduction of the crude product of the Claisen rearrangement of **16** provided a mixture of 3-deoxy-*C*-2-methylene *C*-glycosides **19α** and **19β** (72:28) in good yield (see Table 1, Entry 5). These results suggest that the equatorial –OBn at *C*-4 (that is present in compounds **4** and **16**) strongly influences the product stability and particularly increases the β-*C*-glycoside formation.

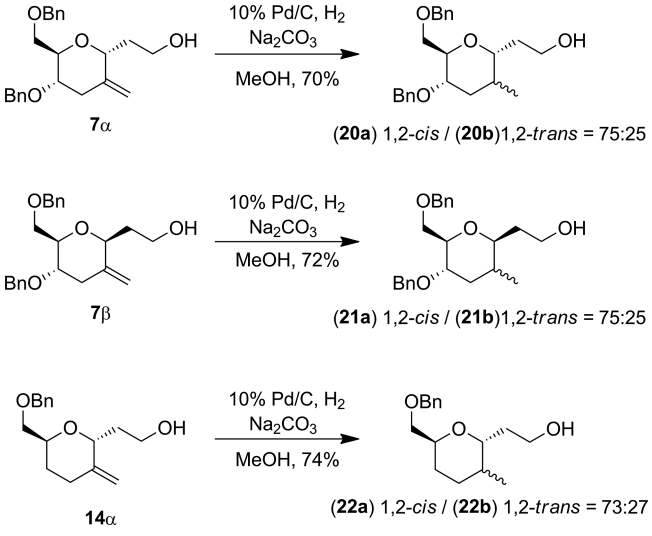
As all of the Claisen rearrangements provided the *C*-2-methylene α-*C*-glycosides as the major products, we then focused on converting the obtained α-*C*-glycosides into their β-*C*-anomers. Towards this goal, we attempted the zinc(II)-mediated epimerization of 2′-carbonylalkyl-α-*C*-glycosides.[20] Thus, the mixture of **5α** and **5β**, which was obtained from the Claisen rearrangement of **4**, was directly treated with $Zn(OAc)_2$ in NaOMe/MeOH. Consequently, the *C*-1 epimerization occurred smoothly, and the anomeric mixture was completely converted into β-*C*-glycoside **5β**.[21] A further reduction of **5β** with $NaBH_4$ provided the diastereomerically pure alcohol **7β**. When a similar protocol was applied to the mixture of anomers **10α** and **10β**, pure β-*C*-glycoside **10β** was formed as a single diastereomer (see Scheme 2).



Scheme 2. Epimerization of α-*C*-glycosides into β-*C*-glycosides.

The significance of the developed method was further evaluated by applying it to the synthesis of a series of deoxy *C*-2-methyl-*C*-glycosides. Towards this, *C*-2-methylene-*C*-glycoside **7α** was subjected to a selective hydrogenation by using 10% Pd/C under hydrogen in the presence of Na_2CO_3 as a catalyst poison.[22] This reaction provided *C*-2-methyl-*C*-glycosides **20a** and **20b** in 70% yield as a 75:25 mixture

of 1,2-*cis* and 1,2-*trans* diastereomers, respectively. Upon hydrogenation, *C*-2-methylene *C*-glycosides **7β** and **14α** provided **21a**/**21b** (75:25) and **22a**/**22b** (73:27)[23] as a mixture of 1,2-*cis*- and 1,2-*trans*-*C*-2-methyl-*C*-glycosides, (see Scheme 3).



Scheme 3. Synthesis of *C*-2-methyl *C*-glycosides.

The 1,2-*cis* and 1,2-*trans* relationship with respect to the C-1- and C-2-branched glycosides was assigned by observing the NOE correlations in a 2D NOESY experiment. The protons of the C-2 methyl group of 1,2-*cis* diastereomer **20a** had an NOE correlation with the α-C-7 protons, whereas the C-2 methyl group of β-C-glycoside **21a** had an NOE correlation with the C-4 proton, which is in an axial orientation (see Figure 3).

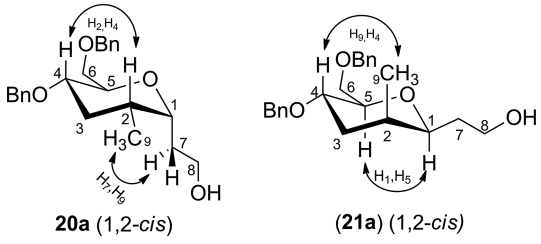
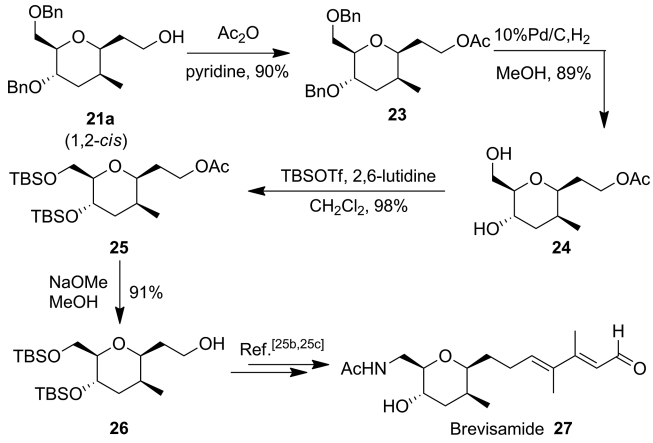


Figure 3. Assignment of the stereochemistry of C-2 methyl group of α- and β-C-glycosides.

Finally we applied this method to the preparation of a natural product that has a *C*-2-methyl-*C*-glycoside subunit and, thus, chose (–)-brevisamide **27**, which is a cyclic ether marine alkaloid that was isolated from the cultures of *Karenia brevis*.[24] Hence, the hydroxy function of alcohol **21a** was acetylated to give compound **23**, which upon hydrogenolysis provided diol **24**. The protection of both the hydroxy groups by using *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf)/2,6-lutidine in CH_2Cl_2 provided **25**. Deprotection of the acetate moiety under Zemplén deacylation conditions provided the advanced intermediate **26**,[25] which was recently employed for the total synthesis of (–)-brevisamide (**27**, see Scheme 4).



Scheme 4. Formal total synthesis of (–)-brevisamide.

