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Large-Scale Synthesis of All Stereoisomers of a 2,3-Unsaturated *C*-Glycoside Scaffold

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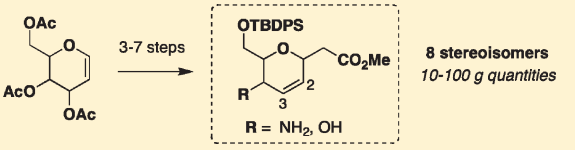
Supporting Information

ABSTRACT: All stereoisomers of a highly functionalized 2,3-unsaturated *C*-glycoside can be accessed in 10−100 g quantities from readily available starting materials and reagents in 3−7 steps. These chiral scaffolds contain three stereogenic centers along with orthogonally protected functional groups for downstream reactivity.



As a result of their synthetic versatility and high level of stereochemical diversity, carbohydrates have served as useful starting points for generating molecular diversity.[1] Carbohydrate-derived glycals in particular have been employed in multiple diversity-oriented synthesis (DOS) pathways.[2] Of interest to us was the utility of *C*-alkyl pseudoglycals for developing new build/couple/pair pathways in the context of library development.[3] In the present study, we focused on the synthesis of 2,3-unsaturated *C*-glycosides **1**−**4** (Figure 1) that incorporate four chemical handles: (1) an ester, (2) an alkene, (3) a primary alcohol, and (4) a secondary alcohol/primary amine, thereby providing a range of options for subsequent modifications and/or functional group pairing reactions.[4] As part of our design strategy we sought to develop methods for the preparation of all eight stereoisomers of the *C*-glycoside template to enable the development of stereo/structure−activity relationships.[3b,5] Herein we describe the preparation of *C*-glycosides **1**−**4** on large (10−100) scale.

To introduce the ester functionality at C-1 we explored a type I Ferrier rearrangement[6] of tri-*O*-acetyl-D- and L-glucal to access *C*-glycosides **1**−**4**. We elected to focus solely on optimizing the large-scale Ferrier reaction for the glucal series with the intention of accessing the galactal-derived material (**2**) *via* Mitsunobu inversion of the C-4 allylic alcohol.[7,8] This late stage epimerization strategy is an attractive alternative as it requires optimization of only one Ferrier reaction as well as access to only one unnatural carbohydrate.

Generally, Lewis acids such as $TiCl_4$,[9] $BF_3 \cdot Et_2O$,[10] and TMSOTf[6c] are employed in the Ferrier reaction to promote rearrangement to form the active glycosyl intermediate. Once activated, a variety of carbon-based nucleophiles have been utilized,[6d] including allyltrimethylsilane,[11] trimethylsilylcyanide,[12] and various silyl ketene acetals.[13] We utilized silylketene acetal **5** (1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene) as a nucleophile for generating the *C*-glycoside as it offers the advantage of installing an ester side chain without further modifications.

The stereochemical outcome of Lewis acid mediated *C*-glycosidation reactions is, in general, highly dependent on the conditions employed.[6d] For example, it has been reported that in the presence of $LiClO_4$ in Et_2O, addition of **5** to tri-*O*-acetyl-D-glucal leads predominantly to the formation of the α-anomer (ratio 3:1, α:β).[13b] In contrast, Csuk et al. reported that treatment of tri-*O*-acetyl-D-glucal with silylketene acetal **5** in the presence of TMSOTf in CH_2Cl_2 affords the β-anomer as the major product (ratio 1:2, α:β).[13c] Since we discovered that the α- and β-glycosides could be easily separated by silica gel

