Note

De novo asymmetric synthesis of a 6-O-methyl-D-glycero-L-gluco-heptopyranose-derived thioglycoside for the preparation of Campylobacter jejuni NCTC11168 capsular polysaccharide fragments

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De novo asymmetric synthesis of a 6-*O*-methyl-D-*glycero*-L-*gluco*-heptopyranose-derived thioglycoside for the preparation of *Campylobacter jejuni* NCTC11168 capsular polysaccharide fragments

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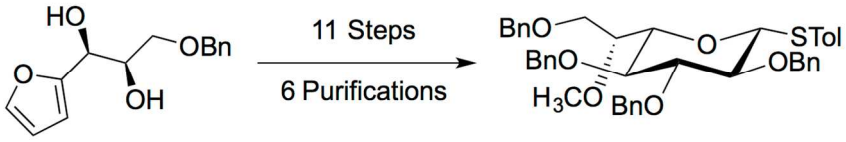
Graphical Abstract:



Abstract:

An enantioselective *de novo* synthesis of a thioglycoside derivative of the 6-*O*-methyl-D-*glycero*-L-*gluco*-heptopyranose residue found in the *Campylobacter jejuni* NCTC11168 (HS:2) capsular polysaccharide is reported. The compound is obtained from a furfural-derived chiral diol in 11 steps. Notably, compared to the only previous synthesis of this molecule, this approach significantly reduces the number of purification steps required to obtain the target.

A common cause of bacterial gastroenteritis worldwide is infection by the Gram-negative bacterium *Campylobacter jejuni*.[1] The symptoms associated with a *C. jejuni* infection range from mild to severe diarrhea, and in some cases the disease can lead to a life-threatening neurological disorder, Guillain–Barré syndrome.[2,3] All campylobacter species produce a species-specific capsular polysaccharide (CPS) that plays key roles in the interaction between the organism, host, and environment. For instance, *C. jejuni* CPSs have been demonstrated to be important for bacterial virulence, serum resistance, and colonization.[4,5] Vaccines generated from *C. jejuni* CPSs are in clinical trials[6,7] and interfering with the biochemical pathways that produce these glycans may lead to novel approaches for treating these infections.

In ongoing efforts toward understanding campylobacter CPS biosynthesis,[8,9] we have focused our attention on *C. jejuni* NCTC11168 (HS:2). This organism produces a CPS with a tetrasaccharide repeating unit containing a number of unusual motifs (Figure 1).[10,11] These include phase-variable modifications (e.g., methyl phosphoramidates, aminoglycerol amides, *O*-methylations) and rare monosaccharides, in particular, an *N*-acetyl-galactosamine residue in the furanose ring form and a 6-*O*-methyl-heptose residue with the D-*glycero*-L-*gluco* stereochemistry.

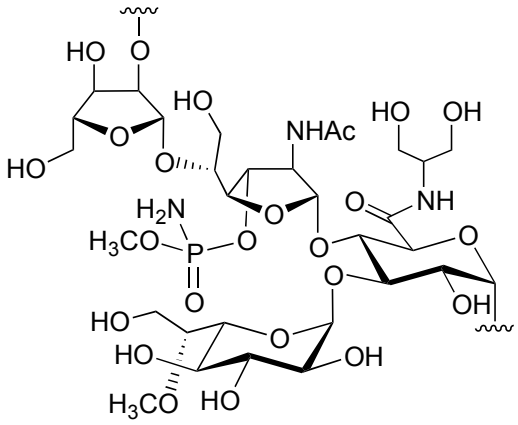


Figure 1. Repeating unit of CPS from *C. jejuni* 11168(HS:2)

Probing the biosynthetic enzymes involved in the assembly of this glycan requires the synthesis of fragments of this structure and in turn access to these unusual carbohydrate derivatives. In a previous publication, we described the synthesis of two derivatives of the heptose residue that could be used as donors in glycosylation reactions: thioglycoside **1** and trichloroacetimidate **2** (Figure 2).[12] The two key steps in that route involved a diastereoselective divinylzinc addition to aldehyde **3** (obtained from D-galactose) followed by ozonolysis of **4**; subsequent modifications led to **1** and **2**. The preparation of **1** and **2** were achieved in 16 and 18 steps, respectively, from D-galactose. Although this approach could be used to prepare gram quantities of these compounds, the number of chromatographic purification steps led us to consider other more efficient approaches.

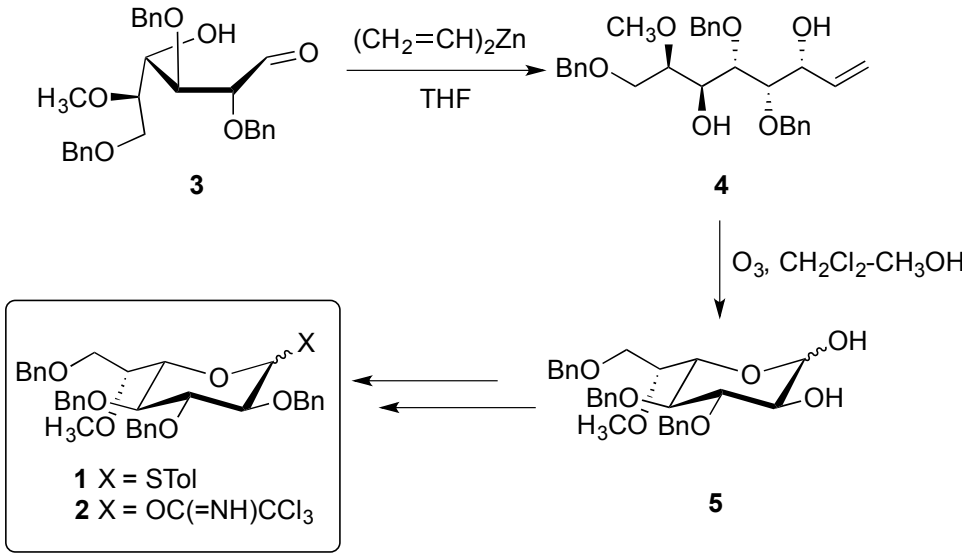


Figure 2. Key steps in a previous route to D-*glycero*-L-*gluco*-heptose-based glycosyl donors **1** and **2**.[12]

Previous reports from the Ogasawara and O'Doherty groups have described the synthesis of D- and L-hexopyranoses from furfural through pathways involving either diol **6** and enone **7**,[13] or pyranone **8** (Figure 3A).[14-17] We envisioned that **1** (and in turn **2**) could be synthesized via a combination of these approaches (Figure 3B). Heptose **1** could be obtained from pyranone **9** through selective reduction and oxidation chemistry. Pyranone **9**, already seven carbons in length, could be produced from the benzyl protected diol **6**[18] after a regioselective methylation, an Achmatowicz reaction, and a selective pivaloylation. We describe here the successful implementation of this approach (Scheme 1).

