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A Short and Economical Synthesis of Orthogonally Protected *C*-Linked 2-Deoxy-2-acetamido-α-D-galactopyranose Derivatives

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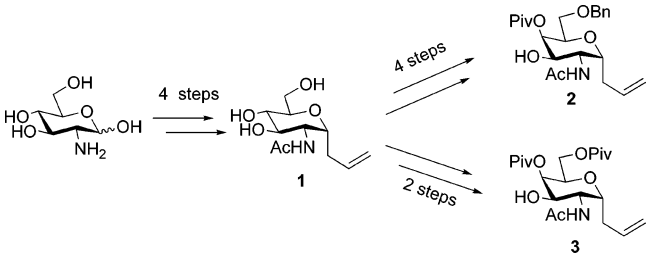

A short and high-yielding synthesis has been devised to prepare *C*-linked 2-deoxy-2-acetamido-α-D-galactopyranose derivative **3**. One of the main advantages of this approach is that it employs commercially available and inexpensive D-glucosamine as the starting material. The key steps include a highly stereoselective *C*-allylation followed by epimerization of the *C*-4 hydroxyl group. Building block **3** and orthogonally protected *C*-linked 2-deoxy-2-acetamido-α-D-galactopyranose derivative **2** were obtained in 44% overall yield (six steps) and 29% overall yield (eight steps), respectively. This represents a significant improvement over previously reported syntheses.

Since the early 1970s, many syntheses of *C*-linked carbohydrate derivatives have been reported.[1a−c,2] The interest in these compounds stems from their applications as glycosidase inhibitors[3] and their attractiveness as intermediates for probing carbohydrate−peptide and/or carbohydrate−lipid interactions[4] in biological systems.[1] The enhanced stability of *C*-linked pyranoses toward basic and acid media as well as resistance to enzymatic degradation makes them ideally suited for this purpose.[5]

Although many methods have been developed to prepare *C*-linked carbohydrate derivatives, the synthesis of *C*-linked glycosylamine derivatives is still lengthy and inefficient.[6] The preparation of *C*-linked 2-deoxy-2-acetamido-α-D-galactopyranose derivatives is especially difficult due to the incompatibility of *C*-2 nitrogen protecting groups with most *C*-glycosylation strategies.[7] Currently available syntheses of *C*-linked 2-deoxy-2-acetamido-α-D-galactopyranose derivatives utilize glucosyl derivatives (via oxime intermediates)[8] or galactosyl pyranose[9] derivatives (via galactal intermediates) as starting materials. The latter approach often introduces a *C*-2 acetamide precursor via azido nitration,[9a] azido chlorination,[9b] or azido selenation,[9c−f] and these intermediates are then subjected to stereoselective carbon−carbon bond-forming reactions. For instance, acetylenic,[9g] allylic,[9h] allenic,[9h] cyano,[9i] and other derivatives[9j−l] have been prepared after azidonitration or chlorination of the appropriate glycal. Similarly, a number of *C*-linked GalNHAc derivatives[9m,n] including *C*-linked disaccharide GalNHAc derivatives[9o] have been prepared via azido selenation of galactal. *C*-Linked *N*-acetylgalactosamine derivatives have also been prepared via direct Keck allylation[7,10,11a] of *N*-acetylgalactosamine.[11b]

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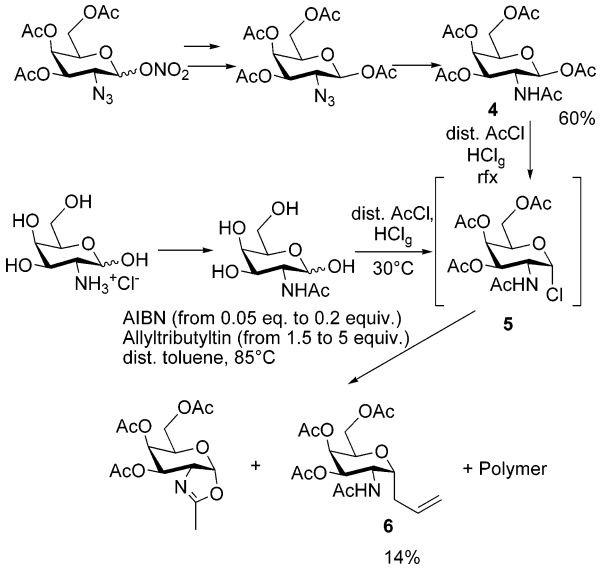
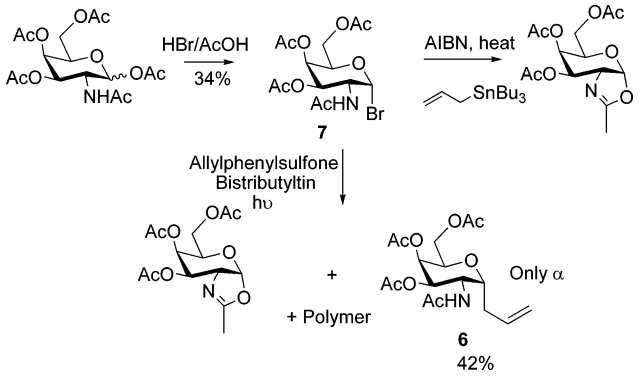
SCHEME 1. Preparation and Allylation of Intermediate 5



