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Aryl sulfonates in inversions at secondary carbohydrate hydroxyls: a new and improved route towards 3-azido-3-deoxy-β-D-galactopyranosides

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ABSTRACT

A method into using benzenesulfonates and imidazylates as leaving groups at the secondary C3 galactopyranose carbon, instead of the commonly used less stable triflate leaving group, in order to facilitate scale up and improve reproducibility is disclosed. The benzenesulfonates and imidazylates were proven to be significantly more stable than the corresponding triflates and the method was used to device an improved route towards 3-azido-3-deoxy-β-D-galactopyranosides.

KEYWORDS benzenesulfonates; imidazylates; inversion; galactose;

INTRODUCTION

3-Azido-3-deoxy-β-D-galactopyranosides are important intermediates in the synthesis of inhibitors for galactose-recognizing proteins, such as galactosyl transferases[1] and galectins. The latter being β-galactoside-binding proteins involved in cancer and inflammation processes.[2,3] Inhibitors of galactosyl transferases and galectins are valuable tools for gaining a better understanding of biological roles of these proteins and may be important in drug development. Some of the most potent

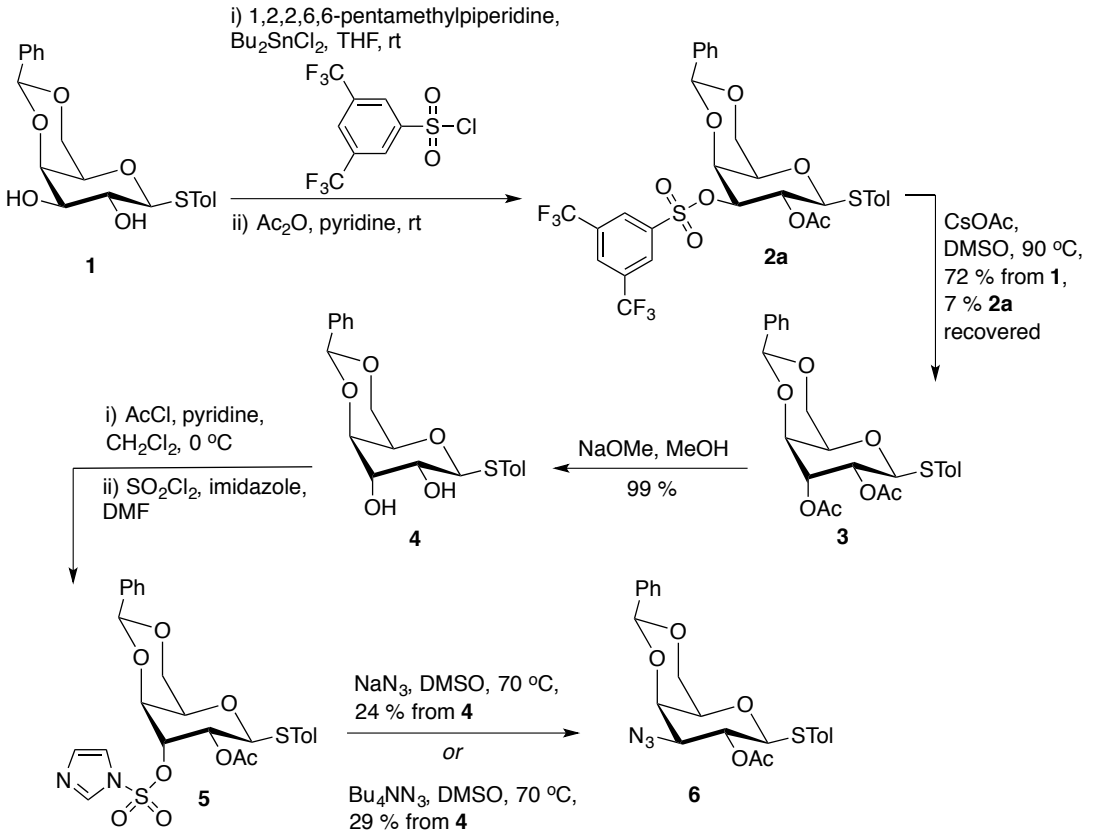
galactosyl transferase[1] and galectin[3-5] inhibitors described are galactoside C3-derivatives derived from 3-azido-3-deoxy-β-D-galactopyranosides, which exemplifies the versatility of 3-azido-3-deoxy-β-D-galactopyranosides as intermediates in the design and synthesis of new inhibitors.