Conclusions

In summary, a general method has been developed for the synthesis of deoxygenated *C*-2-methylene-*C*-glycosides by using the Claisen rearrangement of 2-vinyloxymethyl glycal derivatives. Importantly, this method is applicable to the stereoselective synthesis of *C*-2-methylene α- and β-*C*-glycosides. The generality and stereoselectivity of the rearrangement was evaluated, and this method was extended to the preparation of deoxysugar-derived *C*-2-methyl-*C*-glycosides through the selective hydrogenation of the *C*-2-methylene functionality. It is significant that most of these compounds can serve as key intermediates for the synthesis of several bioactive natural products. The application of the method was further extended to the preparation of an advanced intermediate in the total synthesis of (–)-brevisamide. Further applications of this method to the total syntheses of complex natural products that contain these structural features are in progress.

Experimental Section

General Methods: All chemicals were purchased from Carbosynth, Merck, and Sigma–Aldrich Chemical Companies and were of the highest purity. The reactions were carried out under an inert atmosphere and monitored by thin layer chromatography using silica gel GF_{254} plates. The compounds were visualized by charring with 5% (v/v) H_2SO_4 in methanol, staining with phosphomolybdic acid (PMA), or using ultraviolet light, unless otherwise mentioned. *N*,*N*-Dimethylformamide, ethanol, ethyl vinyl ether, toluene, methanol, and $POCl_3$ were distilled from dehydrating agents prior to use. Silica gel (100–200) was used for column chromatography. The ^1H NMR, ^{13}C NMR, DEPT, COSY, and NOESY spectroscopic data were recorded with Bruker 400 or 500 MHz spectrometers, and $CDCl_3$ was used as the solvent. The chemical shifts for ^1H NMR are reported in ppm (δ) with TMS as the internal standard (δ = 0.00 ppm). The chemical shifts for ^{13}C NMR are reported in ppm (δ) with the solvent as the reference ($CDCl_3$, δ = 77.00 ppm). IR spectra were recorded with a JASCO FT/IR-5300 spectrometer. High resolution mass spectra were recorded with a Bruker maXis ESI-TOF spectrometer.

(2*R*,3*S*)-3-(Benzyloxy)-2-[(benzyloxy)methyl]-3,4-dihydro-2*H*-pyran-5-carbaldehyde (2): To a solution of dry DMF (5 mL) and $POCl_3$

(0.90 mL, 9.67 mmol) at 0 °C was added a precooled solution of 3-deoxy-4,6-di-*O*-benzyl-D-glucal (**1**) (1.0 g, 3.22 mmol) in dry DMF (6 mL) dropwise for approximately 30 min. The mixture was stirred for 5–6 h at room temperature. After the complete consumption of the starting material (monitored by TLC), the reaction was quenched with a saturated aqueous $NaHCO_3$ solution and then diluted with diethyl ether. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (2× 100 mL). The combined ether layers were washed with brine solution, dried with anhydrous Na_2SO_4, and concentrated. The crude residue was purified by chromatography on a silica gel column (hexanes/ethyl acetate) to provide compound **2** (0.80 g, 90% yield) as a colorless gum; R_f = 0.52 (30% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.29 (s, 1 H), 7.29–7.38 (m, 11 H), 4.50–4.69 (m, 4 H), 4.19–4.23 (m, 1 H), 3.81–3.86 (m, 1 H), 3.77–3.79 (m, 2 H), 2.69 (dd, J = 16.0 Hz, J = 4.8 Hz, 1 H), 2.26 (dd, J = 16.4 Hz, J = 7.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.5, 163.2, 137.3, 137.3, 128.1, 127.4, 127.4, 116.5, 79.0, 73.2, 70.5, 68.1, 68.0, 22.4 ppm.

{(2*R*,3*S*)-3-(Benzyloxy)-2-[(benzyloxy)methyl]-3,4-dihydro-2*H*-pyran-5-yl}methanol (3): To a stirred solution of compound **2** (0.47 g, 1.38 mmol) in dry ethanol (5 mL) at 0 °C was added solid $NaBH_4$ (78 mg, 2.07 mmol), and the stirring was continued for 3 h. Upon completion (monitored by TLC), the reaction was quenched with saturated NH_4Cl solution. The ethanol was evaporated under reduced pressure, and the aqueous suspension was extracted with dichloromethane (2× 50 mL). The combined organic layers were washed with water and brine solution, dried with anhydrous Na_2SO_4, and then concentrated. The crude residue was purified by chromatography on a silica gel column to provide compound **3** (0.40 g, 85% yield) as a colorless gum; R_f = 0.5 (40% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.38, (m, 10 H), 6.46 (s, 1 H), 4.69 (d, J = 11.6 Hz, 1 H), 4.65 (d, J = 12 Hz, 1 H), 4.60 (d, J = 12 Hz, 1 H), 4.55 (d, J = 11.6 Hz, 1 H), 3.93–3.98 (m, 3 H), 3.83–3.89 (m, 1 H), 3.80 (d, J = 4 Hz, 2 H), 2.75 (br. s, 1 H), 2.53 (dd, J = 5.6 Hz, J = 16.4 Hz, 1 H), 2.22 (dd, J = 7.6 Hz, J = 16.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.1, 137.6, 137.5, 127.9, 127.8, 127.3, 127.2, 109.8, 76.4, 72.9, 70.4, 69.7, 68.3, 62.7, 27.1 ppm.

