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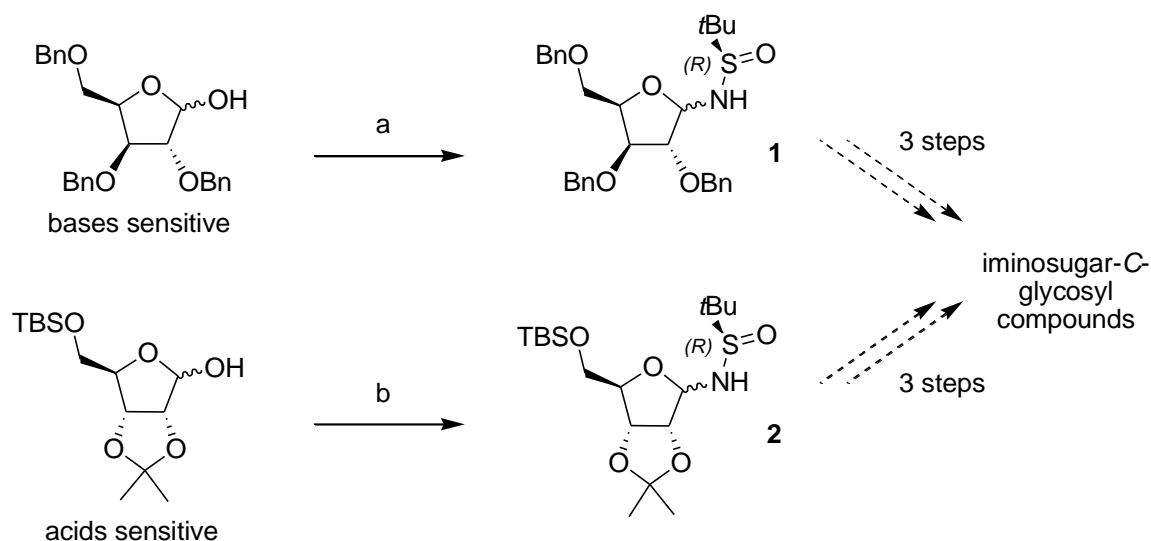
HAL Authorization

# One Step Preparation of Protected *N*-*tert*-Butanesulfinyl *D*-ribo and *D*-xylo furanosylamines from Related Sugar Hemiacetals

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**Reagents and conditions:** a) (*R*)-2-methyl-2-propanesulfinamide,  $\text{Ti}(\text{OEt})_4$ , 4Å MS, dry toluene, 70 °C, 22 h, (65%); b) (*R*)-2-methyl-2-propanesulfinamide,  $\text{Cs}_2\text{CO}_3$ , 4Å MS,  $\text{Cl}(\text{CH}_2)_2\text{Cl}$ , 60 °C, 17–30 h, (65%).

*N*-protected glycosylamines are important synthetic scaffolds in bioorganic and medicinal chemistry and precursors of a diversity of compounds of biological interest. In particular, such sugar derivatives behave as latent imine equivalents and are capable of reacting with a variety of *C*-nucleophiles to provide, after an activation-cyclization reaction sequence, iminosugar-*C*-glycosyl

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compounds.<sup>1</sup> Over the past three decades, *N*-benzyl, *N*-alkyl and *N*-carbonylated glycosylamines have been efficiently used in that respect. For instance, glycosylamines carrying *N*-benzyl and *N*-alkyl groups have been shown to react mostly with large excess of Grignard reagents to provide the 1,2-*syn* aminoalditols in good yields and moderate to good degrees of stereoselectivity.<sup>1c,2,3,4</sup> However, the resulting diastereomers are often difficult to separate by conventional chromatography techniques, limiting their use for synthetic purposes. *N*-Benzyl-*N*-glycosyl compounds are somewhat unstable substrates; they slowly hydrolyze to the parent aldoses.<sup>5</sup> More recently, *N*-carbonylated glycosylamines have been shown to behave under Lewis acid catalysis also as imine equivalents for the stereoselective reaction with silylated nucleophiles, opening an approach to 1,2-*syn*-iminosugar-*C*-glycosyl compounds carrying a greater diversity of aglycones (allyl, allenyl, oxoalkyl, etc).<sup>6,1c,3c,7</sup> The addition process occurs at lower temperature, with good degrees of stereoselectivity. The limited stability of carbonylated glycosylamines can make them act as activated glycosyl donors, leading to *C*-glycosyl compounds.

Recently, we have reported the first study on the preparation and the reactivity of *N*-*tert*-butanesulfinyl glycosylamines.<sup>8</sup> The synthetic utility of these new scaffolds was demonstrated by their conversion with a range of organomagnesium reagents into the related 1,2-*syn*-aminoalditols in good yields with moderate to good stereoselectivities. The diastereoselectivity could be boosted using LiCl as an additive, giving access to the 1,2-*syn* derivatives with excellent stereoselection (up to 100% d.e.). *N*-*tert*-Butanesulfinyl glycosylamines were found to exhibit reactivity similar to that of *N*-benzyl-glycosylamines.