The synthesis of a 3-azido-3-deoxy-β-D-galactopyranoside derivative was first described from glucose by Lowary and Hindsgaul[1] and has more recently been described by our group[2] through a double inversion at C3 of 4,6-*O*-benzylidene-β-D-galactopyranosides with triflate as the leaving group. In the latter method, instability issues with triflate intermediates, due to early onset of exothermic decomposition, have compromised scale up. Imidazylates and tosylates are more stable and have been known to act, in a few cases, as leaving group in inversion reactions on secondary carbohydrate hydroxyls.[6-8] By replacing triflates with less reactive sulfonates as leaving groups at C3 of 4,6-*O*-benzylidene galacto- and gulopyranosides, a scalable and more robust synthetic route towards 3-azido-3-deoxy-β-D-galactopyranosides was hypothesized. An initial study showed that the commonly used tosylate and mesylate leaving group at C3 of 4,6-*O*-benzylidene galactosides did not allow for inversion reactions to occur, which is not surprising as literature[9-10] reports inversions at furanose and open-chain carbohydrate secondary carbons but rarely on pyranose secondary carbons, why tuning the sulfonate leaving ability was required. Herein, we report an alternative synthetic route towards 3-azido-3-deoxy-β-D-galactopyranosides replacing labile triflates with more stable, but still sufficiently reactive, aryl sulfonates.

RESULTS AND DISCUSSION

Following the sulfonylation method developed by Muramatsu[11], regioselective introduction of reactive benzenesulfonate leaving groups at C3 of the known[12] *p*-tolyl

4,6-*O*-benzylidene-1-thio- β-D-galactopyranoside **1** was accomplished in up to 4 g scale. The subsequent *in situ* 2-*O*-acetylation yielded *p*-tolyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-*O*-[3,5-bis(trifluoromethyl)benzenesulfonyl]-1-thio-β-D-galactopyranoside **2a** (Scheme 1) and *p*-tolyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-*O*-(3,5-difluorobenzenesulfonyl)-1-thio-β-D-galactopyranoside **2b** in near quantitative yields over two steps from **1**. Upon inversion with cesium acetate, compound **2a** gave the resulting gulopyranoside **3** in better yield (72 % from **1**) than compound **2b** (41 % from **1**), which may be explained by the trifluoromethyl group (δ 4.97 ppm for **2a** H-3) being more electron-withdrawing[13] than a fluoro substituent (δ 4.82 ppm for **2b** H-3). Inversion of compound **2a** with CsOAc was performed in up to 9 g scale with 45 – 70 % yields. In cases of a lower yield, this was accompanied with a larger recovery of of compound **2a**. Inversion of the corresponding 3-*O*-benzenesulfonates without 2-*O*-acetyl protection resulted in only degradation products, which confirmed the importance of a neighboring ester group for efficient inversion, as earlier shown by Dong and Ramström.[14,15] The use of CsOAc as the nucleophile in inversion of compound **2a** results in a need for de-*O*-acetylation of di-acetate **3** to give the diol **4**, which in turn requires selective 2-*O*-acetylation prior to 3-*O*-sulfonylations. Hence, an alternative approach to directly introduce the axial 3OH from **2a**, with $NaNO_2$ as the nucleophile in a Lattrell-Dax inversion, was investigated. However, this resulted in substantial 2-*O*-acyl migration along with lower conversion. Other nucleophiles than CsOAc and $NaNO_2$ were investigated, but gave degradation products (KOH), failed to substitute **2a** (NaI and CsO_2CCF_3), or proceeded with lower yields (CsOLev).

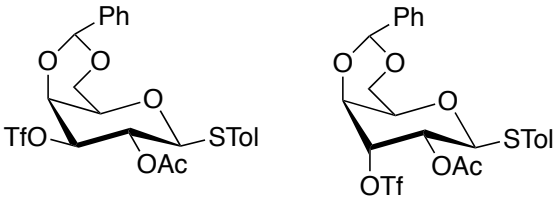


Scheme 1. Synthesis of the 3-azido-3-deoxy-β-D-galactopyranoside **6.**

The axial 3-*O*-sulfonylation of gulopyranoside diol **4**, obtained after de-*O*-acetylation of the di-acetate **3**, proved more challenging. Regioselective 2-*O*-acetylation of **4**, followed by reaction with different benzenesulfonyl chlorides failed to produce 3-*O*-sulfonates. Instead, an imidazylate was installed on a 3 g scale following the method developed by Hanessian[7] to give compound **5**. However, the stable imidazylate **5** proved difficult to separate from unreacted 2-*O*-acetylated intermediate and minor undesired 2,3-di-*O*-acetylated byproduct **3**, why crude **5** was preferably treated directly with either sodium azide or tetrabutylammonium azide to yield the target 3-azido-3-deoxy-β-D-galactopyranoside **6**, which lead to easier purification by column chromatography. Nevertheless, in order to elucidate the cause of the low yield in the second inversion, a smaller batch of pure imidazylate **5** was