(2*R*,3*S*)-3-(Benzyloxy)-2-[(benzyloxy)methyl]-5-[(vinyloxy)methyl]-3,4-dihydro-2*H*-pyran (4): A solution of compound **3** (0.40 g, 1.17 mmol), ethyl vinyl ether (freshly distilled from sodium, 20 mL), and mercuric acetate (85 mg, 0.26 mmol) were stirred at 50 °C under nitrogen. After 24 h, the reaction was cooled to 25 °C and then diluted with an equal volume of hexane. The obtained solution was washed with 5% aqueous KOH, water, and then brine solution. The organic layer was concentrated under reduced pressure, and the obtained residue was purified by using basic alumina to afford compound **4** (260 mg, 60% yield) as a colorless gum; R_f = 0.64 (10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.27–7.34 (m, 10 H), 6.51 (s, 1 H), 6.44 (dd, J = 7.0 Hz, J = 14.0 Hz, 1 H), 4.67 (d, J = 11.5 Hz, 1 H), 4.62 (d, J = 12.5 Hz, 1 H), 4.57 (d, J = 12.0 Hz, 1 H), 4.52 (d, J = 12.0 Hz, 1 H), 4.24 (dd, J = 2.0 Hz, J = 14.0 Hz, 1 H), 4.08 (s, 2 H), 4.02 (dd, J = 2.0 Hz, J = 7.0 Hz, 1 H), 3.91–3.94 (m, 1 H), 3.84 (td, J = 5.5 Hz, J = 8.0 Hz, 1 H), 3.77–3.78 (m, 2 H), 2.49 (dd, J = 5.5 Hz, J = 16.0 Hz, 1 H), 2.17 (dd, J = 8.0 Hz, J = 16.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.3, 142.4, 138.1, 138.0, 128.4, 128.3, 127.8, 127.7, 127.6, 106.6, 87.3, 76.8, 73.5, 71.0, 70.0, 69.4, 68.8, 28.0 ppm. HRMS (ESI): calcd. for $C_{23}H_{26}O_4Na$ [M + Na]$^+$ 389.1729; found 389.1729.

2-{(5*S*,6*R*)-5-(Benzyloxy)-6[(benzyloxy)methyl]-3-methylenetetrahydro-2*H*-pyran-2-yl}acetaldehyde (5α/5β) and (6*S*,7*R*,*E*)-6,8-Bis(benzyloxy)-7-hydroxy-4-methyleneoct-2-enal (6): In sealed tube, a solution of compound **4** (0.25 g, 0.68 mmol) in toluene (7 mL) was heated at 180–185 °C for 5–6 h. The reaction mixture was cooled, and the toluene was evaporated by using a rotary evaporator. Purification of the crude product over silica gel provided **5α** and **5β** as an inseparable mixture and pure compound **6** as a colorless gum (0.21 g, 85% combined yield); R_f = 0.52 (for **5α/5β**) and 0.36 (for **6**, 20% EtOAc/hexanes). Data for **6**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.58 (d, J = 7.6 Hz, 1 H), 7.21–7.38 (m, 10 H), 7.11 (d, J = 16.0 Hz, 1 H), 6.28 (dd, J = 7.6 Hz, J = 16.0 Hz, 1 H), 5.60 (d, J = 6.8 Hz, 2 H), 4.57 (s, 2 H), 4.48 (s, 2 H), 3.84–3.88 (m, 1 H), 3.60–3.68 (m, 3 H), 2.71 (dd, J = 2.8 Hz, J = 14.4 Hz, 1 H), 2.52 (dd, J = 8.8 Hz, J = 14.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.0, 154.4, 141.9, 137.8, 137.6, 129.1, 128.5, 128.3, 128.1, 128.0, 127.9, 127.9, 127.8, 78.1, 73.5, 73.1, 71.9, 70.6, 33.6 ppm.

2-{(5*S*,6*R*)-5-(Benzyloxy)-6-[(benzyloxy)methyl]-3-methylenetetrahydro-2*H*-pyran-2-yl}ethanol (7α/7β): In sealed tube, a solution of compound **4** (0.25 g, 0.68 mmol) in toluene (7 mL) was heated at 180–185 °C for 5–6 h. The reaction mixture was cooled to 25 °C, and the toluene was evaporated by using a rotary evaporator under reduced pressure. The obtained crude product was dissolved in dry EtOH (5 mL), and the mixture was cooled to –10 °C. $NaBH_4$ (38.55 mg, 1.02 mmol) was added, and the solution was stirred for 3 h. Upon complete consumption of the starting material, the reaction was quenched with saturated aqueous NH_4Cl. The EtOH was evaporated under reduced pressure, and the obtained slurry was dissolved in CH_2Cl_2 (100 mL). The mixture was washed with water and brine solution, and the organic layer was dried with anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure provided the crude product, which was purified by chromatography on a silica gel column to obtain *C*-2-methylene-*C*-glycosides **7α/7β** (0.2 g, 81% yield) as a colorless gum; R_f = 0.61 (for **7α**) and 0.62 (for **7β**, 40% EtOAc/hexanes).

2-{(2*R*,5*S*,6*R*)-5-(Benzyloxy)-6-[(benzyloxy)methyl]-3-methylenetetrahydro-2*H*-pyran-2-yl}ethanol (7α): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.36 (m, 10 H), 4.89 (s, 1 H), 4.87 (s, 1 H), 4.62 (d, J = 12.4 Hz, 1 H), 4.55 (d, J = 12 Hz, 1 H), 4.41–4.44 (m, 2 H), 3.88–3.93 (m, 1 H), 3.82–3.85 (m, 2 H), 3.76 (dd, J = 2.4 Hz, J = 6.4 Hz, 1 H), 3.59 (dd, J = 6.8 Hz, J = 10.8 Hz, 1 H), 3.43–3.49 (m, 1 H), 2.76 (dd, J = 4.8 Hz, J = 13.2 Hz, 1 H), 2.41 (dd, J = 11.2 Hz, J = 12.8 Hz, 1 H), 2.29–2.33 (m, 2 H), 1.63–1.68 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.6, 138.1, 138.0, 128.4, 128.3 127.8, 127.7, 127.6, 127.6, 111.0, 77.6, 75.0, 73.4, 72.3, 70.8, 69.8, 61.1, 34.9, 33.0 ppm. HRMS (ESI): calcd. for $C_{23}H_{28}O_4Na$ [M + Na]$^+$ 391.1886; found 391.1886.

2-{(2*S*,5*S*,6*R*)-5-(Benzyloxy)-6-[(benzyloxy)methyl]-3-methylenetetrahydro-2*H*-pyran-2-yl}ethanol (7β): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.36 (m, 10 H), 4.90 (s, 1 H), 4.87 (s, 1 H), 4.63 (d, J = 11.6 Hz, 1 H), 4.53–4.58 (m, 2 H), 4.44 (d, J = 11.6 Hz, 1 H), 4.06 (t, J = 6.4 Hz, 1 H), 3.89 (m, 2 H), 3.77 (dd, J = 2 Hz, J = 10 Hz, 1 H), 3.56–3.65 (m, 2 H), 3.47–3.51 (m, 1 H), 3.12 (br. s, 1 H), 2.88 (dd, J = 5.2 Hz, J = 13.2 Hz, 1 H), 2.27 (dd, J = 7.6 Hz, J = 13.2 Hz, 1 H), 1.95–2.00 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.6, 138.1, 138.0, 128.4, 128.4, 127.8, 127.7, 127.7, 127.6, 109.4, 79.9, 78.9, 74.7, 73.4, 71.0, 69.9, 61.5, 38.5, 33.4 ppm. HRMS (ESI): calcd. for $C_{23}H_{28}O_4Na$ [M + Na]$^+$ 391.1886; found 391.1885.