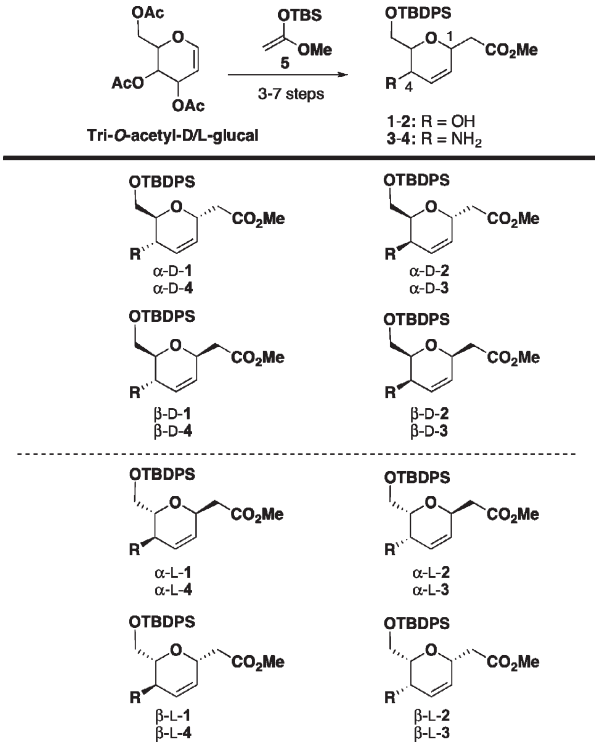


Figure 1. Full stereochemical matrix of *C*-glycosides **1**−**4**.

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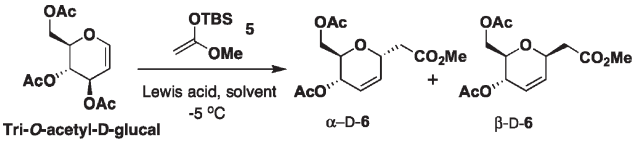
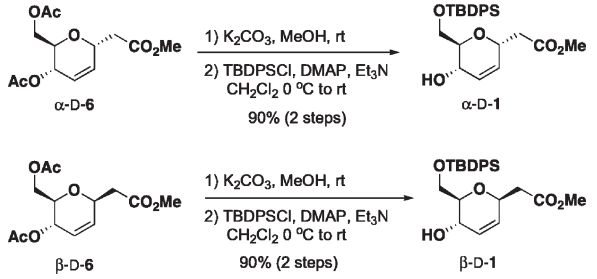
Table 1. Optimization of the Ferrier Reaction



entry	Lewis acid	solvent	ratio (α:β)[c]	yield (%)
1[a]	$BF_3 \cdot Et_2O$	CH_2Cl_2	1:2	45[d]
2[a]	TMSOTf	CH_2Cl_2	1:1.5	73[d]
3[a]	TMSOTf	CH_3CN	1.5:1	65[d]
4[a]	TMSOTf	CH_2Cl_2/CH_3CN (1:1)	1.2:1	72 (39:33)[e]
5[b]	TMSOTf	CH_2Cl_2/CH_3CN (1:1)	1.2:1	77 (42:35)[e]

[a] 1.2 equiv of Lewis acid, 0.15 M, 2.5 mmol scale. [b] 1.2 equiv of Lewis acid, 0.15 M, 735 mmol scale. [c] Ratio between α and β stereoisomers determinated by ^{1}H NMR. [d] Isolated yield for the mixture of α-D-**6** and β-D-**6**. [e] Isolated yield for each anomer (α-D-**6**:β-D-**6**)

Scheme 1. Deacetylation and TBDPS-Protection



chromatography and we required access to equal quantities of both anomers, we elected to develop reaction conditions that would achieve a closer to 1:1 α:β ratio.

As shown in Table 1, we evaluated the Ferrier reaction of tri-*O*-acetyl-D-glucal with **5** under a range of conditions, mainly focused on varying the nature of the Lewis acid and solvent. Use of $BF_3 \cdot Et_2O$ as the Lewis acid in CH_2Cl_2 led to the formation of *C*-glycoside **6** in 45% yield as a 1:2 mixture of anomers favoring the β-anomer (entry 1). Changing the Lewis acid to TMSOTf led to a higher isolated yield (73%) and a more favorable ratio of anomers of 1:1.5 (entry 2). Using TMSOTf we next investigated the effect of solvent on reaction selectivity. When CH_3CN was employed as a solvent the formation of the α-anomer was slightly favored (α/β ratio = 1.5:1) and a lower yield was obtained (65%, entry 3). The yield of the glycosidation reaction could be improved to 77% on large scale (200 g), using CH_2Cl_2 as a cosolvent (entries 4 and 5), providing a 1.2:1 mixture of anomers. The α/β isomers could be easily separated by silica gel chromatography to provide 42% of the α-anomer (α-D-**6**) and 35% of the β-anomer (β-D-**6**).[14] Deacetylation and subsequent selective 6-*O*-TBDPS protection provided allylic alcohols α-D-**1** and β-D-**1** in 90% yield over two steps (Scheme 1). This protocol was also applied to tri-*O*-acetyl-L-glucal[15] on 100-g scale to afford allylic alcohols α-L-**1** and β-L-**1**.[16]