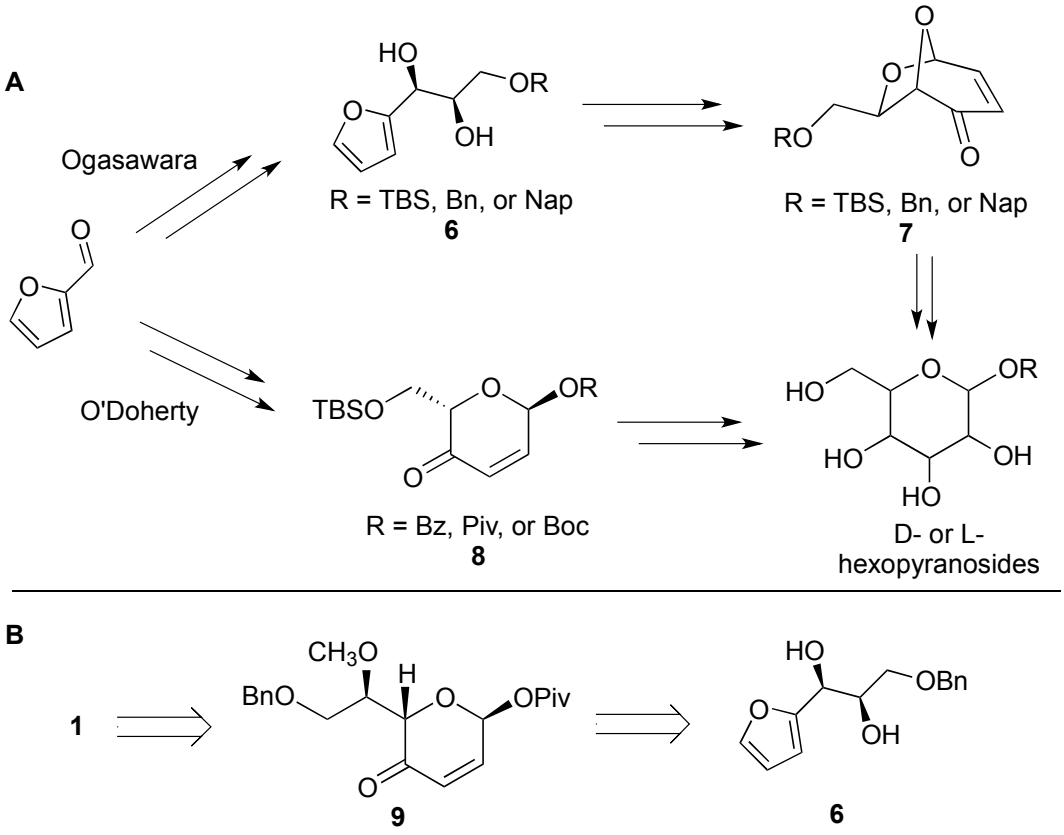
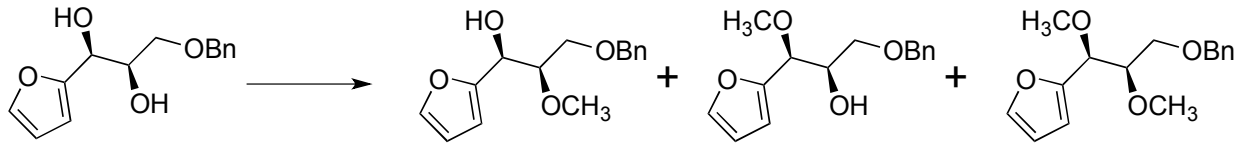


Figure 3. A. Previous syntheses of hexopyranoses from furfural. B. Retrosynthesis analysis of **1**.

After synthesizing the benzyl-protected diol **6**,[13,18] which can be easily obtained on a multi-gram scale in four steps and a 48% overall yield from furfural, various conditions for

regioselective methylation were explored (Table 1). The 2-aminoethyl diphenylborinic acid catalyzed alkylation, described by Taylor and coworkers, proved to be the optimal method although no regioselectivity was observed (Scheme 1).[19,20] This approach showed complete (TLC) conversion of **6** into **10a** and **10b**, albeit in an approximately 1:1 inseparable mixture as determined by ^{1}H NMR spectroscopy. Subsequent Achmatowicz reaction of **10a** and **10b** using NBS as the oxidant in the presence of NaOAc and $NaHCO_3$, followed by an α-selective pivaloylation afforded pure pyranone **9** in 38% yield over three steps (average yield of 72% per step) from **6**. The structure of pyranone **9** is supported by $J_{1,2}$ coupling constant value of 3.7 Hz, which closely matches the 1,2-allylic coupling constants in similar pyranones.[16,21]