{(2*S*,4*S*)-4-(Benzyloxy)-2-[(benzyloxy)methyl]-3,4-dihydro-2*H*-pyran-5-yl}methanol (8): By following the procedure described for **3**, (2*S*,4*S*)-4-(benzyloxy)-2-[(benzyloxy)methyl]-3,4-dihydro-2*H*-pyran-5-carbaldehyde was employed to prepare compound **8** (85%

yield); R_f = 0.6 (30% EtOAc/hexanes). $[\alpha]_D$ = +47 (c = 0.37, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.36 (m, 10 H), 6.51 (s, 1 H), 4.68 (d, J = 11.6 Hz, 1 H), 4.49–4.62 (m, 3 H), 4.33 (t, J = 7.2 Hz, 1 H), 4.15–4.21 (m, 1 H), 4.02 (q, J = 12 Hz, 2 H), 3.67 (dd, J = 6.4 Hz, J = 10 Hz, 1 H), 3.55 (dd, J = 4.4 Hz, J = 10.4 Hz, 1 H), 2.33 (br. s, 1 H), 2.22–2.27, (m, 1 H), 1.88–1.96 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.4, 137.9, 137.8, 128.5, 128.4, 127.9, 127.8, 113.5, 73.7, 73.5, 71.5, 71.1, 70.8, 62.3, 30.0 ppm. HRMS (ESI): calcd for $C_{21}H_{24}O_4Na$ $[M + Na]^+$ 363.1573; found 363.1571.

(2*S*,4*S*)-4-(Benzyloxy)-2-[(benzyloxy)methyl]-5-[(vinyloxy)methyl]-3,4-dihydro-2*H*-pyran (9): By following the procedure described for **4**, compound **8** was employed to prepare compound **9** (74% yield); R_f = 0.5 (10% EtOAc/hexanes). $[\alpha]_D$ = +35.7 (c = 0.35, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.35 (m, 10 H), 6.53 (s, 1 H), 6.42 (dd, J = 6.8 Hz, J = 14.4 Hz, 1 H), 4.48–4.64 (m, 5 H), 4.23–4.27 (m, 3 H), 4.01 (dd, J = 1.6 Hz, J = 6.8 Hz, 1 H), 3.92 (d, J = 10.8 Hz, 1 H), 3.68 (dd, J = 6.8 Hz, J = 10.4 Hz, 1 H), 3.54 (dd, J = 4.4 Hz, J = 10.4 Hz, 1 H), 2.16–2.22 (m, 1 H), 1.88–1.96 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.5, 145.1, 138.3, 137.9, 128.4, 128.3, 127.7, 127.7,127.6, 110.9, 87.1, 74.0, 73.4, 71.5, 71.0, 68.3, 66.5, 29.7 ppm. HRMS (ESI): calcd for $C_{23}H_{26}O_4Na$ $[M + Na]^+$ 389.1729; found 389.1729.

2-{(2*R*,4*S*,6*S*)-4-(Benzyloxy)-6-[(benzyloxy)methyl]-3-methylenetetrahydro-2*H*-pyran-2-yl}acetaldehyde (10α) and 2-{(2*S*,4*S*,6*S*)-4-(Benzyloxy)-6-[(benzyloxy)methyl]-3-methylenetetrahydro-2*H*-pyran-2-yl}acetaldehyde (10β): By following the procedure described for compounds **5α** and **5β**, compound **9** was employed to prepare compounds **10α** and **10β** (65% yield, 90:10 diastereomeric ratio); R_f = 0.6 (30% EtOAc/hexanes). Only **10α** was isolated by chromatography on a silica gel column. Data for **10α**: ^1H NMR (400 MHz, $CDCl_3$): δ = 9.75–9.76 (q, 1 H), 7.27–7.35 (m, 10 H), 5.23 (s, 1 H), 5.03 (s, 1 H), 4.96 (dd, J = 5.6 Hz, J = 14.4 Hz, 1 H), 4.51–4.60 (m, 4 H), 4.10 (dd, J = 4.8 Hz, J = 9.2 Hz, 1 H), 4.00–4.06 (m, 1 H), 3.67 (dd, J = 6.4 Hz, J = 10.4 Hz, 1 H), 3.45 (dd, J = 4.4 Hz, J = 10 Hz, 1 H), 2.83 (ddd, J = 3.2 Hz, J = 8.8 Hz, J = 16 Hz, 1 H), 2.59 (ddd, J = 2.0 Hz, J = 6.0 Hz, J = 16 Hz, 1 H), 2.16 (dt, J = 4.4 Hz, J = 12.8 Hz, 1 H), 1.57 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.1, 144.4, 138.2, 138.1, 128.4, 128.3, 127.7, 127.6, 127.3, 110.1, 74.2, 73.3, 71.9, 71.4, 70.5, 70.2, 53.4, 45.6, 35.8 ppm. HRMS (ESI): calcd. for $C_{23}H_{27}O_4$ $[M + H]^+$ 367.1909; found 367.1908.: Compound **10β** was not isolated by column chromatography but obtained as a mixture with **10α**.

(*S*)-{2-[(Benzyloxy)methyl]-3,4-dihydro-2*H*-pyran-5-yl}methanol (11): By following the procedure described for **3**, (*S*)-2-[(benzyloxy) methyl]-3,4-dihydro-2*H*-pyran-5-carbaldehyde was employed to prepare compound **11** (80% yield); R_f = 0.52 (40% EtOAc/hexanes). $[\alpha]_D$ = +51 (c = 0.29, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3419, 2854, 1671 cm^{-1}. ^1H NMR (400 MHz , $CDCl_3$): δ = 7.31–7.36 (m, 5 H), 6.50 (s, 1 H), 4.60 (d, J = 12.0 Hz, 1 H), 4.56 (d, J = 12.0 Hz, 1 H), 3.96–3.99 (m, 3 H), 3.56 (ddd, J = 6.4 Hz, J = 10.4 Hz, J = 22.8 Hz, 2 H), 2.09–2.17 (m, 2 H), 1.90–1.94 (m, 1 H), 1.72–1.74 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.6, 138.0, 128.4, 127.7, 127.7, 112.7, 74.1, 73.4, 72.2, 64.3, 24.0, 20.8 ppm. HRMS (ESI): calcd. for $C_{14}H_{18}O_3Na$ $[M + Na]^+$ 257.1154; found 257.1154.