treated with sodium azide to give compound **6** in 49 % yield. Since the overall yield for one-pot imidazylation and substitution with sodium azide was 24 %, the yield for the formation of imidazylate **5** from compound **4** can be estimated to 50 %. Overall, compound **6** was synthesized in yields comparable to those obtained with triflates, but with a more reliable and reproducible protocol involving more stable sulfonates.[2]

Having established an alternative route to 3-azido galactopyranoside derivatives via substitutions of supposedly more stable benzenesulfonate and imidazylate intermediates, the corresponding triflates **7** and **8** (Figure 1) were synthesized following published conditions[2] to allow for a stability comparison with **2a** and **5**. Indeed, differential scanning calorimetry (DSC) experiments revealed significantly higher thermal degradation onset temperatures for sulfonates **2a** and **5** (Table 1). This is in agreement with the observation that, while triflates, such as **7** and **8**, often decompose in an unpredictable manner even at lower temperatures, compounds **2a** and **5** show long shelf-stability even at ambient temperature.



7 **8**

Figure 1. Structure of triflates **7** and **8**

Table 1. Exothermic onset measurements for triflates and aryl sulfonates

Compound	**Onset of exothermic decomposition (^{o}C)**
2a	143
7	112
5	148

CONCLUSION

In summary, we have devised a novel and robust galactopyranose C3 double inversion route towards 3-azido-3-deoxy-β-D-galactopyranosides on up to 9 g scale in the first inversion and up to 3 g in the second inversion. The use of a more stable, yet sufficiently reactive, sulfonate **2a** resulted in a more robust method and facilitated scale up of the synthesis, while the double inversion route using triflates[2] notoriously gives irreproducible results on this scale.

EXPERIMENTAL

Materials

DSC measurements were performed on a TA Instrument model DSC Q2000 using a temperature gradient of 2 ^{o}C/min. Specific rotations were measured on a Perkin Elmer model 341 polarimeter. NMR spectra were recorded on a Bruker Avance II 400 MHz spectrometer at ambient temperature. ^{1}H NMR spectra were assigned using 2D-methods (COSY). Chemical shifts are given in ppm downfield from the signal for Me_4Si, with reference to residual $CHCl_3$. HRMS was recorded on a Micromass Q-TOF micro spectrometer (ESI). Reactions were monitored by TLC using aluminum-backed silica gel plates (Merck $60F_{254}$) and visualized using UV light and by charring with ethanolic H_2SO_4 (7%). Preparative chromatography was performed using silica gel (Amicon Matrex 35-70 μm, 60 Å) columns. Solvents were dried by either a MBraun 7656 dry solvent dispenser SPS system (THF and CH_2Cl_2) or an IT PS-Micro solvent dispenser (DMF) and stored over activated M.S. Reagents were supplied by Sigma-Aldrich and used as it is.

***p*-Tolyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-*O*-[3,5-bis(trifluoromethyl)benzenesulfonyl]-1-thio-β-D-galactopyranoside (2a)**