SCHEME 2. Preparation and Allylation of Intermediate 7



As part of our ongoing studies toward the rational design and synthesis of *C*-linked antifreeze glycoprotein analogues, we required large quantities of *C*-linked 2-deoxy-2-acetamido-α-D-galactopyranose derivatives. On the basis of literature precedent, we chose to perform a direct allylation on *N*-acetylgalactosamine derivative **5** (Scheme 1).[11b] Chloropyranose **5** was generated from *N*-acetylgalactosamine **4**, which in turn was prepared via azido nitration of the corresponding glycal.[9a]

Unfortunately, in our hands, conversion of **4** to **6** via generation of chloro intermediate **5** failed to proceed with yields greater than 14% even when previously reported optimal conditions (3 equiv of allyl tributylstannane and 0.15 molar equiv of AIBN) were employed.[11b] Changes in temperature and different Lewis acids also failed to improve the yield of **6**.[12] Generation of **5** starting from D-galactosamine produced a similar result. Next, we explored the possibility of performing either a Keck allylation[11a] or photochemical-mediated radical allylation on bromo derivative **7** (Scheme 2). Unlike chloro intermediate **5**, we were able to purify bromo derivative **7** using silica gel chromatography. However, when **7** was subjected to a Keck allylation, the *only* product obtained was the bicyclic oxazoline. A photochemically-mediated allylation[13] improved the yield of **6** only slightly (42%). While this sequence seems attractive given that only one anomer is generated, preparation of the requisite starting material (2-acetamido-l,3,4,6-tetra-*O*-acetyl-2-deoxy-α,*β*-D-galactopyranose) is not trivial. For instance, preparation from D-galactosamine hydrochloride is only one step,[12a] but galactosamine is prohibitively expensive. Furthermore, the preparation from galactose pentaacetate requires five to seven steps,[9a] with tedious purifications by column chromatography. Consequently, this approach was abandoned. Given that Keck allylation of D-glucosamine derivatives[10] has been reported, we decided to combine different literature strategies and explore a novel synthetic route to access *C*-linked 2-deoxy-2-acetamido-α-D-galactopyranose derivatives **2** and **3** starting from commercially available and inexpensive D-glucosamine.

The proposed strategy installed an allyl group at the anomeric position and inverted the stereochemistry at *C*-4 late in the synthesis. The inversion of stereochemistry at *C*-4 of various pyranose derivatives[14a,b] has been well studied on *O*-linked oligosaccharides.[14c−e] In fact, a similar inversion has been reported in the synthesis of *C*-linked 2-acetamido-2-deoxy-α-D-galactose where the *C*-2 acetamido group was introduced using an oxime early in the synthesis.[8a] This approach was also attractive in that the *C*-3 hydroxyl group of **2** and **3** would be unprotected and available for a glycosidic coupling after the migration/epimerization sequence.

The first step in the synthesis centers on the preparation of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride **8** (Scheme 3) from D-glucosamine in 78% yield.[12b,c] Compound **8** was smoothly converted into *C*-linked derivative **9** via Keck allylation[10a] in 73% yield as a α/*β* mixture (12/1) of diastereomers. Optimized conditions for this allylation utilized 4.8 equiv of allyl tributylstannane and 0.3 equiv of AIBN in refluxing THF. While the α/*β* ratios are not as high as those previously reported,[12c] these conditions have advantages in that no polymer byproducts are observed. Furthermore, the amount of allylstannane in the reaction mixture can be reduce by half compared to the Bertozzi procedure.[7] Deacetylation furnished intermediate **1**, which was readily converted into *C*-linked 2-deoxy-2-acetamido-α-D-galactopyranose derivatives **2** and **3**.