(*S*)-2-[(Benzyloxy)methyl]-5-[(vinyloxy)methyl]-3,4-dihydro-2*H*-pyran (12): By following the procedure described for **4**, compound **11** was employed to prepare compound **12** (65% yield); R_f = 0.7 (10% EtOAc/hexanes). $[\alpha]_D$ = +45 (c = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3024, 2920, 1671, 1638, 1616 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.38 (m, 5 H), 6.56 (s, 1 H), 6.44 (q, J = 6.8 Hz, J = 14.4 Hz, 1 H), 4.57 (q, J = 12 Hz, J = 17.2 Hz, 2 H), 4.23 (dd, J = 1.6 Hz, J = 14 Hz, 1 H), 4.04–4.07 (m, 2 H), 4.03 (d, J = 2 Hz, 1 H), 4.01 (d, J = 2 Hz, 1 H), 3.54–3.64 (m, 2 H), 2.14–2.19 (m, 1 H), 2.06–2.11 (m, 1 H), 1.89–1.96 (m, 1 H), 1.71–1.79 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.4, 143.1, 138.0, 128.4, 127.7, 108.9, 87.0, 74.2, 73.4, 72.1, 70.1, 23.9, 21.1 ppm. HRMS (ESI): calcd. for $C_{16}H_{20}O_3Na$ $[M + Na]^+$ 283.1310; found 283.1327.

2-{(6*S*)-6-[(Benzyloxy)methyl]-3-methylenetetrahydro-2*H*-pyran-2-yl}acetaldehyde (13): By following the procedure described for **5α** and **5β**, compound **12** was employed to prepare compound **13**, which was obtained as an inseparable mixture of **13α** and **13β** (see Supporting Information). HRMS (ESI): calcd. for $C_{16}H_{20}O_3Na$ $[M + Na]^+$ 283.1310; found 283.1308.

2-{(2*R*,6*S*)-6-[(Benzyloxy)methyl]-3-methylenetetrahydro-2*H*-pyran-2-yl}ethanol (14α): By following the procedure described for compounds **7α** and **7β**, compound **12** was employed to prepare compounds **14α** and **14β** (69% yield); R_f = 0.4 (40% EtOAc/hexanes). Data for **14α**: $[\alpha]_D$ = +17 (c = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3446, 2920, 1654, 1457 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.35 (m, 5 H), 4.79 (s, 1 H), 4.77 (s, 1 H), 4.50 (q, J = 26.8 Hz, 1 H), 4.44 (dd, J = 4.4 Hz, J = 10.8 Hz, 1 H), 4.04–4.10 (m, 1 H), 3.84–3.89 (m, 2 H), 3.76–3.82 (m, 2 H), 3.38–3.46 (m, 2 H), 2.37–2.46 (m, 1 H), 2.28–2.36 (m, 2 H), 1.67–1.73 (m, 1 H), 1.51–1.58 (m, 1 H), 1.36–1.47 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.4, 137.8, 128.2, 127.4, 109.1, 78.2, 73.2, 72.8, 68.6, 61.2, 33.2, 29.0, 28.1 ppm. HRMS (ESI): calcd. for $C_{16}H_{22}O_3Na$ $[M + Na]^+$ 285.1467; found 285.1455.

[(2*R*,3*S*)-2-(Azidomethyl)-3-(benzyloxy)-3,4-dihydro-2*H*-pyran-5-yl]-methanol (15): By following the procedure described for **3**, (2*R*,3*S*)-2-(azidomethyl)-3-(benzyloxy)-3,4-dihydro-2*H*-pyran-5-carbaldehyde was employed to prepare compound **15** (87% yield); R_f = 0.67 (30% EtOAc/hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.41, (m, 5 H), 6.46 (s, 1 H), 4.72 (d, J = 12.4 Hz, 1 H), 4.56 (d, J = 11.6 Hz, 1 H), 4.00 (s, 2 H), 3.84–3.87 (m, 1 H), 3.74–3.80 (m, 1 H), 3.64 (dd, J = 2.8 Hz, J = 13.2 Hz, 1 H), 3.55 (dd, J = 5.2 Hz, J = 12.8 Hz, 1 H), 2.62 (dd, J = 6.0 Hz, J = 16.0 Hz, 1 H), 2.21 (dd, J = 8.4 Hz, J = 16.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.6, 137.7, 128.5, 127.9, 127.8, 110.7, 76.4, 70.9, 70.6, 63.4, 51.1, 27.9 ppm. HRMS (ESI): calcd. for $C_{14}H_{17}N_3O_3Na$ $[M + Na]^+$ 298.1168; found 298.1168.

(2*R*,3*S*)-2-(Azidomethyl)-3-(benzyloxy)-5-[(vinyloxy)methyl]-3,4-dihydro-2*H*-pyran (16): By following the procedure described for **4**, compound **15** was employed to prepare compound **16** (66% yield); R_f = 0.65 (5% EtOAc/hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.39, (m, 5 H), 6.50 (s, 1 H), 6.46 (dd, J = 6.8 Hz, J = 14.4 Hz, 1 H), 4.71 (d, J = 11.2 Hz, 1 H), 4.53 (d, J = 11.2 Hz, 1 H), 4.25 (dd, J = 2.0 Hz, J = 14.4 Hz, 1 H), 4.09 (s, 2 H), 4.05 (dd, J = 2.0 Hz, J = 6.8 Hz, 1 H), 3.84–3.87 (m, 1 H), 3.76–3.80 (m, 1 H), 3.65 (dd, J = 2.4 Hz, J = 13.2 Hz, 1 H), 3.55 (dd, J = 5.2 Hz, J = 12.8 Hz, 1 H), 2.58 (dd, J = 6.0 Hz, J = 16.4 Hz, 1 H), 2.18 (dd, J = 8.8 Hz, J = 16.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.2, 142.0, 137.6, 128.5, 127.9, 127.8, 107.1, 87.4, 76.6, 70.9, 70.4, 69.0, 51.1, 28.2 ppm.