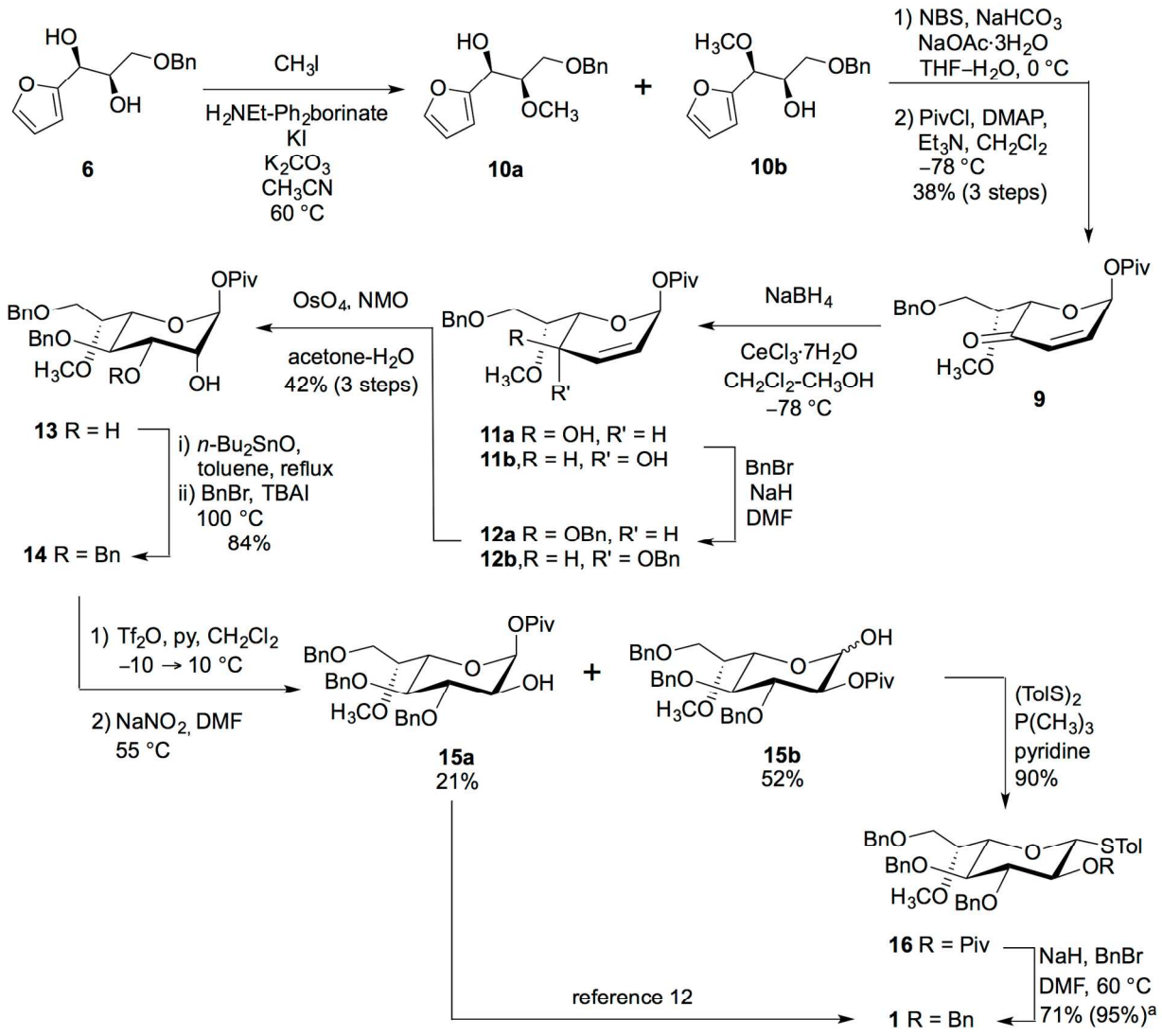
Table 1. Conditions explored for the regioselective methylation of **6**.



6 **10a** **10b** **10c**

entry	conditions	Product 10a:10b:10c	yield
1	i) nBu$_2$SnO, toluene, reflux ii) CH_3I (1.5 equiv), 40 °C	-----	0%
2	i) nBu$_2$SnO, toluene, reflux ii) CH_3OTf (1.2 equiv)	0:1:0[a]	~10%[b,c]
3	i) nBu$_2$SnO, toluene, reflux ii) CH_3OTf (1.2 equiv), 0 °C	~1:4:0[a]	55%[b]
4	CH_3I (8 equiv), AgO, CH_3CN, reflux	~2:3:0[a]	~22%[d]
5	CH_3I (1.5 equiv), NaH, THF	~0:0:1[e]	n.d.
6	CH_3I (3 equiv), K_2CO_3, borinate,[f] CH_3CN, 60 °C	~1:1:0[a]	95%[b]

[a] product ratio determined by ^{1}H NMR spectroscopy. [b] isolated yield. [c] unknown impurity present. [d] yield based on ^{1}H NMR spectroscopy. [e] TLC analysis showed dimethylation to be the favored adduct with little to no monomethylation product. [f] borinate = 2-aminoethyl diphenylborinate.

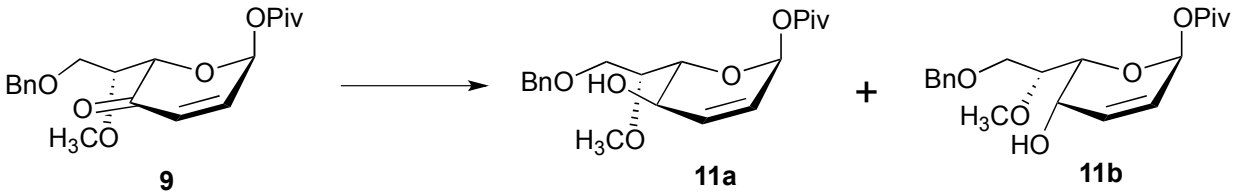


Scheme 1. Synthetic scheme for the asymmetric *de novo* synthesis of **1**. [a]Yield based on recovered starting material and product lacking a Piv group.

The stereoselective reduction of pyranone **9** was then explored (Table 2). Despite precedence for the stereoselective reduction of similar substrates that lack an additional substituent at C-6,[14,16,17,21-23] the reduction of **9** suffered from modest stereoselectivity albeit in favor of the desired diastereomer **11a**. Although complete stereoselective reduction was achieved using L-selectride, substantial amounts of the 1,4-conjugate addition product were also observed.

It was subsequently discovered that the best results were obtained by Luche reduction of **9** at −78 °C. Under these conditions, an approximately 2:1 inseparable mixture of diastereomeric alcohols **11a/11b**, in which the desired isomer **11a** predominated, was formed.

Table 2. Conditions explored for the stereoselective reduction of **9**.