With respect to the latter, the *C*-6 and *C*-3 hydroxyls were selectively protected using 2 equiv of pivaloyl chloride to furnish **12** in 92% yield as an inseparable α/*β* mixture (12:1). Inversion of the *C*-4 hydroxyl group was accomplished by treatment with triflic anhydride followed by stirring in water overnight leading to *C*-linked 2-acetamido-α-D-galactose derivative **3** in six steps and an overall yield of 44%. The inversion of the *C*-4 hydroxyl group has been studied using various adjacent esters[14] and is rationalized as outlined in Scheme 4. Intramolecular displacement of the triflate via the carbonyl oxygen of the pivaloyl group at *C*-2 produces dioxolenium ion intermediate **A**. Hydration occurs from the least hindered face to give hemi-ortho ester intermediate **B** after proton transfer. Intermediate **B** collapses

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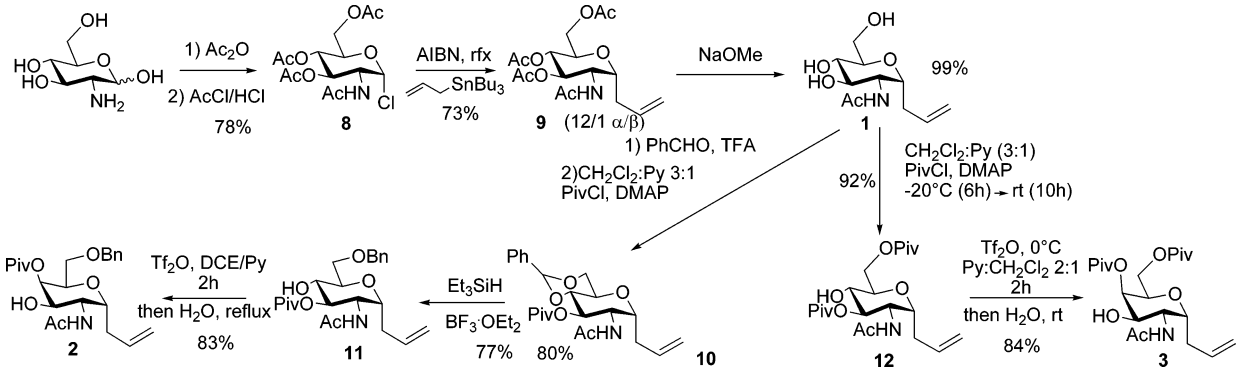
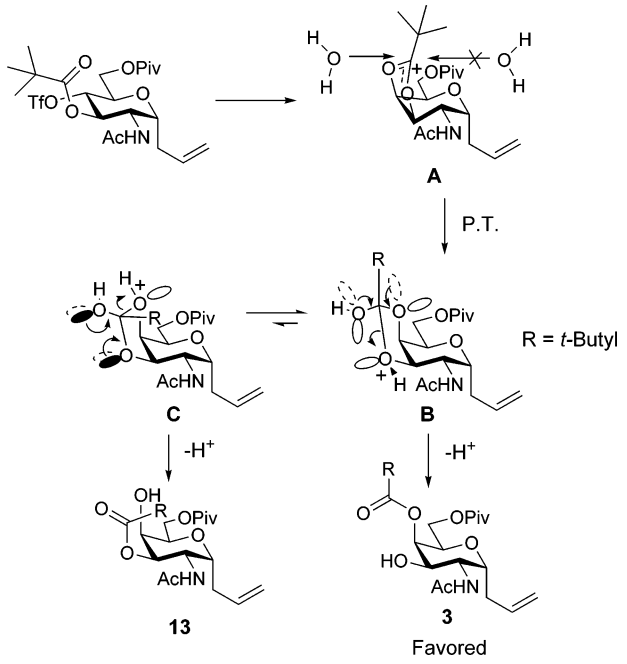
SCHEME 3. Synthesis of the *C*-Linked 2-Deoxy-2-acetamido-α-D-galactopyranose Derivatives 2 and 3