A mixture of **1** (2.00 g, 5.34 mmol) and dibutyltin dichloride (162 mg, 0.53 mmol) in THF (30 mL) was stirred for 10 min at rt before 3,5-bis(trifluoromethyl)benzenesulfonyl chloride (1.84 g, 5.88 mmol) dissolved in THF (5 mL) and 1,1,2,2,6-pentamethylpiperidine (1.93 mL, 10.68 mmol) were added under N_2 atmosphere and the resulting solution was stirred at rt o.n. The reaction was quenched with sat. aq. NH_4Cl followed by evaporation of the solvent, the residue was diluted with EtOAc and washed with water and brine. The organic phase was dried and evaporated. The obtained residue was dissolved in acetic anhydride (15 mL) and pyridine (15 mL) and stirred at rt o.n. An amorphous white solid was obtained after evaporation of the solvents to give crude **2a**, which was used directly in the following inversion. mp 143 – 146 ^{o}C. $[\alpha]_D$ -4.1 (c 0.73, $CDCl_3$). ^{1}H NMR ($CDCl_3$): δ 8.28 (s, 2H, Ph), 8.06 (s, 1H, Ph), 7.48 (d, *J* = 8.0, 2H, Ph), 7.32-7.26 (m, 5H, Ph), 7.07 (d, *J* = 8.0, 2H, Ph), 5.35 (s, 1H, CH), 5.24 (t, *J* = 9.6, 1H, H-2), 4.97 (dd, *J* = 9.6, 3.6, 1H, H-3), 4.64 (d, *J* = 9.6, 1H, H-1), 4.44 (d, *J* = 3.2, 1H, H-4), 4.38 (dd, *J* = 12.4, 1.2, 1H, H-6), 4.01 (dd, *J* = 12.4, 1.2, 1H, H-6), 3.58 (s, 1H, H-5), 2.33 (s, 3H, CH_3), 2.02 (s, 3H, Ac). ^{13}C NMR ($CDCl_3$): δ 169.0, 138.9, 136.9, 134.7, 133.4, 133.1, 129.7, 129.4, 128.2, 127.9, 127.5, 126.5, 126.4, 123.6, 120.9, 101.3, 84.9, 80.7, 74.1, 69.4, 69.0, 66.4, 21.4, 20.8. HRMS calcd for $[C_{30}H_{26}F_6O_8S_2Na]^+$, 715.0871; found: 715.0882.

***p*-Tolyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-*O*-(3,5-difluorobenzenesulfonyl)-1-thio-β-D-galactopyranoside (2b)**

A mixture of **1** (800 mg, 2.14 mmol) and dibutyltin dichloride (65 mg, 0.21 mmol) in THF (13 mL) was stirred for 10 min at rt before 3,5-difluorobenzenesulfonyl chloride (500 mg, 2.35 mmol) dissolved in THF (2 mL) and 1,1,2,2,6-pentamethylpiperidine (0.77 mL, 4.27 mmol) were added under N_2 atmosphere and the resulting solution was stirred at rt o.n. The reaction was quenched with sat. aq. NH_4Cl followed by evaporation of the solvent, the residue was diluted with CH_2Cl_2 and washed with water and brine. The organic phase was dried and evaporated. The obtained residue was dissolved in acetic anhydride (10 mL) and pyridine (10 mL) and stirred at rt o.n. An amorphous white solid was obtained after evaporation of the solvents to give crude **2b**, which was used directly in the following inversion. ^{1}H NMR ($CDCl_3$): δ 7.47 (d, *J* = 8.1, 2H, Ph), 7.39-7.29 (m, 8H, Ph), 7.06 (d, *J* = 8.1, 2H, Ph), 5.38 (s, 1H, CH), 5.22 (t, *J* = 9.8, 1H, H-2), 4.82 (dd, *J* = 9.7, 3.6, 1H, H-3), 4.61 (d, *J* = 9.8, 1H, H-1), 4.38 (m, 2H, H-4 and H-6), 4.01 (d, *J* = 12.5, 1H, H-6), 3.57 (s, 1H, H-5), 2.32 (s, 3H, CH_3), 2.01 (s, 3H, Ac). ^{13}C NMR ($CDCl_3$): δ 169.0, 137.1, 134.7, 129.7, 129.4, 128.4, 128.3, 126.6, 126.2, 111.1, 101.3, 85.0, 80.5, 74.2, 69.5, 69.0, 66.5, 21.4, 20.9. HRMS calcd for $[C_{28}H_{26}F_2O_8S_2Na]^+$, 615.0935; found: 615.0939.

***p*-Tolyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-1-thio-β-D-gulopyranoside (3)**

From **2a**: CsOAc (1.21 g, 6.3 mmol) was added to crude **2a** (≤2.1 mmol) in DMSO (8 mL) and the mixture was stirred for 3 days at 90 °C under N_2 atmosphere. The mixture was diluted with EtOAc and washed with water and brine. The organic phase was dried with Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography (heptane:ethyl acetate 3:1->1:1) to give **3** (695 mg, 72 % from **1**) as an amorphous white solid and recover compound **2a** (100 mg, 7%).