We next investigated the conversion of α/β-D-**1** and α/β-L-**1** to the corresponding C-4 epimers *via* Mitsunobu inversion.[8] After varying parameters such as phosphine, solvent, and temperature, we arrived at a reliable and robust protocol for the Mitsunobu reaction. Focusing initially on the L-series, allylic

Scheme 2. Mitsunobu Inversion of C-4 Allylic Alcohol

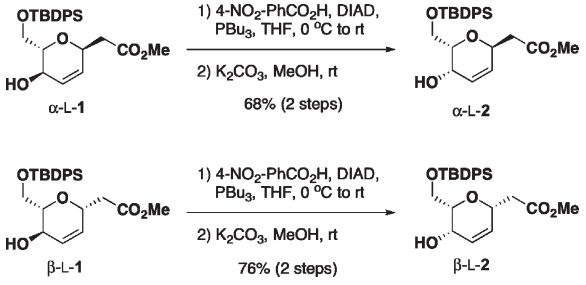
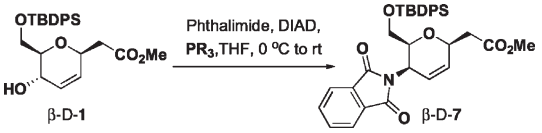


Table 2. Introduction of C-4 Amine *via* Mitsunobu Reaction



entry	SM	product	PR_3	yield (%)[a]
1	α-D-**1**	α-D-**7**	PPh_3	62
2	β-D-**1**	β-D-**7**	PPh_3	54
3	α-D-**1**	α-D-**7**	PBu_3	75
4	β-D-**1**	β-D-**7**	PBu_3	84
5	α-D-**2**	α-D-**8**	PPh_3	85
6	β-D-**2**	β-D-**8**	PPh_3	89

[a] Isolated yield after silica gel chromatography.

alcohols α-L-**1** and β-L-**1** were displaced with *p*-nitrobenzoic acid in the presence of PBu_3 and DIAD at 0 °C (Scheme 2). Hydrolysis of the resulting benzoates cleanly afforded the enantiopure allylic alcohols α-L-**2** and β-L-**2** in 68% and 76% yield over two steps, respectively. This procedure could then be applied to allylic alcohols α-D-**1** and β-D-**1** to afford glycosides α-D-**2** and β-D-**2**, thereby completing the full matrix of eight stereosiomers.

Conversion of allylic alcohols **1** and **2** to amines **3** and **4** was our final task to prepare the desired scaffolds. Introduction of an azido substituent as a precursor to the amine was initially considered using diphenylphosphoryl azide (DPPA)[17] or the zinc complex $Zn(N_3)_2Py_2$,[18] but neither of these options proved useful on multigram scale. In most cases, complex mixtures were obtained and the desired products were isolated in low yield. Successful introduction of the C-4 amine was achieved using phthalimide as a nitrogen nucleophile[19] *via* a Mitsunobu reaction (Table 2). Essential to reproducible high yields and selectivity was the use of PBu_3, which proved to be more efficient than triphenylphosphine (PPh_3) for the Mitsunobu reaction of glucal-based derivatives α-D-**1** and β-D-**1** to yield α-D-**7** and β-D-**7** in 75% and 84% yield, respectively (entries 3 and 4). Under these conditions, the formation of undesired S_N2' byproducts,[19,20] which had been observed during the PPh_3-mediated Mitsunobu reactions, was diminished. By contrast, for the C-4 epimeric glycosides (α-D-**2** and β-D-**2**) PPh_3 proved to be the optimal Mitsunobu reagent affording allylic phthalimides α-D-**8** and β-D-**8** in 85% and 89% yield (entries 5 and 6).[21]

Lastly, removal of the phthalimide protecting group was achieved *via* treatment with ethylenediamine[22] to afford allylic amines **3** and **4** (Scheme 3). Application of these conditions to all

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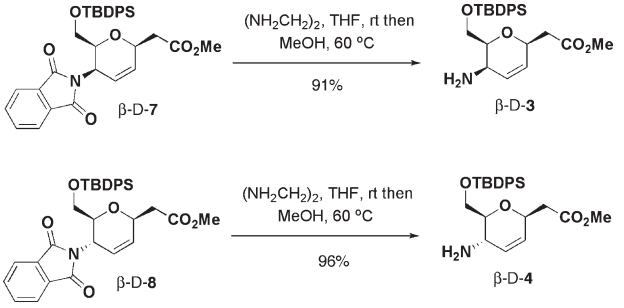
Scheme 3. Phthalimide Removal To Yield Amines 3 and 4



stereoisomers led to isolation of the desired eight allylic amines in high yield (>90%).(See Supporting Information.)