SCHEME 4. Stereoselectivity in the Ring Opening of Hemiortho ester Intermediates B and C



with the assistance of two primary stereoelectronic effects[15] resulting in formation of axial ester **3** as the α-anomer after purification by column chromatography. While the corresponding equatorial ester **13** can be formed via intermediate **C**, this product is not observed due to severe steric interactions between the *tert*-butyl group and the pyranose ring. In addition, collapse of intermediate **B** to form **3** furnishes an ester with the more stable "*Z*" conformation, while collapse of intermediate **C** produces an ester **13** with the less stable "*E*" ester conformation.

Preparation of orthogonally protected *C*-linked 2-deoxy-2-acetamido-α-D-galactopyranose derivative **2** is possible by conversion of **1** to benzylidene acetal **10** in 80% overall yield, via the benzylidene acetal intermediate (84% yield) and subsequent pivaloylation (95% yield). The diastereomeric mixture (α/β = 12:1) was used directly in the next step. Selective cleavage of benzylidene acetal[16] **10** using triethylsilane and boron trifluoride etherate afforded the α-anomer of **11** in 77% yield after purification by column chromatography. Inversion of the *C*-4 hydroxyl group and migration of the pivaloyl protecting group was accomplished by treatment with triflic anhydride in refluxing dichloroethane/water to afford orthogonally protected *C*-linked 2-deoxy-2-acetamido-α-D-galactopyranose derivative **2** in 83% yield. This route required only eight steps and produced **2** in 29% overall yield.

In summary, the synthesis of intermediates **2** and **3** can be accomplished in eight and six steps, respectively, with an overall yield of 29% and 44%. To date, the most efficient synthesis of **3** starting from D-glucose was carried out in 14 steps and 11% overall yield,[8a] and no syntheses using D-glucosamine have been reported. The synthetic sequence is amenable to large scale and consequently could be used to generate large quantities of **3** as well as differentially protected galactosamine derivative **2**. In both cases, a diastereomeric mixture (α/β anomers) is carried through until late into the synthesis where facile purification by column chromatography furnishes products with the desired α-configuration. Other attractive features of this approach include the fact that D-glucosamine is inexpensive, and all steps in the synthetic sequences are high yielding. In summary, this strategy affords a fast, efficient, and affordable synthesis of **2** and **3**, which are useful building blocks to synthesize different polysaccharide targets.

Experimental Section:

2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-d-glucopyranosyl chloride (8) (α:β = 3:1):[12a,b] white powder (26.4 g, 72.3 mmol, 78% yield); (α anomer) ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.16 (d, J = 3.6 Hz, 1H), 5.84 (d, J = 8.7 Hz, 1H), 5.29 (t, J = 10.1 Hz, 1H), 5,18 (t, J = 9.1 Hz, 1H), 4.54−5.15 (m, 1H), 4.25−4.23 (m, 2H), 4.10 (d, J = 10.5 Hz), 2.07 (s, 3H), 2.02 (bs, 6H), 1.96 (s, 3H); ^{13}C NMR (56 MHz, $CDCl_3$) δ 171.6, 170.8, 170.3, 169.3, 93.8, 71.1, 70.3, 67.1, 61.3, 53.7, 23.3, 20.9, 20.8, 20.7 LRMS (ES, NH_4^+) m/z 330.1 (M^+ − Cl).

3-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-d-glucopyranosyl)propene (9) (α: β = 12:1):[7] white powder (4.4 g, 11.9 mmol, 73% yield); (α anomer) ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.63 (d, J = 8.5 Hz, 1H), 5.82−5.74 (m, 1H), 5.16−5.10 (m, 3H), 4.94 (t, J = 7.5 Hz, 1H), 4.13 (dt, J_t = 10 Hz, J_d = 5 Hz, 1H), 4.08 (dd, J = 12, 7.5 Hz, 1H), 4.01 (dt, J_t = 3.1, J_d = 7.4 Hz, 1H), 3.93−3.89 (m, 1H), 3.72 (dt, J_t = 7.5 Hz, J_d = 3.5 Hz, 1H), 2.31−2.25 (m, 1H), 2.16−2.11 (m, 1H), 1.87 (bs, 9H), 1.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 170.7, 170.0, 169.2, 133.4, 117.6, 71.2, 70.3, 70.0, 68.2, 61.8, 50.4, 31.8, 23.1, 20.8, 20.8, 20.7; LRMS (ES, NH_4^+) m/z: 372.1 (M^+ + H), 394.1 (M^+ + Na), 765.1 ($2M^+$ + Na); HRMS m/z calcd for $C_{14}H_{20}NO_8$ (M^+ − allyl) 330.1189, found 330.1188.