From **2b**: CsOAc (1.21 g, 6.3 mmol) was added to crude **2b** (≤2.1 mmol) in DMSO (8 mL) and the mixture was stirred for 3 days at 90 °C under N_2 atmosphere. The mixture was diluted with EtOAc and washed with water and brine. The organic phase was dried with Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography (heptane:ethyl acetate 3:1->1:1) to give **3** (395 mg, 41 % from **1**) as an amorphous white solid. mp 115 – 117 ^{o}C. $[\alpha]_D$ -36.1 (c 1.46, $CDCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.49 (d, *J* = 8.0, 2H, Ph), 7.40-7.34 (m, 5H, Ph), 7.08 (d, *J* = 8.0, 2H, Ph), 5.48 (s, 1H, CH), 5.41 (t, *J* = 3.4, 1H, H-3), 5.06 (dd, *J* = 10.3, 3.1, 1H, H-2), 4.99 (d, *J* = 10.3, 1H, H-1), 4.38 (dd, *J* = 12.5, 1.3, 1H, H-6), 4.03 (dd, *J* = 12.0, 1.6, 1H, H-6), 4.01 (s, 1H, H-4), 3.79 (d, *J* = 1.0, 1H, H-5), 2.34 (s, 3H, CH_3), 2.14 (s, 3H, Ac), 2.04 (s, 3H, Ac). ^{13}C NMR ($CDCl_3$): δ 169.4, 168.9, 138.5, 137.5, 134.4, 129.7, 129.3, 128.3, 127.1, 126.6, 101.4, 81.9, 74.1, 69.3, 68.6, 68.0, 65.9, 22.8, 21.0, 20.9. HRMS calcd for $[C_{24}H_{26}O_7SNa]^+$, 481.1297; found: 481.1300.

***p*-Tolyl 4,6-*O*-benzylidene-1-thio-β-D-gulopyranoside (4)**

NaOMe (1 M, 4 mL) was added to a stirred solution of **3** (1.38 g, 3.01 mmol) in MeOH (6 mL). After 4 hours was the solution adjusted to pH 7 by Dowex and concentrated to give compound **4** (1.13 g, 99 %) as an amorphous white solid. mp 157 – 159 ^{o}C. $[\alpha]_D$ -127.1 (c 0.72, CH_3OH). ^{1}H NMR ($CDCl_3$): δ 7.57 (d, *J* = 8.1, 2H, Ph), 7.41-7.34 (m, 5H, Ph), 7.12 (d, *J* = 7.8, 2H, Ph), 5.51 (s, 1H, CH), 4.89 (d, *J* = 9.8, 1H, H-1), 4.38 (dd, *J* = 12.5, 1.4, 1H, H-6), 4.15 (t, *J* = 3.3, 1H, H-3), 4.11 (dd, *J* = 3.0, 1.0, 1H, H-4), 4.03 (dd, *J* = 11.5, 1.7, 1H, H-6), 3.85 (d, *J* = 1.2, 1H, H-5), 3.73 (dd, *J* = 9.8, 3.0, 1H, H-2), 2.36 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 138.6, 138.0, 134.2, 129.9, 128.3, 126.6, 101.4, 84.3, 75.6, 69.6, 68.8, 67.9, 65.9, 21.4. HRMS calcd for $[C_{20}H_{22}O_5SNa]^+$, 397.1086; found: 397.1086.

***p*-Tolyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-*O*-(*N*-imidazole-1-sulfonyl)-1-thio-β-D-gulopyranoside (5)**

AcCl (0.42 mL, 5.95 mmol) was added dropwise to a solution of **4** (2.97 g, 7.93 mmol) in dry CH_2Cl_2 (100 mL) and pyridine (3.85 mL, 47.59 mmol) cooled to 0 ^oC. After 30 min stirring at rt was the solution diluted with CH_2Cl_2 and washed with 1 M HCl, sat. aq. $NaHCO_3$ and brine. The organic phase was dried, concentrated and the obtained residue was dissolved in DMF (50 mL) together with imidazole (3.24 g, 47.59 mmol). The mixture was cooled to -41 ^oC before sulfuryl choride (0.96 mL, 11.90 mmol) was added and the solution was stirred 1 h at rt before quenching with water. The solution was extracted twice with CH_2Cl_2, the pooled organic phases were washed with water, dried and evaporated to give crude **5**, which was used directly in the next inversion.

***p*-Tolyl 2-*O*-acetyl-3-azido-3-deoxy-4,6-*O*-benzylidene-1-thio-β-D-galactopyranoside (6)**

Method 1: Sodium azide (1.0 g, 15.6 mmol) was added to a solution of crude **5** (≤3.9 mmol) in DMSO (10 mL) under N_2 atmosphere and the mixture was stirred at 70 ^oC o.n. The mixture was diluted with CH_2Cl_2 and washed with water and brine. The organic phase was dried, concentrated and purified by column chromatography (heptane:ethyl acetate 3:1) to give **6** (420 mg, 24 % from **4**) as an amorphous white solid.