In summary, we have demonstrated that all possible stereochemical permutations of two highly functionalized *C*-glycosides can be prepared from tri-*O*-acetyl-D- and L-glucal on large scale. The use of these 16 pyran scaffolds for library synthesis is forthcoming.[23]

EXPERIMENTAL SECTION

Representative Procedure for Ferrier Reaction: *C*-Glycosides (1*R*,4*S*,5*R*)-(+)-α-D-6 and (1*S*,4*S*,5*R*)-(+)-β-D-6. Into a 5-L flask containing CH_2Cl_2 (1.8 L) and CH_3CN (2.0 L) was added. tri-*O*-acetyl-D-glucal (200 g, 735 mmol). The reaction mixture was cooled to −5 °C and silyl ketene acetal **5** (135 mL, 882 mmol, 1.2 equiv) was added slowly so as to maintain a constant temperature. A solution of TMSOTf (153 mL, 845 mmol, 1.1 equiv) in CH_2Cl_2 (200 mL) was added slowly *via* an addition funnel over 30 min. After complete addition of the Lewis acid, the bath temperature was kept at −5 °C for 2 h. The reaction mixture was poured slowly into sat. aq. $NaHCO_3$ solution (1.5 L). Excess solvent was removed *in vacuo* and the crude yellow mixture was extracted with CH_2Cl_2 (3 × 1 L). The combined organic layers were washed with brine and then dried over $MgSO_4$. Solvent was removed *in vacuo* and the crude material was purified by silica gel chromatography (hexanes/EtOAc 95:5 to 70:30) to afford first 73 g (35%) of β-D-**6** and then 88 g (42%) of α-D-**6** as yellow oils.[14]

Representative Procedure for Deacetylation/TBDPS Protection: Allylic Alcohol (1*S*,4*S*,5*R*)-(+)-β-D-1. To a 5-L flask containing β-D-**6** (95 g, 332 mmol) dissolved in 4:1 MeOH/CH_2Cl_2 (3.3 L) was added K_2CO_3 (2.30 g, 16.6 mmol, 0.05 equiv). The reaction mixture was stirred at rt for 100 min and then AcOH (3.80 mL, 66.4 mmol, 0.2 equiv) was added. Solvent was removed *in vacuo* and the product was filtered through a column of silica gel and eluted with 1 L of 70% hexanes/EtOAc followed by 3 L of straight EtOAc to provide the desired diol, which was isolated as a yellow oil (67 g, 99% yield).

To a 5-L flask containing diol (67 g, 332 mmol) was added CH_2Cl_2 (1.5 L) followed by Et_3N (93 mL, 664 mmol, 2.0 equiv) and DMAP (4.06 g, 33.2 mmol, 0.1 equiv). The reaction mixture was cooled to 0 °C and TBDPS-Cl (90 mL, 349 mmol, 1.05 equiv) was slowly added. The reaction was slowly warmed to rt and stirred for 46 h. The solvent was removed *in vacuo* and the crude oil was diluted with Et_2O and filtered through Celite to remove the resulting white solid. The mixture was concentrated and the resulting oil was redissolved in Et_2O, washed with sat. NH_4Cl and brine. After drying over $MgSO_4$, the solvent was removed *in vacuo*. The yellow oil was then purified by silica gel chromatography (hexanes/EtOAc 95:5 to 70:30) to afford allylic alcohol β-D-**1** as a colorless oil (131 g, 90% yield). $[\alpha]^{20}_D$ +4.1 (*c* 1.0, $CHCl_3$). IR (film) *ν* 2930, 2858, 1736, 1427, 1361, 1277, 1200, 1111, 1088; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.67 (m, 4H), 7.40 (m, 6H), 5.83 (m, 1H), 5.73 (m, 1H), 4.52 (m, 1H), 4.27 (m, 1H), 3.90 (dd, *J* = 10.2, 5.1 Hz, 1H), 3.76 (dd, *J* = 10.2, 7.2 Hz, 1H), 3.64 (s, 3H), 3.50 (m, 1H), 2.45 (m, 1H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 171.2, 135.8, 135.7, 132.9, 132.8, 130.1, 129.7, 129.6, 128.9, 128.0, 127.8, 77.7, 71.3, 66.7, 66.3, 51.9, 40.4, 27.0, 19.3; HRMS (ESI+) calcd for $C_{25}H_{32}O_5Si$ $[M + H_2O]^+$ 458.2363, found 458.2359