2-[(2*R*,5*S*,6*R*)-6-(Azidomethyl)-5-(benzyloxy)-3-methylenetetrahydro-2*H*-pyran-2-yl]acetaldehyde (17α), 2-[(2*S*,5*S*,6*R*)-6-(Azidomethyl)-5-(benzyloxy)-3-methylenetetrahydro-2*H*-pyran-2-yl]acetaldehyde (17β), and (6*S*,7*R*,*E*)-8-Azido-6-(benzyloxy)-7-hydroxy-4-methyleneoct-2-enal (18): By following the procedure described for **5α**, **5β**, and **6**, compound **16** was employed to prepare compounds **17α**, **17β**, and **18**. Data for **17α**: (39% yield); R_f = 0.6 (30% EtOAc/hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.86 (t, J = 2.0 Hz, 1

H), 7.32–7.40, (m, 5 H), 4.97 (s, 1 H), 4.80 (s, 1 H), 4.67 (d, J = 11.6 Hz, 1 H), 4.47 (d, J = 11.6 Hz, 1 H), 4.40 (t, J = 6.4 Hz, 1 H), 3.65 (dtd, J = 2.4 Hz, J = 6.0 Hz, J = 11.2 Hz, 1 H), 3.55 (dd, J = 2.4 Hz, J = 13.2 Hz, 1 H), 3.42–3.48 (m, 1 H), 3.37 (dd, J = 6.0 Hz, J = 13.2 Hz, 1 H), 2.97 (dd, J = 4.8 Hz, J = 12.8 Hz, 1 H), 2.79 (dd, J = 2.4 Hz, J = 6.4 Hz, 2 H), 2.30 (dd, J = 11.6 Hz, J = 12.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.6, 142.3, 137.7, 128.5, 127.9, 127.8, 110.5, 80.2, 74.8, 73.7, 71.0, 51.6, 45.2, 38.4 ppm. Compound **17β** was only observed in the NMR spectra of the crude product, and it was not detected after column chromatography. Compound **18** was only observed during the purification of compounds **17α** and **17β** over silica gel. Data for **18**: (40% yield); R_f = 0.5 (30% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.59 (d, J = 7.6 Hz, 1 H), 7.29–7.38, (m, 5 H), 7.14 (d, J = 15.6 Hz, 1 H), 6.26 (dd, J = 7.6 Hz, J = 16 Hz, 1 H), 5.63 (d, J = 14.4 Hz, 2 H), 4.54 (d, J = 5.2 Hz, 2 H), 3.81–3.83 (m, 1 H), 3.60–3.65 (m, 1 H), 3.50 (d, J = 5.6 Hz, 2 H), 2.66 (dd, J = 3.2 Hz, J = 13.6 Hz, 1 H), 2.57 (dd, J = 8.4 Hz, J = 14.4 Hz, 1 H), 2.29 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.9, 154.0, 141.4, 137.4, 129.2, 128.5, 128.1, 128.0, 78.3, 73.2, 71.9, 53.4, 33.2 ppm.

2-[(2*R*,5*S*,6*R*)-6-(Azidomethyl)-5-(benzyloxy)-3-methylenetetrahydro-2*H*-pyran-2-yl]ethanol (19α) and 2-[(2*S*,5*S*,6*R*)-6-(Azidomethyl)-5-(benzyloxy)-3-methylenetetrahydro-2*H*-pyran-2-yl]ethanol (19β): By following the procedure described for **7α** and **7β**, compounds **19α** and **19β** were obtained as an inseparable anomeric mixture (74% yield, see Supporting Information). R_f = 0.65 (for **19α**) and 0.66 (for **19β**).

Zn^{II}-Mediated Anomerization of α-*C*-Glycoside into β-*C*-Glycoside

2-{(5*S*,6*R*)-5-(Benzyloxy)-6-[(benzyloxy)methyl]-3-methylenetetrahydro-2*H*-pyran-2-yl}ethanol (7β): To a solution of crude **5α/5β** (0.1 g, 0.27 mmol) in 4% NaOMe/MeOH (3 mL) was added anhydrous $Zn(OAc)_2$ (249 mg, 1.36 mmol) at 25 °C, and the mixture was stirred for a period of 24 h. After complete consumption of the α-*C*-glycoside (monitored by TLC), the reaction mixture was slowly neutralized by the addition of AcOH. The suspension was filtered through a pad of Celite, and the filter cake was washed with ethyl acetate (50 mL). The filtrate was washed with water and brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure to provide crude **5β** as a colorless gum, which was used in the next step without further purification (attempts to purify **5β** were unsuccessful). Crude **5β** [75% (crude)] was immediately dissolved in dry ethanol (3 mL), and the resulting solution was treated with $NaBH_4$ (15 mg, 0.40 mmol) at 0 °C. The stirring was continued for 3 h. Upon complete consumption of the starting material, the reaction was quenched by the addition of saturated aqueous NH_4Cl. The ethanol was removed under reduced pressure, and the obtained residue was dissolved in CH_2Cl_2 (50 mL). The resulting solution was washed with brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain the crude β-*C*-glycoside. Purification of the crude product by chromatography on a silica gel column provided pure **7β** (67 mg, 67% yield) as a colorless gum; R_f = 0.62 (40% EtOAc/hexanes).

2-{(2*S*,4*S*,6*S*)-4-(Benzyloxy)-6-[(benzyloxy)methyl]-3-methylenetetrahydro-2*H*-pyran-2-yl}acetaldehyde (10β): By following the procedure described for **5β**, the crude **10α/10β** mixture was employed to prepare compound **10β** (65% yield); R_f = 0.64 (30% EtOAc/toluene). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.82 (t, J = 1.6 Hz, 1 H), 7.26–7.36 (m, 10 H), 5.36 (d, J = 2 Hz, 1 H), 4.89 (s, 1 H), 4.61–4.68 (m, 2 H), 4.51–4.57 (m, 2 H), 4.27 (t, J = 6 Hz, 1 H), 4.00 (dd, J = 4.8 Hz, J = 11.2 Hz, 1 H), 3.79 (m, 1 H), 3.50 (dd, J = 5.2 Hz, J = 10.8 Hz, 1 H), 3.45 (dd, J = 8.8 Hz, J = 16 Hz, 1 H), 2.76–2.87 (m, 2 H), 2.17 (ddd, J = 1.6 Hz, J = 4 Hz, J = 11.2 Hz, 1 H), 1.42 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.8, 145.5, 138.3, 138.1, 128.4, 128.4, 127.7, 127.3, 106.4, 75.4, 73.4, 72.8, 71.0, 60.4, 45.3, 37.1 ppm. HRMS (ESI): calcd. for $C_{23}H_{26}O_4Na$ $[M + Na]^+$ 389.1729; found 389.1718.