Method 2: Tetrabutylammonium azide (4.4 g, 15.6 mmol) was added to a solution of crude **5** (≤3.9 mmol) in DMSO (10 mL) under N_2 atmosphere and the mixture was stirred at 70 ^oC o.n. The mixture was diluted with CH_2Cl_2 and washed with water and brine. The organic phase was dried, concentrated and purified by column

chromatography (heptane:ethyl acetate 3:1) to give **6** (504 mg, 29 % from **4**) as an amorphous white solid. mp 135 – 138 ^{o}C. $[\alpha]_D$ -10.0 (c 1.10, $CDCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.48 (d, *J* = 8.0, 2H, Ph), 7.40-7.34 (m, 5H, Ph), 7.05 (d, *J* = 8.0, 2H, Ph), 5.56 (s, 1H, CH), 5.29 (t, *J* = 10.0, 1H, H-2), 4.63 (d, *J* = 9.6, 1H, H-1), 4.38 (dd, *J* = 12.4, 3.2, 1H, H-6), 4.31 (d, *J* = 3.2, 1H, H-4), 4.06 (dd, *J* = 13.2, 1.6, 1H, H-6), 3.53 (s, 1H, H-5), 3.38 (dd, *J* = 10.0, 3.2, 1H, H-3), 2.32 (s, 3H, CH_3), 2.17 (s, 3H, Ac). ^{13}C NMR ($CDCl_3$): δ 169.3, 138.5, 137.3, 134.1, 129.7, 129.2, 128.3, 127.5, 126.5, 101.3, 85.8, 75.4, 70.3, 69.3, 67.4, 62.7, 21.4, 21.1. HRMS calcd for $[C_{22}H_{23}N_3O_5SNa]^+$, 464.1256; found: 464.1260. IR (KBr) ν: 2985.9, 2947.3, 2926.1, 2885.6, 2862.5, 2096.7 (N_3), 1736.0, 1494.9, 1402.3, 1363.7, 1253.8, 1226.8, 1084.0 cm^{-1}.

***p*-Tolyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-*O*-trifluoromethanesulfonyl-1-thio-β-D-galactopyranoside (7)**

Compound **1** (100 mg, 0.27 mmol) was subjected to the published[2] procedure followed by filtration through a short silica column using CH_2Cl_2 to give compound **7** (83 mg, 56 %). Due to instability issues, it was used without further purification in the subsequent inversion. ^{1}H NMR ($CDCl_3$): δ 7.48 (d, *J* = 8.1, 2H, Ph), 7.38 (m, 5H, Ph), 7.06 (d, *J* = 8.0, 2H, Ph), 5.53 (s, 1H, CH), 5.36 (t, *J* = 9.7, 1H, H-2), 4.96 (dd, *J* = 9.8, 3.6, 1H, H-3), 4.64 (d, *J* = 9.7, 1H, H-1), 4.45 (d, *J* = 3.6, 1H, H-4), 4.41 (dd, *J* = 12.5, 1.6, 1H, H-6), 4.04 (dd, *J* = 12.6, 1.6, 1H, H-6), 3.58 (s, 1H, H-5), 2.32 (s, 3H, CH_3), 2.15 (s, 3H, Ac).

***p*-Tolyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-*O*-trifluoromethanesulfonyl-1-thio-β-D-gulopyranoside (8)**

Compound **4** (500 mg, 1.34 mmol) was subjected to the published[2] procedure followed by filtration through a short silica column using CH_2Cl_2 to give compound **7**

(480 mg, 66 %). Due to instability issues, it was used without further purification in the subsequent inversion. ^{1}H NMR ($CDCl_3$): δ 7.48 (d, *J* = 8.1, 2H, Ph), 7.40-7.34 (m, 5H, Ph), 7.10 (d, *J* = 8.1, 2H, Ph), 5.53 (s, 1H, CH), 5.18 (t, *J* = 3.2, 1H, H-3), 5.06 (dd, *J* = 10.3, 2.9, 1H, H-2), 5.00 (d, *J* = 10.2, 1H, H-1), 4.41 (dd, *J* = 12.7, 1.5, 1H, H-6), 4.22 (d, *J* = 2.9, 1H, H-4), 4.08 (dd, *J* = 12.6, 1.6, 1H, H-6), 3.82 (s, 1H, H-5), 2.35 (s, 3H, CH_3), 2.15 (s, 3H, Ac).

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