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3-(2-Acetamido-4,6-benzylidene-2-deoxy-α-d-glucopyranosyl)propene (α: $\boldsymbol{\beta}$ **= 12:1):** white powder (172 mg, 518 μmol, 84% yield); ^{1}H NMR (500 MHz) (CD_3OD) δ 7.60−7.33 (m, 5H), 5.82−5.74 (m, 1H), 5.60 (s, 1H), 5.15 (dd, J = 1.5, 17 Hz, 1H), 5.07 (d, J = 10 Hz, 1H), 4.18−4.09 (m, 3H), 3.87 (t, J = 8.0 Hz, 3H), 3.71 (t, J = 10 Hz, 1H), 3.62−3.58 (m, 1H), 3.52 (t, J = 8.0 Hz, 1H), 2.61−2.55 (m, 1H), 2.32−2.27 (m, 1H), 1.98 (bs, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 172.1, 137.6, 132.5, 129.2, 128.4, 127.9, 127.5, 126.0, 115.7, 101.6, 83.0, 74.2, 68.7, 67.7, 63.4, 54.2, 30.3, 20.1; LRMS (CI, Isobutylene) m/z 334.2 (M^+ + H), 316 (M^+ − OH); HRMS m/z calcd for $C_{15}H_{18}NO_8$ (M^+ − allyl) 292.1185, found 292.1185.

3-(2-Acetamido-4,6-benzylidene-2-deoxy-3-pivaloyl-α-d-glucopyranosyl)propene (10) (α: $\boldsymbol{\beta}$ **= 12:1):** white powder (148 mg, 354 μmol, 95% yield); (α anomer) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.31 (m, 5H), 5.97 (d, J = 7.5 Hz, 1H), 5.75−5.61 (m, 1H), 5.54 (s, 1H), 5.19 (t, J = 10.2 Hz, 1H), 5.05 (d, J = 7.2 Hz, 1H), 5.01 (s, 1H), 4.42−4.34 (m, 1H), 4.31−4.20 (m, 2H), 3.76−3.66 (m, 2H), 3.60 (dd, J = 4.2, 9.6 Hz, 1H), 2.53−2.41 (m, 1H), 2.34−2.25 (m, 1H), 1.89 (bs, 3H), 1.17 (bs, 9H); ^{13}C NMR (56 MHz, $CDCl_3$) δ 180.4, 170.3, 137.2,133.6, 129.1, 128.4, 126.0, 117.8, 101.3, 79.9, 74.4, 70.1, 69.4, 64.1, 53.4, 39.3, 30.9, 27.2, 23.2; LRMS (CI, H^+) m/z 418 (M^+ + H), (M^+ + K) 458; HRMS m/z calcd for $C_{23}H_{31}NO_6$ (M^+) 417.2151, found 417.2151.

3-(2-Acetamido-6-*O*-benzyl-2-deoxy-3-pivaloyl-α-d-glucopyranosyl)propene (11) (α: $\boldsymbol{\beta}$ **> 98:2):** white powder (α-anomer, 33 mg, 87 μmol, 77% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.21 (m, 5H), 6.28 (d, J = 8.7 Hz, 1H), 5.81−5.67 (m, 1H), 5.09 (d, J = 17.1 Hz, 1H), 5.05 (d, J = 9.3 Hz, 1H), 4.99 (dd, J = 7.5, 9.6 Hz, 1H), 4.55 (d, J = 12 Hz, 1H), 4.49 (d, J = 12 Hz, 1H), 4.24−4.16 (m, 1H), 4.09−4.04 (m, 1H), 3.75−3.68 (m, 3H), 3.60−3.56 (m, 1H), 3.05 (bs, 1H), 2.53−2.41 (m, 1H), 2.34−2.19 (m, 1H), 1.87 (bs, 3H), 1.17 (bs, 9H); ^{13}C NMR (56 MHz, $CDCl_3$) δ 180.1, 170.1, 137.8, 134.0, 128.6, 128.0, 127.9, 117.5, 73.9, 72.9, 72.5, 71.8, 70.6, 70.5, 51.6, 39.2, 31.4, 27.2, 23.3 LRMS (CI, Isobutylene) m/z 420 (M^+ + H), 401 (M^+ − 18); HRMS m/z calcd for $C_{20}H_{28}NO_6$ (M^+ − allyl) 378.1916, found 378.1916.