2-{(2*R*,3*R*,5*S*,6*R*)-5-(Benzyloxy)-6-[(benzyloxy)methyl]-3-methyltetrahydro-2*H*-pyran-2-yl}ethanol (20a) and 2-{(2*R*,3*S*,5*S*,6*R*)-5-(Benzyloxy)-6-[(benzyloxy)methyl]-3-methyltetrahydro-2*H*-pyran-2-yl}ethanol (20b): To a stirred solution of **7α** (30 mg, 0.08 mmol) in methanol (3 mL) were added Na_2CO_3, (25 mg, 0.24 mmol) and 10% Pd/C (6 mg). The mixture was stirred for 4 h under H_2. Upon completion of the reaction (monitored by TLC), the suspension was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The obtained residue was purified by chromatography on a silica gel column to provide compound **20a** as a pure compound and **20b** as a mixture with **20a** (21 mg, 70% yield); R_f = 0.64 (40% EtOAc/hexanes). Data for **20a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.36 (m, 10 H), 4.63 (d, J = 12.0 Hz, 1 H), 4.62 (d, J = 11.6 Hz, 1 H), 4.56 (d, J = 12.4 Hz, 1 H), 4.40 (d, J = 11.6 Hz, 1 H), 3.99–4.03 (m, 1 H), 3.85–3.87 (m, 2 H), 3.78–3.80 (m, 2 H), 3.58 (dd, J = 7.2 Hz, J = 10.4 Hz, 1 H), 3.36–3.41 (m, 1 H), 2.78 (br. s, 1 H), 2.06–2.21 (m, 3 H), 1.35–1.47 (m, 2 H), 0.90 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.4, 138.2, 128.4, 128.3, 127.7, 127.6, 127.5, 77.2, 74.1, 73.5, 71.8, 70.6, 70.2, 61.7, 32.9, 32.8, 26.2, 17.1 ppm. HRMS (ESI): calcd. for $C_{23}H_{30}O_4Na$ $[M + Na]^+$ 393.2042; found 393.2042. Compound **20b** was not isolated by column chromatography but obtained as a mixture with **20a**.

2-{(2*S*,3*S*,5*S*,6*R*)-5-(Benzyloxy)-6-[(benzyloxy)methyl]-3-methyltetrahydro-2*H*-pyran-2-yl}ethanol (21a) 2-{(2*S*,3*R*,5*S*,6*R*)-5-(Benzyloxy)-6-[(benzyloxy)methyl]-3-methyltetrahydro-2*H*-pyran-2-yl}ethanol (21b): By following the procedure described for **20a** and **20b**, compound **7β** was employed to prepare compounds **21a** and **21b** (72% yield); R_f = 0.66 (40% EtOAc/hexanes). Data for **21a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24–7.35 (m, 10 H), 4.60 (d, J = 12.0 Hz, 1 H), 4.57 (d, J = 11.5 Hz, 1 H), 4.55 (d, J = 12.0 Hz, 1 H), 4.39 (d, J = 11.5 Hz, 1 H), 3.80–3.86 (m, 2 H), 3.77 (dd, J = 1.5 Hz, J = 11.0 Hz, 1 H), 3.73 (dt, J = 2.5 Hz, J = 10.5 Hz, 1 H), 3.60 (dd, J = 6.5 Hz, J = 10.5 Hz, 1 H), 3.50–3.53 (m, 2 H), 2.11–2.14 (m, 1 H), 1.87–1.92 (m, 2 H), 1.47–1.52 (m, 2 H), 1.00 (d, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.4, 138.3, 128.3, 127.7, 127.6, 127.6, 127.5, 80.9, 80.8, 73.4, 71.0, 70.3, 70.1, 62.3, 36.9, 34.7, 33.1, 13.0 ppm. HRMS (ESI): calcd. for $C_{23}H_{30}O_4Na$ $[M + Na]^+$ 393.2042; found 393.2042. Compound **21b** was not isolated by column chromatography but obtained as a mixture with **21a**.

2-{(2*R*,3*R*,6*S*)-6-[(Benzyloxy)methyl]-3-methyltetrahydro-2*H*-pyran-2-yl}ethanol (22a) and 2-{(2*R*,3*S*,6*S*)-6-[(Benzyloxy)methyl]-3-methyltetrahydro-2*H*-pyran-2-yl}ethanol (22b): By following the procedure described for **20a** and **20b**, compounds **22a** and **22b** were obtained as a diastereomeric mixture that was inseparable by column chromatography (74% yield, see Supporting Information); R_f = 0.44 (40% EtOAc/hexanes). HRMS (ESI): calcd. for $C_{16}H_{25}O_3$ $[M + H]^+$ 265.1804; found 265.1804.

2-{(2*S*,3*S*,5*S*,6*R*)-5-(Benzyloxy)-6-[(benzyloxy)methyl]-3-methyltetrahydro-2*H*-pyran-2-yl}ethyl Acetate (23): Acetic anhydride (0.36 mL, 3.80 mmol) was slowly added at 0 °C to a solution of **21a** (0.35 g, 0.95 mmol) in dry pyridine (7 mL). After stirring for 4 h at room temperature, the pyridine was evaporated under reduced pressure, and the obtained residue was dissolved in CH_2Cl_2 (50 mL). The solution was washed with aqueous copper sulfate solution, water, and brine and then dried with anhydrous Na_2SO_4.