9 **11a** **11b**

entry	conditions (equiv.)	solvent	temp	product[d] 11a:11b	yield
1	$NaBH_4$ (1) $CeCl_3 \cdot 7H_2O$ (0.5)	1:1 CH_2Cl_2–CH_3OH	0 °C	~1:2	86%[a]
2	$NaBH_4$ (1) $CeCl_3 \cdot 7H_2O$ (0.5)	1:1 CH_2Cl_2–CH_3OH	–30 °C	~1:1	90%[a]
3	$NaBH_4$ (1) $CeCl_3 \cdot 7H_2O$ (0.5)	1:1 CH_2Cl_2–CH_3OH	–78 °C	~2:1	89%[a]
4	$NaBH_4$ (1) $CeCl_3 \cdot 7H_2O$ (0.2)	1:1 CH_2Cl_2–CH_3OH	–78 °C	~7:2	~55%[a,b,c]
5	L-Selectride (1)	THF	–78 °C	1:0	~40%[a,b,c]
6	$NaBH_4$ (1)	THF	–78 °C	~4:1	~35%[a,b,c]

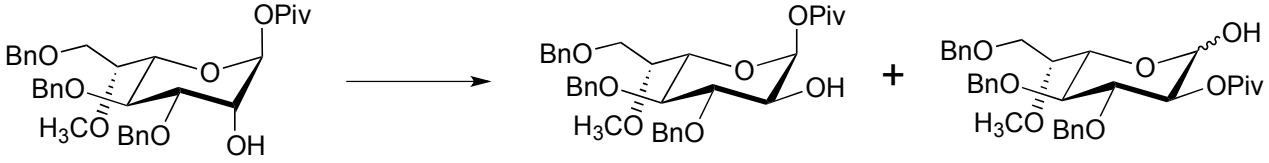
[a] isolated yield. [b] 1,4-conjugate addition observed. [c] impurity of unknown structure present. [d] product ratio determined by ^{1}H NMR spectroscopy.

Benzylation of this mixture of **11a**/**11b** provided **12a/12b**. Although purification of the diastereomers can be achieved at this step, we instead carried the mixture forward. Dihydroxylation proceeded selectively from the face opposite that of the pivalate ester to afford **13** in 42% yield over three steps from **9** (average yield of 75% per step). Importantly, only diastereomer **12a** underwent dihydroxylation, presumably due to the pseudoaxial orientation of the groups at C-1 and C-4 in **12b**. This fortuitous chemoselectivity significantly eased purification of the desired product. Tin-catalyzed alkylation of diol **13** afforded the desired 3,4,7-

tri-*O*-benzylated adduct **14** in 84% yield. The $J_{3,4}$ and $J_{4,5}$ coupling constant values of 9.5 and 9.5 Hz supports the correct configuration of C-2, C-3, and C-4 stereocenters in alcohol **14**.

Subsequent stereoinversion of C-2 alcohol was achieved by triflation followed by treatment with sodium nitrite in DMF at 60 °C. These conditions produced a 73% yield of an approximately 2:5 mixture of **15a** and **15b**, which was formed through migration of the pivalate ester from O-1 to O-2. The respective $J_{1,2}$ coupling constant values of 3.6, 3.7, and 8.3 Hz of alcohols **15a**, **15bα**, and **15aβ** supports the stereoinversion at C-2. Other conditions (Table 3) were explored to either prevent or further promote the migration of the pivalate group, but these conditions also afforded a mixture of regioisomers. Alternative stereoinversion approaches, such as a Mitsunobu reaction or oxidation to the ketone and subsequent reduction either did not produce the desired compound, or were poorly selective. Regioisomers **15a** and **15b** were then treated with *p*-tolyl disulfide and trimethylphosphine to afford **16** (**15a** remained unreactive) in 90% yield, based on the amount of **15b** in the mixture. Thioglycoside **16** was then treated with excess NaH in the presence of benzyl bromide at 60 °C. Under these conditions, we could conveniently both remove the pivalate ester and protect the resulting alcohol as a benzyl ether leading, in 95% yield, to the heptose thioglycoside **1**. The data for 1 matched that previously reported.[12] The minor adduct formed in the inversion step, **15a**, could also be converted to **1** following the original protocol published after acetylation of the alcohol.[12]

Table 3. Conditions explored to invert C-2 stereochemistry in **14**.



14 **15a** **15b**

entry	conditions	product obtained	yield
1	1) Swern oxidation 2) $NaBH_4$, CH_2Cl_2–CH_3OH, –78 °C	~3:2[b] **15a–14**	88%[a]
2	1) Tf_2O, pyridine, CH_2Cl_2, –10 to 10 °C 2) $NaNO_2$, DMF, 60 °C	~2:5[b] **15a–15b**	73%[a]
3	1) Tf_2O, pyridine, CH_2Cl_2, –10 to 10 °C 2) H_2O, DMF	~4:1[b] **15a–15b**	79%[a]

[a] isolated yield. [b] product ratio determined by ^1H NMR spectroscopy.

In summary, we describe the *de novo* asymmetric synthesis of the D-*glycero*-L-*gluco*-heptose-derived thioglycoside **1**. This route provides the target molecule, which is a useful donor in the synthesis of *C. jejuni* HS:2 CPS glycoconjugates, more efficiently than the only other previously reported synthesis of this compound or any other D-*glycero*-L-*gluco*-heptose derivative.[12] Thioglycoside **1** was produced in 11 steps from the easily prepared benzyl protected diol **6** (15 steps from furfural), compared to 16 steps from D-galactose. Importantly, the route described here significantly reduced the number of purification steps required. From **6**, only six purification steps (via flash chromatography) were used, compared to 15 steps required by our previously reported route starting from D-galactose. The reduction in the number of required purifications, significantly facilitates the large-scale synthesis of **1**. Efforts are currently underway to use **1**, and the related trichloroacetimidate **2**, in the preparation of glycoconjugates containing this monosaccharide.

Experimental Section

General Experimental Methods. All reagents were purchased from commercial sources and were used without further purification unless noted. Solvents used in reactions were purified by successive passage through columns of alumina and copper under argon. Unless stated otherwise, all reactions were carried out at room temperature and monitored by TLC on Silica Gel G-25 F_{254} (0.25 mm). TLC spots were detected under UV light and/or by charring with a solution of *p*-anisaldehyde in ethanol, acetic acid and H_2SO_4. Column chromatography was performed on Silica Gel 60 (40–60 μm). In some cases, a dry loading technique (substrate adhered to silica, solvent removed, then loaded on column) was used for purification. Solvents were evaporated under reduced pressure on a rotary evaporator. ^{1}H NMR spectra were recorded using 400, 500, or 600 MHz NMR instruments and were referenced to residual proton signal of $CDCl_3$ (7.26 ppm). ^{13}C NMR spectra were recorded using 126 MHz (cold probe) NMR instrument and were referenced to residual ^{13}C signals of $CDCl_3$ (77 ppm). ^{1}H NMR data are reported as though they were first order, and peak assignments were made on the basis of 2D-NMR (^{1}H –^{1}H COSY and HSQC) experiments. ESI-MS spectra (time-of-flight analyzer) were recorded on samples dissolved in THF or CH_3OH and added NaCl. Optical rotations were measured at 22 ± 2 °C at the sodium D line (589 nm) and are in a microcell (10 cm, 1 mL) in units of deg·mL(dm·g)$^{-1}$.