Representative Procedure for Mitsunobu Inversion at C-4: Allylic Alcohol (1*S*,4*S*,5*S*)-(+)-α-L-2. To an oven-dried 3-neck 1-L round-bottom flask equipped with a 150 mL oven-dried addition funnel and placed under argon was added a solution of (+)-α-L-**1** (29.0 g, 65.8 mmol, 1.0 equiv) and *p*-nitrobenzoic acid (12.1 g, 72.4 mmol, 1.1 equiv) in dry THF (370 mL). The mixture was degassed with argon (sparged for 30 min) and then cooled to 0 °C. PBu_3 (24.4 mL, 99.0 mmol, 1.5 equiv) was added *via* syringe to the reaction mixture and a solution of DIAD (19.5 mL, 99.0 mmol, 1.5 equiv) in degassed THF (70 mL) was slowly added *via* addition funnel over 30 min. After stirring at rt overnight, the solvents were removed *in vacuo* and the crude product was taken onto the next step without purification.

A 1-L round-bottom flask was charged with the crude *p*-nitrobenzoic ester as a solution in CH_2Cl_2 (130 mL) and MeOH (530 mL) and K_2CO_3 (455 mg, 3.3 mmol, 0.05 equiv) was added. The resulting dark orange mixture was stirred at rt for 2 h and then AcOH (0.57 mL, 9.9 mmol, 0.15 equiv) was added. After evaporation of the solvents, the crude product was dissolved in Et_2O and washed with sat. NH_4Cl aq. solution. The aqueous phase was extracted with Et_2O and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography (hexanes to 7:3 hexanes/EtOAc) to afford allylic alcohol α-L-**2** (19.8 g, 68% yield, over two steps) as a thick colorless oil. $[\alpha]^{20}_D$ +78.2 (*c* 1.5, $CHCl_3$); IR (film) *ν* 2930, 2856, 1735, 1428, 1361, 1272, 1200, 1100, 1086; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.67 (m, 4H), 7.39 (m, 6H), 6.08 (ddd, *J* = 9.9, 5.5, 1.5, 1H), 5.89 (dd, *J* = 10.1, 3.2 Hz, 1H), 4.73 (m, 1H), 3.96 (dd, *J* = 8.7, 6.1 Hz, 1H), 3.86 (dd, *J* = 8.8, 4.4 Hz, 1H), 3.77 (m, 1H), 3.62 (s, 3H), 2.66 (d, *J* = 15.2, 9.0 Hz, 1H), 2.43 (d, *J* = 15.3, 5.5 Hz, 1H), 1.85 (d, *J* = 8.9 Hz, 1H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 171.2, 135.8, 135.8, 133.6, 133.5, 131.8, 130.0, 129.9, 127.9, 127.8, 127.6, 72.4, 70.1, 63.6, 62.2, 52.0, 37.4, 27.0, 19.3; HRMS (ESI+) calcd for $C_{25}H_{32}O_5Si$ $[M + H]^+$ 441.2097, found 441.2100.