Evaporation of the solvent followed by purification of the crude product by chromatography on a silica gel column gave **23** (0.31 g, 90% yield) as a colorless oil; R_f = 0.65 (20% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.35 (m, 10 H), 4.66 (d, J = 12.4 Hz, 1 H), 4.56 (d, J = 12 Hz, 2 H), 4.40 (d, J = 11.2 Hz, 1 H), 4.13–4.23 (m, 2 H), 3.76 (dd, J = 2.0 Hz, J = 10.8 Hz, 1 H), 3.71 (dd, J = 4.8 Hz, J = 10.8 Hz, 1 H), 3.59–3.66 (m, 1 H), 3.55–3.58 (m, 1 H), 3.39 (ddd, J = 2.0 Hz, J = 4.8, J = 9.6 Hz, 1 H), 2.14 (ddd, J = 2.4 Hz, J = 4.4 Hz, J = 12.4 Hz, 1 H), 2.06 (s, 3 H), 1.85–1.94 (m, 2 H), 1.64–1.72 (m, 2 H), 0.99 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 138.6, 138.5, 128.3 128.2, 127.7, 127.5, 127.4, 81.3, 76.4, 73.4, 71.0, 69.9, 69.8, 62.0, 37.0, 32.6, 32.0, 21.0, 12.7 ppm. HRMS (ESI): calcd. for $C_{25}H_{32}O_5Na$ $[M + Na]^+$ 435.2147; found 435.2144.

2-[(2*S*,3*S*,5*S*,6*R*)-5-Hydroxy-6-(hydroxymethyl)-3-methyltetrahydro-2*H*-pyran-2-yl]ethyl Acetate (24): To a solution of ester **23** (240 mg, 0.58 mmol) in MeOH (8 mL) was added 10% Pd/C (20 mg). The reaction mixture was stirred for 24 h under H_2 and then filtered through a pad of Celite. The filtrate was concentrated in vacuo. Purification of the residue by chromatography on a silica gel column afforded compound **24** (120 mg, 89% yield) as a colorless oil; R_f = 0.5 (5% MeOH/$CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.17 (dd, J = 6.0 Hz, J = 7.2 Hz, 2 H), 3.83 (td, J = 4.0 Hz, J = 7.6 Hz, 1 H), 3.77 (dd, J = 4.8 Hz, J = 11.6 Hz, 2 H), 3.56–3.58 (m, 1 H), 3.16–3.18 (m, 1 H), 2.06 (s, 3 H), 1.98–2.03 (m, 1 H), 1.77–1.90 (m, 2 H), 1.65–1.67 (m, 2 H), 0.98 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 82.0, 76.2, 63.9, 63.5, 61.7, 40.1, 32.8, 31.9, 21.0, 12.6 ppm. HRMS (ESI): calcd. for $C_{11}H_{20}O_5Na$ $[M + Na]^+$ 255.1208; found 255.1209.

2-[(2*S*,3*S*,5*S*,6*R*)-5-[(*tert*-butyldimethylsilyl)oxy]-6-{[(*tert*-butyldimethylsilyl)oxy]methyl}-3-methyltetrahydro-2*H*-pyran-2-yl]ethyl Acetate (25): A solution of diol **24** (100 mg, 0.43 mmol) and 2,6-lutidine (0.40 mL, 3.44 mmol) in dry CH_2Cl_2 (8 mL) was cooled to –78 °C. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (0.39 mL, 1.72 mmol) was added at the same temperature, and the reaction mixture was warmed to 0 °C over a period of 1 h. Upon completion of the reaction (monitored by TLC), the mixture was diluted with CH_2Cl_2 (30 mL). The resulting solution was washed with water and brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to obtain the crude product as an oil. Purification of the crude product over silica gel provided compound **25** (195 mg, 98% yield) as a colorless oil; R_f = 0.5 (5% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.14–4.19 (m, 2 H), 3.72–3.81 (m, 3 H), 3.53 (ddd, J = 2.4 Hz, J = 3.6 Hz, J = 10.6 Hz, 1 H), 3.04 (ddd, J = 2.4 Hz, J = 4.4 Hz, J = 10.2 Hz, 1 H), 2.06 (s, 3 H), 1.76–1.90 (m, 3 H), 1.54–1.67 (m, 2 H), 0.96 (d, J = 6.8 Hz, 3 H), 0.90 (s, 9 H), 0.88 (s, 9 H), 0.07 (s, 6 H), 0.06 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 83.5, 75.7, 62.8, 62.7, 62.1, 40.9, 33.0, 32.0, 25.8, 25.7, 21.0, 18.3, 17.9, 12.6, –4.3, –4.9, –5.0, –5.2 ppm. HRMS (ESI): calcd. for $C_{23}H_{48}O_5Si_2Na$ $[M + Na]^+$ 483.2938; found 483.2938.

2-[(2*S*,3*S*,5*S*,6*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-6-{[(*tert*-butyldimethylsilyl)oxy]methyl}-3-methyltetrahydro-2*H*-pyran-2-yl]ethanol (26): To a solution of compound **25** (150 mg, 0.33 mmol) in dry MeOH (6 mL) was added a catalytic amount of sodium methoxide at 25 °C, and the stirring was continued for 1 h. Upon completion of reaction, the pH of the mixture was neutralized by the careful addition of Amberlite IR 120 acidic resin. The suspension was filtered, and the filtrate was concentrated. The obtained crude product was purified by chromatography on a silica gel column to give alcohol **26** (130 mg, 91% yield) as a colorless oil; R_f = 0.5 (10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.71–3.85 (m, 3 H), 3.61–3.71 (m, 3 H), 3.19 (ddd, J = 2.4 Hz, J = 6.4 Hz, J = 10.2 Hz, 1 H), 1.81–1.88 (m, 3 H), 1.61 (td, J = 4.4 Hz, J = 11.2 Hz, 1 H), 1.38–1.41 (m, 1 H), 0.99 (d, J = 7.2 Hz, 3 H), 0.90 (s, 9 H), 0.87 (s, 9 H), 0.06 (s, 6 H), 0.05 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 83.6, 81.4, 63.2, 63.2, 62.9, 40.9, 34.4, 33.5, 25.9, 25.7, 18.3, 17.9, 13.0, –4.1, –4.9, –5.3, –5.4 ppm. HRMS (ESI): calcd. for $C_{21}H_{46}O_4Si_2Na$ $[M + Na]^+$ 441.2832; found 441.2833.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H and ^{13}C NMR spectra (COSY and NOESY spectra for C-glycosides) and HRMS spectra.

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