(*R*)-2-(benzyloxy)-1-((2*S*,6*S*)-3-oxo-6-(pivaloyloxy)-3,6-dihydro-2*H*-pyran-2-yl)ethyl pivalate (9). To benzyl protected diol **6** (1 g, 4.03 mmol) under argon were sequentially added 2-aminoethyl diphenylborinate (181 mg, 0.806 mmol), K_2CO_3 (613 mg, 4.43 mmol), anhydrous CH_3CN (40 mL), and CH_3I (5.55 mL, 12.09 mmol). The reaction mixture was heated to 60 °C and stirred for 16 h. The mixture was poured over a solution of brine (20 mL) and H_2O (20 mL),

then extracted with EtOAc (3 × 40 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. To the resulting residue were sequentially added $NaHCO_3$ (677 mg, 8.06 mmol), $NaOAc·3H_2O$ (548 mg, 4.03 mmol), and a 4:1 THF–H_2O solution (40 mL). The mixture was cooled to 0 °C and NBS (932 mg, 5.24 mmol) was added in portions over ~20 min. For optimal results either newly purchased or freshly recrystallized (from H_2O) NBS should be used. After complete addition of the NBS, the reaction mixture was stirred at 0 °C for 1.5 h. The excess NBS was quenched by addition of a saturated aqueous $Na_2S_2O_3$ solution (20 mL), stirred for ~20 min, poured over a saturated aqueous $NaHCO_3$ solution (20 mL), and then extracted with EtOAc (3 × 40 mL). The organic layers were combined and then washed with a minimal amount of brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was dried under vacuum in the presence of P_2O_5 for ~2 h. To the residue under argon were added anhydrous CH_2Cl_2 (20 mL), Et_3N (1.69 mL, 12.09 mmol) and DMAP (25 mg, 0.20 mmol). The mixture was cooled to –78 °C, then PivCl (744 μL, 6.05 mmol) was added dropwise over ~3 min. The reaction mixture was stirred at –78 °C for 1.5 h. The reaction mixture was poured over a saturated aqueous NH_4Cl solution (30 mL) and extracted with CH_2Cl_2 (100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography in 4:1→3:1 hexanes–EtOAc to afford **9** (555 mg, 38%) as a pale yellow oil. R_f 0.37 (3:1 hexanes–EtOAc); $[\alpha]_D$ +55.4 (1.0 *c*, $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.38–7.29 (m, 5H, Ar), 6.95 (dd, 1H, *J* = 10.3, 3.7 Hz, H-2), 6.63 (d, 1H, *J* = 3.7 Hz, H-1), 6.30 (d, 1H, *J* = 10.3 Hz, H-3), 4.71 (d, 1H, *J* = 1.8 Hz, H-5), 4.57 (d, 1H, *J* = 12.4 Hz, PhC$\underline{H}_2$O) 4.55 (d, 1H, *J* = 12.3 Hz, PhC$\underline{H}_2$O), 4.19 (ddd, 1H, *J* = 8.0, 5.9, 2.0 Hz, H-6), 3.71 (dd, 1H, *J* = 9.4, 5.7 Hz, H-7a), 3.66 (dd, 1H, *J* = 9.4, 8.2 Hz, H-7b), 3.43 (s, 3H, OC$\underline{H}_3$), 1.20 (s, 9H, C(C$\underline{H}_3$)$_3$); ^{13}C NMR (126 MHz; $CDCl_3$): δ 194.1 (C4=O), 176.7 (C=O), 142.2 (C2), 138.0 (Ar), 129.2 (C3), 128.4 (Ar),

127.6 (Ar), 127.4 (Ar), 87.0 (C-1), 77.8 (C-6), 75.8 (C-5), 73.4 (Ph<u>C</u>H_2O), 67.3 (C-7), 59.8 (O<u>C</u>H_3), 39.2 (<u>C</u>$(CH_3)_3$, 27.0 (C(<u>C</u>$H_3)_3$; HRMS (ESI) Calc. for (M + Na) $C_{20}H_{26}NaO_6$: 385.1622. Found 385.1620. *Note: When scale was increased to 30 mmol, the yield decreased to 26% over 3 steps.

4,7-Di-*O*-benzyl-6-*O*-methyl-1-*O*-pivolyl-D-*glycero*-α-L-*manno*-heptopyranose (13). To pyranone **9** (1.3 g, 3.59 mmol) was added an anhydrous 1:1 CH_2Cl_2–CH_3OH solution (18 mL); $CeCl_3 \cdot 7H_2O$ (670 mg, 1.80 mmol) was then added. The mixture was stirred, with sonication if necessary, until a homogenous solution was achieved. The mixture was cooled to –78 °C and then $NaBH_4$ (136 mg, 3.59 mmol) was added in five portions over ~5 min. The reaction mixture was stirred at –78 °C for 30 min before being diluted with Et_2O (10 mL). A saturated aqueous $NaHCO_3$ solution (10 mL) was added and the mixture was then extracted with Et_2O (3 × 40 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was dried under vacuum in the presence of P_2O_5 for ~3 h. To the residue under argon was added anhydrous DMF (26 mL) and BnBr (1.12 mL, 7.18 mmol). The mixture was stirred and NaH (215 mg, 5.39 mmol) was added in three portions over 0.5 h before being stirred for an additional 1.5 h. Excess NaH was quenched by addition of HOAc (150 μL). The mixture was concentrated and the resulting residue was diluted with EtOAc (100 mL) and washed with a solution of brine (15 mL) and then H_2O (15 mL). The organic layer was then concentrated. To the residue were sequentially added a 5:1 acetone–H_2O solution (30 mL), NMO (630 mg, 5.39 mmol), and a 5% OsO_4 in *t*BuOH (600 μL, ~3 mol%). The reaction mixture was stirred for 30 h and the mixture was poured over a solution of saturated aqueous $Na_2S_2O_3$ solution diluted with equal volume of H_2O (60 mL), then extracted with EtOAc (3 × 50 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by flash chromatography in 1:1→2:1 EtOAc–hexanes to afford diol **13** (739 mg, 42%) as