Representative Procedure for Phthalimide Mitsunobu Reaction: Allylic Phthalimide (1*S*,4*R*,5*S*)-(−)-β-D-7. To an oven-dried 3-neck 2-L round-bottom flask equipped with a 250-mL addition funnel was added a solution of (+)-β-D-**1** (46.5 g, 106 mmol, 1.0 equiv) and phthalimide (23.3 g, 158 mmol, 1.5 equiv) in dry THF (800 mL). The mixture was degassed with argon (sparged for 60 min) and then cooled to 0 °C. Tributylphosphine (35.0 mL, 137.1 mmol, 1.3 equiv) (or triphenylphosphine, 1.3 equiv) was added, followed by a solution of DIAD (28.7 mL, 137.1 mmol, 1.3 equiv) in degassed THF (200 mL) *via* addition funnel (over 60 min). After stirring at rt overnight, the solvent was removed *in vacuo* and the crude product was purified by silica gel chromatography (hexanes to 7:3 hexanes/EtOAc) to afford allylic phthalimide β-D-**7** (50.7 g, 84% yield). $[\alpha]^{20}_D$ −86.2 (*c* 1.0, $CHCl_3$). IR (film) *ν* 2926, 2856, 1716, 1352, 1112; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.75 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.67 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.57 (dd, *J* = 7.9, 1.4 Hz, 2H), 7.49 (dd, *J* = 7.9, 1.1 Hz, 2H), 7.37 − 7.25 (m, 4H), 7.17 (t, *J* = 7.5 Hz, 2H), 6.09 (d, *J* = 10.0 Hz, 1H), 5.78 (ddd, *J* = 10.0, 5.5, 2.0 Hz, 1H), 4.81 (br d, *J* = 3.6 Hz, 1H), 4.67 (br t, *J* = 6.9 Hz, 1H), 3.97 (td, *J* = 6.0, 3.5 Hz, 1H), 3.67 (s, 3H), 3.65 (dd, *J* = 10.8, 5.7 Hz, 3H), 3.59 (dd, *J* = 10.8, 6.5 Hz, 1H), 2.89 (dd, *J* = 15.8, 7.4 Hz, 1H), 2.71 (dd, *J* = 15.8, 6.5 Hz, 1H), 0.92 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 171.5, 167.8, 135.5, 135.4, 133.9, 133.8, 133.2, 133.1, 131.8, 129.5, 129.4, 127.5, 127.4, 123.1, 121.4, 75.9, 71.5, 63.6, 51.6, 44.7, 38.8, 26.6, 18.9; HRMS (ESI+) calcd for $C_{33}H_{35}NO_6Si$ $[M + Na]^+$ 592.2131, found 592.2134.

Representative Procedure for Phtalimide Removal: Allylic Amine (1*S*,4*R*,5*S*)-(−)-β-D-3. A 2-neck 2-L flask equipped with a reflux condenser was charged with the allylic phthalimide β-D-7 (25 g, 43.9 mmol,

1.0 equiv) in THF (44 mL) and 1,2-ethylenediamine (8.8 mL, 131.7 mmol, 3.0 equiv) was added at rt *via* syringe. The reaction mixture was stirred at rt for 2−4 h and then MeOH (835 mL) was added. The reaction mixture was stirred at 60 °C for 16 h, by which time a white precipitate had formed and the reaction was deemed complete (LC−MS). The solvents were partially evaporated and Et_2O was added to the crude product. After filtration through a pad of Celite, the solvents were partially evaporated and the process was repeated once more to remove any excess of white byproduct. The solution was evaporated to dryness and the crude product was purified by silica gel chromatography (CH_2Cl_2/MeOH 100:0 to 90:10) to afford allylic amine β-D-**3** as a pale yellow oil (17.6 g, 91% yield). $[\alpha]^{20}_D$ −44.2 (*c* 1.2, $CHCl_3$). IR (film) *v* 2930, 2856, 1740, 1428, 1168, 1112; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 6.6 Hz, 2H), 7.63 (d, *J* = 6.5 Hz, 2H), 7.42 − 7.35 (m, 6H), 6.02 (dd, *J* = 9.8, 5.6 Hz, 1H), 5.69 (d, *J* = 10.1 Hz, 1H), 4.46 (br t, *J* = 5.8 Hz, 1H), 3.82 (dd, *J* = 14.6, 10.0 Hz, 1H), 3.73 − 3.66 (m, 2H), 3.63 (s, 3H), 3.24 (br d, *J* = 5.2 Hz, 1H), 2.50 (dd, *J* = 15.4, 7.5 Hz, 1H), 2.43 (dd, *J* = 15.4, 5.8 Hz, 1H), 1.21 (br s, 2H), 1.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 135.5, 133.3, 133.2, 130.0, 130.0, 129.7, 129.6, 127.7, 127.6, 77.2, 71.9, 62.7, 51.6, 45.0, 40.0, 26.8, 19.1; HRMS (ESI+) calcd for $C_{25}H_{33}NO_4Si$ $[M + H]^+$ 440.2257, found 440.2252.

■ ASSOCIATED CONTENT

Supporting Information. Complete experimental procedures and characterization for all new compounds, including copies of ^{1}H and ^{13}C NMR spectra. Crystallographic information files in CIF format of compounds β-D-**7** and α-D-**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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