3-(2-Acetamido-6-*O*-benzyl-2-deoxy-4-pivaloyl-α-d-galactopyranosyl)propene (2): white powder (2.32 g, 5.54 mmol, 83% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.27 (m, 5H), 6.10 (d, J = 7.5 Hz, 1H), 5.80−5.72 (m, 1H), 5.18 (t, J = 3.6 Hz, 1H), 5.08 (d, J = 13.2 Hz, 1H), 5.05 (d, J = 7.8 Hz, 1H), 4.53 (d, J = 12 Hz, 1H) 4.47 (d, J = 12 Hz, 1H), 4.35−4.31 (m, 1H), 4.17−4.13 (m, 1H), 4.08−4.03 (m, 1H), 3.95 (dd, J = 3.3, 7.2 Hz, 1H), 3.71 (dd, J = 6.8 Hz, J = 10.4 Hz, 1H), 3.51 (dd, J = 4.2 Hz, J = 10.5 Hz, 1H), 3.42 (bs, 1H), 2.36−2.30 (m, 1H), 2.18 (dt, J_t = 6.3 Hz, J_d = 15.3 Hz, 1H), 1.99 (bs, 3H), 1.16 (bs, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 171.3, 137.8, 134.2, 128.7, 128.1, 128.1, 117.7, 73.7, 73.7, 71.4, 69.0, 67.9, 67.8, 52.3, 39.3, 33.2, 27.3, 23.4; LRMS (CI, Isobutylene) m/z 420 (M^+ + H), 401 (M^+ − 18); HRMS m/z calcd for $C_{20}H_{28}NO_6$ (M^+ − allyl) 378.1916, found 378.1916.

3-(2-Acetamido-2-deoxy-6,3-dipivaloyl-α-d-glucopyranosyl)propene (12) (α: $\boldsymbol{\beta}$ **= 12:1):** compound **12** was obtained as an inseparable α/β mixture (1.54 g, 3.74, 92% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.18 (d, J = 8.4 Hz, 1H), 5.81−5.68 (m, 1H), 5.12−4.92 (m, 3H), 4.52 (dd, J = 6.3, 12 Hz, 1H), 4.23−4.11 (m, 3H), 3.76 (dt, J_t = 6,9 J_d = 2.7, 1H), 3.5 (t, J = 7.5 Hz, 1H), 2.47−2.37 (m, 1H), 2.29−2.22 (m, 1H), 1.91 (bs, 3H), 1.19 (bs, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.1, 179.6, 170.4, 134.1, 117.8, 72.9, 72.5, 72.1, 68.8, 63.2, 51.4, 39.4, 32.0, 27.6, 27.4, 23.6, 23.6; LRMS (ES, H^+) m/z 414.2 (M^+ + H).

3-(2-Acetamido-2-deoxy-6,4-dipivaloyl-α-d-galactopyranosyl)propene (3):[8a] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (d, J = 7.5 Hz, 1H), 5.81−5.68 (m, 1H), 5.13−5.03 (m, 3H), 4.59 (t, J = 10.2 Hz, 1H), 4.38−4.32 (m, 1H), 4.18−4.08 (m, 2H), 4.01 (dd, J = 3.6, 6.3 Hz, 1H), 3.98 (d, J = 3.9 Hz, 1H), 2.35−2.25 (m, 1H), 2.21−2.12 (m, 1H), 1.98 (bs, 3H), 1.21 (bs, 9H) 1.16 (bs, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 178.2, 171.3, 134.1, 117.3, 70.7, 68.7, 67.3, 61.0, 60.5, 52.2, 39.1, 38.7, 27.2, 27.2, 23.0, 23.0; LRMS (ES, H^+) m/z 414.1 (M^+ + H), 436.1 (M^+ + Na), 849.2 ($2M^+$ + Na).

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **2**, **3**, and **8**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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