a clear oil. R_f 0.43 (2:1 EtOAc–hexanes); $[\alpha]_D$ –26.6 (1.0 *c*, $CHCl_3$); ^{1}H NMR (498 MHz; $CDCl_3$): δ 7.43–7.29 (m, 10H, Ar), 6.12 (d, 1H, *J* = 1.7 Hz, H-1), 4.90 (d, 1H, *J* = 11.3 Hz, PhC$\underline{H}_2$O), 4.75 (d, 1H, *J* = 11.3 Hz, PhC$\underline{H}_2$O), 4.53 (s, 2H, PhC$\underline{H}_2$O), 3.97–3.89 (m, 3H, H-2, H-3, H-4), 3.83 (ddd, 1H, *J* = 6.0, 6.0, 1.7, H-6), 3.81 (dd, 1H, *J* = 9.2, 1.3 Hz, H-5), 3.75 (dd, 1H, *J* = 9.7, 6.0 Hz, H-7), 3.60 (dd, 1H, *J* = 9.7, 6.1 Hz, H-7b), 3.49 (s, 3H, OC$\underline{H}_3$), 2.98 (br s, 1H, C2-O$\underline{H}$), 2.63 (d, 1H, *J* = 6.2 Hz, C3-O$\underline{H}$), 1.16 (s, 9H, C(C$\underline{H}_3$)$_3$); ^{13}C NMR (126 MHz; $CDCl_3$): δ 176.1 (C=O), 138.2 (Ar), 138.1 (Ar), 128.7 (Ar), 128.4 (Ar), 128.1 (2C, Ar, Ar), 127.6 (Ar), 127.5 (Ar), 93.0 (C-1), 76.5 (C-6), 75.0 (Ph$\underline{C}$H$_2$O), 74.9 (C-3/C-4), 73.4 (Ph$\underline{C}$H$_2$O), 72.9 (C-5), 72.2 (C-3/C-4), 70.1 (C-2), 69.3 (C-7), 58.6 (O$\underline{C}$H$_3$), 39.0 ($\underline{C}$(CH$_3$)$_3$), 27.0 (C($\underline{C}$H$_3$)$_3$; HRMS (ESI) Calc. for (M + Na) $C_{27}H_{36}NaO_8$: 511.2302. Found 511.2299.

3,4,7-Tri-*O*-benzyl-6-*O*-methyl-1-*O*-pivolyl-D-*glycero*-α-L-*manno*-heptopyranose (14). To diol **13** (1.5 g, 3.07 mmol) in anhydrous toluene (30 mL), *n*Bu_2SnO (841 mg, 3.38 mmol) was added. A Dean–Stark apparatus was attached, filled w/ toluene, and the mixture was heated to reflux for 8 h. The mixture was cooled to room temperature, the Dean–Stark apparatus was removed and then *n*Bu_4NI (1.25 g, 3.38 mmol) and BnBr (450 μL, 3.79 mmol) were added. The reaction mixture was heated to 100 °C and stirred for 17 h, before being cooled and then poured over a solution of saturated aqueous $Na_2S_2O_4$ solution (30 mL) and H_2O (30 mL) and then extracted with EtOAc (120 mL). The organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was then purified by flash chromatography in 3:2→1:1 hexanes–EtOAc to afford **14** (1.5 g, 84%) as clear viscous oil. R_f 0.50 (1:1 hexanes–EtOAc); $[\alpha]_D$ –41.3 (1.0 *c*, $CHCl_3$); ^{1}H NMR (498 MHz; $CDCl_3$): δ 7.39–7.28 (m, 15H, Ar), 6.14 (d, 1H, *J* = 1.8 Hz, H-1), 4.98 (d, 1H, *J* = 10.9 Hz, PhC$\underline{H}_2$O), 4.75 (d, 1H, *J* = 11.8 Hz, PhC$\underline{H}_2$O), 4.73 (d, 1H, *J* = 11.7 Hz, PhC$\underline{H}_2$O), 4.69 (d, 1H, *J* = 10.9 Hz, PhC$\underline{H}_2$O), 4.52 (app. s, 2H,

PhC$\underline{H}_2$O), 4.12 (dd, 1H, J = 9.5, 9.5 Hz, H-4), 3.90–3.80 (m, 4H, H-2, H-3, H-5, H-6), 3.75 (dd, 1H, J = 9.7, 6.0 Hz, H-7a), 3.59 (dd, 1H, J = 9.7, 6.1 Hz, H-7b), 3.47 (s, 3H, OC$\underline{H}_3$), 2.56 (d, 1H, J = 2.6 Hz, C2-O$\underline{H}$), 1.13 (s, 9H, C(C$\underline{H}_3$)$_3$); ^{13}C NMR (126 MHz; $CDCl_3$): δ 175.9 (C=O), 138.3 (Ar), 138.2 (Ar), 137.5 (Ar), 128.6 (Ar), 128.5 (Ar), 128.3 (Ar), 128.2 (Ar), 128.1 (Ar), 128.0 (Ar), 127.9 (Ar), 127.5 (2C, Ar, Ar), 92.8 (C-1), 79.7 (C-2/C-3/C-4/C-5), 76.3 (C-2/C-3/C-4/C-5), 75.4 (Ph$\underline{C}$H$_2$O), 73.4 (Ph$\underline{C}$H$_2$O), 73.2 (C-2/C-3/C-4/C-5), 73.1 (C-2/C-3/C-4/C-5), 72.1 (Ph$\underline{C}$H$_2$O), 69.3 (C-7), 67.7 (C-2), 58.6 (OC$\underline{H}_3$), 39.0 (C(CH$_3$)$_3$), 27.0 (C(C$\underline{H}_3$)$_3$; HRMS (ESI) Calc. for (M + Na) $C_{34}H_{42}NaO_8$: 601.2772. Found 601.2768.

3,4,7-Tri-*O*-benzyl-6-*O*-methyl-1-*O*-pivolyl-D-*glycero*-α-L-*gluco*-heptopyranose (15a) and **3,4,7-tri-*O*-benzyl-6-*O*-methyl-2-*O*-pivolyl-D-*glycero*-α/β-L-*gluco*-heptopyranose (15b).** To **14** (1.5 g, 2.59 mmol) in anhydrous CH_2Cl_2 (26 mL) under argon was added anhydrous pyridine (1.9 mL, 23.31 mmol). The mixture was cooled to –10 °C and Tf_2O (1.3 mL, 7.77 mmol) was added dropwise via syringe over ~7 min. The reaction mixture was gradually warmed to 10 °C over 2.5 h. After which, the reaction mixture was poured over an ice cold 1M HCl solution (25 mL) and extracted with CH_2Cl_2 (75 mL). The organic layer was then sequentially washed with ice cold H_2O (25 mL), a saturated aqueous $NaHCO_3$ solution (25 mL), and brine (25 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was dried under vacuum in the presence of P_2O_5 for 1 h. To the residue under argon was added anhydrous DMF (18 mL) and $NaNO_2$ (894 mg, 12.95 mmol). The reaction mixture was heated to 60 °C for 10 h. The mixture was concentrated, diluted with EtOAc (120 mL), and then washed with brine (25 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by flash chromatography in 3:1→2:1 hexanes–EtOAc to afford isomers **15a** (320 mg, 21%) and **15b** (780 mg, 52%). **Data for 15a**: Pale yellow oil. R_f 0.45 (2:1 hexanes–

EtOAc); $[\alpha]_D$ –50.4 (1.0 *c*, $CHCl_3$); ^{1}H NMR (498 MHz; $CDCl_3$): δ 7.41–7.29 (m, 15H, Ar), 6.20 (d, 1H, *J* = 3.6 Hz, H-1), 4.98 (d, 1H, *J* = 10.9 Hz, PhC$\underline{H}_2$O), 4.95 (d, 1H, *J* = 11.3 Hz, PhC$\underline{H}_2$O), 4.87 (d, 1H, *J* = 11.3 Hz, PhC$\underline{H}_2$O), 4.70 (d, 1H, *J* = 10.9 Hz, PhC$\underline{H}_2$O), 4.53 (s, 2H, PhC$\underline{H}_2$O), 3.90–3.79 (m, 5H, H-2, H-3, H-4, H-5, H-6), 3.73 (dd, 1H, *J* = 9.7, 5.9 Hz, H-7a), 3.58 (dd, 1H, *J* = 9.7, 6.2 Hz, H-7b), 3.48 (d, 3H, *J* = 1.7 Hz, OC$\underline{H}_3$), 1.88 (s, 1H, O$\underline{H}$), 1.19 (s, 9H, C(C$\underline{H}_3$)$_3$); ^{13}C NMR (126 MHz; $CDCl_3$): δ 176.7 (C=O), 138.3 (Ar), 138.0 (2C, Ar, Ar), 128.6 (2C, Ar, Ar), 128.4 (Ar), 128.1 (Ar), 128.0 (3C, Ar, Ar, Ar), 127.6 (Ar), 127.5 (Ar), 91.6 (C-1), 82.5 (C-2/C-3/C-4/C-5/C-6), 76.9 (C-2/C-3/C-4/C-5/C-6), 76.2 (C-2/C-3/C-4/C-5/C-6), 75.3 (Ph$\underline{C}$H$_2$O), 75.2 (Ph$\underline{C}$H$_2$O), 73.4 (Ph$\underline{C}$H$_2$O), 72.8 (C-2/C-3/C-4/C-5/C-6), 71.7 (C-2/C-3/C-4/C-5/C-6), 69.3 (C-7), 58.7 (O$\underline{C}$H$_3$), 39.2 ($\underline{C}$(CH$_3$)$_3$), 27.1 (C($\underline{C}$H$_3$)$_3$); HRMS (ESI) Calc. for (M + Na) $C_{34}H_{42}NaO_8$: 601.2772. Found 601.2768. **Data for 15a**: (~2:1 α/β mixture) clear oil. R_f 0.63 & 0.57 (2:1 hexanes–EtOAc); ^{1}H NMR (498 MHz; $CDCl_3$): δ 7.38–7.28 (m, 30H, Ar), 5.38 (d, 0.67H, *J* = 3.7 Hz, H-1α), 4.94 (d, 0.67H, *J* = 11.1 Hz, PhC$\underline{H}_2$O), 4.93–4.78 (m, 3.33H, H-2α, H-2β, 5 × PhC$\underline{H}_2$O), 4.66 (d, 1H, *J* = 11.2 Hz, 2 × PhC$\underline{H}_2$O), 4.60 (d, 0.67H, *J* = 12.0 Hz, PhC$\underline{H}_2$O), 4.59 (d, 0.67H, *J* = 12.1 Hz, PhC$\underline{H}_2$O), 4.55 (d, 0.33H, *J* = 11.9 Hz, PhC$\underline{H}_2$O), 4.51 (d, 0.67H, *J* = 12.0 Hz, PhC$\underline{H}_2$O), 4.51 (d, 0.33H, *J* = 8.3 Hz, H-1β), 4.11 (dd, 0.67H, *J* = 9.5, 9.5 Hz, H-3α), 4.05 (dd, 0.67H, *J* = 10.0, 1.4 Hz, H-5α), 3.92 (dd, 0.33H, *J* = 9.7, 9.0 Hz, H-4β), 3.87–3.73 (m, 3.33H, H-3β, H-4α, H-6α, H-6β, H-7α, H-7β, H-7'β), 3.67 (dd, 0.676H, *J* = 9.7, 6.3 Hz, H-7'α), 3.55 (dd, 0.33H, *J* = 9.8, 1.4 Hz, H-5β), 3.48 (s, 3H, 2 × OC$\underline{H}_3$), 1.23 (s, 9H, 2 × C(C$\underline{H}_3$)$_3$); ^{13}C NMR (126 MHz; $CDCl_3$): δ 179.2 (C=O), 177.8 (C=O), 138.4 (2C, Ar, Ar), 138.2 (2C, Ar, Ar), 138.1 (Ar), 138.0 (Ar), 128.5 (2C, Ar, Ar), 128.4 (3C, Ar, Ar, Ar), 128.1 (2C, Ar, Ar), 127.8 (2C, Ar, Ar), 127.9 (Ar), 127.7 (3C, Ar, Ar, Ar), 127.6 (Ar), 127.5 (Ar), 127.4 (Ar), 96.6 (C-1β), 90.3 (C-1α), 82.8 (C-3β), 80.1 (C-3α), 77.3, 77.1, 76.3, 76.2, 76.1, 75.3 (Ph$\underline{C}$H$_2$O), 75.1 (Ph$\underline{C}$H$_2$O), 74.9 (3C, C-5β, 2 × Ph$\underline{C}$H$_2$O), 74.0, 73.5 (Ph$\underline{C}$H$_2$O), 73.3 (Ph$\underline{C}$H$_2$O), 70.0 (C-5α), 69.3 (2C, C-

7α, C-7β), 58.9 (OCH_3), 58.8 (OCH_3), 39.0 ($\underline{C}(CH_3)_3$), 38.8 ($\underline{C}(CH_3)_3$), 27.2 ($C(\underline{C}H_3)_3$), 27.1 ($C(\underline{C}H_3)_3$); HRMS (ESI) Calc. for (M + Na) $C_{34}H_{42}NaO_8$: 601.2772. Found 601.2769.

***p*-Tolyl 3,4,7-tri-*O*-benzyl-6-*O*-methyl-2-*O*-pivloyl-1-thio-D-*glycero*-β-L-*gluco*-heptopyranoside (16).** To **15b** (799 mg, 1.38 mmol) in anhydrous pyridine (7.5 mL) under argon were sequentially added $(TolS)_2$ (680 mg, 2.76 mmol) and 1M $P(CH_3)_3$ in THF (2.76 mL, 2.76 mmol). The reaction mixture was stirred for 21 h and then poured over a solution of brine (5 mL) and H_2O (5 mL) and then extracted with EtOAc (2 × 40 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash chromatography (dry loading) in 4:1 hexanes–EtOAc to afford **16** (850 mg, 90%) as a pale yellow viscous oil. R_f 0.56 (3:1 hexanes–EtOAc); $[\alpha]_D$ –9.7 (1.0 *c*, $CHCl_3$); ^{1}H NMR (498 MHz; $CDCl_3$): δ 7.39–7.26 (m, 17H, Ar), 7.04 (d, 2H, *J* = 7.9 Hz, Ar), 5.15 (dd, 1H, *J* = 10.1, 9.2 Hz, H-2), 4.89 (d, 1H, *J* = 11.0 Hz, PhC$\underline{H}_2$O), 4.77 (d, 1H, *J* = 11.0 Hz, PhC$\underline{H}_2$O), 4.73 (d, 1H, *J* = 11.0 Hz, PhC$\underline{H}_2$O), 4.65 (d, 1H, *J* = 11.0 Hz, PhC$\underline{H}_2$O), 4.57 (d, 1H, *J* = 10.2 Hz, H-1), 4.44 (d, 1H, *J* = 11.8 Hz, PhC$\underline{H}_2$O), 4.42 (d, 1H, *J* = 11.8 Hz, PhC$\underline{H}_2$O), 3.94 (dd, 1H, *J* = 9.4, 9.4 Hz, H-4), 3.83–3.80 (m, 2H, H-6, H-7a), 3.78 (dd, 1H, *J* = 9.1, 9.1 Hz, H-3), 3.63 (dd, 1H, *J* = 11.5, 9.1 Hz, H-7b), 3.51 (dd, 1H, *J* = 9.8, 1.7 Hz, H-5), 3.46 (s, 3H, OC$\underline{H}_3$), 2.29 (s, 3H, (ArC$\underline{H}_3$)), 1.26 (s, 9H, $C(C\underline{H}_3)_3$); ^{13}C NMR (126 MHz; $CDCl_3$): δ 176.8 (C=O), 138.3 (Ar), 138.1(4) (Ar), 138.1(1) (Ar), 137.8 (Ar), 132.7 (Ar), 130.4 (Ar), 129.6 (Ar), 128.4 (3C, Ar, Ar, Ar), 127.7 (2C, Ar, Ar), 127.6 (2C, Ar, Ar), 127.5 (Ar), 127.4 (Ar), 88.2 (C-1), 85.1 (C-3), 78.6 (C-5), 76.9 (C-4), 76.2 (C-6), 75.1 (Ph$\underline{C}H_2$O), 74.9 (Ph$\underline{C}H_2$O), 73.4 (Ph$\underline{C}H_2$O), 72.0 (C-2), 68.9 (C-7), 58.4 (O$\underline{C}H_3$), 38.8 ($\underline{C}(CH_3)_3$), 27.2 ($C(\underline{C}H_3)_3$), 21.1 (Ar$\underline{C}H_3$); HRMS (ESI) Calc. for (M + NH_4) $C_{41}H_{52}NO_7S$: 702.3459. Found 702.3445.

***p*-Tolyl 2,3,4,7-tetra-*O*-benzyl-6-*O*-methyl-1-thio-D-*glycero*-β-L-*gluco*-heptopyranoside (1).** To **16** (800 mg, 1.17 mmol) in anhydrous DMF (12 mL) under argon were sequentially added

BnBr (280 μL, 2.34 mmol) and NaH (94 mg, 2.34 mmol). The reaction mixture was stirred for 0.5 h, then heated to 60 °C and stirred for another 3 h. The mixture was then cooled to room temperature and additional NaH (94 mg, 2.34 mmol) was added before the mixture was heated again 60 °C and stirred for another 3 h. After cooling to room temperature, excess NaH was quenched by addition of CH_3OH (~1 mL). The mixture was then concentrated. The residue was diluted with EtOAc (100 mL) and washed with a solution of brine (20 mL) and then H_2O (20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by flash chromatography (dry loading) in 10:1→4:1 hexanes–EtOAc to afford **1** (575 mg, 71%, 95% based on recovered **16** and substrate lacking Piv group) as a pale yellow viscous oil. Obtained $[\alpha]_D$ –17.8 (0.7 *c*, $CHCl_3$); reported $[\alpha]_D$ –15.9 (0.7 *c*, $CHCl_3$); ^1H and ^{13}C NMR data matched that reported previously.

Supporting Information Available. ^1H and ^{13}C NMR spectra for compounds **9**, **13**, **14**, **15a**, **15b**, and **16**.

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Notes

The authors declare no competing financial interest.

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