Recently, we have observed that the chiral sulfinyl moiety directs the stereoselectivity of the addition of certain nucleophiles; for example, the 1,2-*syn*- or 1,2-*anti* isomer is obtained by reacting LiCF<sub>2</sub>P(O)(OEt)<sub>2</sub> with the (*S*<sub>R</sub>)-*N*-*tert*-butanesulfinyl-D-xylofuranosylamine or with the

(*S<sub>S</sub>*)-*N*-*tert*-butanesulfinyl-D-xylofuranosylamine respectively.<sup>9</sup> Therefore, *N*-*tert*-butanesulfinyl glycosylamines constitute much more reliable and versatile synthetic intermediates than their *N*-benzyl-, *N*-alkyl- and *N*-carbonylated analogues en route to the diastereoselective synthesis of iminosugar-C-glycosyl compounds.

In this chapter, we describe the one step preparation of two typical *N*-*tert*-butanesulfinyl glycofuranosylamines using acidic or basic conditions. The two representative reactions proceed using enantiopure (*R*)-2-methyl-2-propanesulfinamide and related base- or acid-sensitive, protected sugar hemiacetals, with titanium (IV) ethoxide or cesium carbonate as reagent to give the 2,3,5-tri-*O*-benzyl-(*S<sub>R</sub>*)-*N*-*tert*-butanesulfinyl- $\alpha/\beta$ -D-xylofuranosylamine **1** and (*S<sub>R</sub>*)-*N*-*tert*-butanesulfinyl-5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene- $\alpha,\beta$ -D-ribofuranosylamine **2** respectively. The detailed experimental conditions described herein complement similar procedures reported recently.<sup>8,10</sup>

## EXPERIMENTAL

**General Methods.** Unless otherwise stated, all reagents were purchased from commercial sources and used as received. 2,3,5-tri-*O*-benzyl-D-xylofuranose was prepared as described.<sup>11</sup> 5-*O*-*tert*-Butyldiphenylsilyl-2,3-*O*-isopropylidene-D-ribofuranose and (*S*)- and (*R*)-2-methyl-2-propanesulfinamide were purchased from Carbosynth. Cs<sub>2</sub>CO<sub>3</sub> (99.9%, metal basis) was purchased from AlfaAesar. Ti(OEt)<sub>4</sub> (50 mL in glass bottle), toluene (puriss. p.a., ACS reagent,  $\geq$  99.7% (GC)), toluene (anhydrous, 99.8%) and 4 Å activated molecular sieves (pellets, 1.6 mm diameter) were purchased from Sigma-Aldrich. Toluene (puriss. p.a., ACS reagent,  $\geq$  99.7% (GC)) was purified by passage through a column containing activated alumina under nitrogen pressure (Dry Solvent Station GT S100, GlassTechnology, Geneva, CH). Toluene (anhydrous, 99.8%) was used as received. 4 Å MS was activated by drying in an oven at 500°C (48 h) followed by storing at 150°C. It was then allowed to reach room temperature and kept over CaCl<sub>2</sub> in a desiccator. 1,2-Dichloroethane (99.8%, extra pure) was purchased from Acros Organics. Ethyl acetate (EA) (99.8% GC, tech. grade, pure for synthesis), petroleum ether (PE) (tech.

grade, pure for synthesis, bp 40-65 °C) and dichloromethane (99.95% GC, tech. grade, pure for synthesis, stab. with ethanol) were purchased from Carlo Erba. NMR spectra were recorded at 298 K with a Bruker Avance 400 MHz spectrometer equipped with a PABBO BBO probe. The nuclei-signal assignments were done with the aid of 1 D [ $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, Distortionless Enhancement by Polarization Transfer (DEPT)] and 2 D Correlation Spectroscopy [( $^1\text{H}$ - $^1\text{H}$  COSY and  $^1\text{H}$ - $^{13}\text{C}$  Heteronuclear Single Quantum Coherence (HSQC)] experiments.  $^1\text{H}$  NMR (400 MHz) chemical shift values are listed in parts per million (ppm) downfield from TMS as the internal standard or relative to  $\text{CHCl}_3$ . Data are reported as follows: chemical shift (ppm on the  $\delta$  scale), multiplicity (s = singlet, d = doublet, dd = doublet of doublet, t = triplet and m = multiplet), coupling constant  $J$  (Hz), and integration.  $^{13}\text{C}$  NMR (101 MHz) chemical shifts are given in ppm relative to  $\text{CHCl}_3$  as the internal standard. High-resolution mass spectra were recorded with a MaXis ESI qTOF ultrahigh-resolution mass spectrometer (FR2708, Orléans). Infrared spectra were recorded with a Thermo Scientific Nicolet IS10 FTIR spectrometer using diamond ATR golden gate sampling and are reported in wave numbers ( $\text{cm}^{-1}$ ). Analytical thin-layer chromatography (TLC) was performed with Merck Silica Gel 60 F254 precoated plates. Visualization of spots was done by UV light (254 nm) and by charring with acidic ceric ammonium molybdate (470 mL  $\text{H}_2\text{O}$ , 28 mL  $\text{H}_2\text{SO}_4$ , 24 g ammonium molybdate, 0.5 g cerium ammonium nitrate). Flash chromatography was performed on Silica Gel 60 (230–400 mesh) with petroleum ether (PE, bp 40–65 °C) and ethyl acetate (EA) as eluents. Solutions were concentrated under reduced pressure with a Buchi rotary evaporator.

### **2,3,5-tri-*O*-benzyl-( $S_R$ )-*N*-tert-butanesulfinyl- $\alpha/\beta$ -D-xylofuranosylamine (1)**

(*R*)-2-Methyl-2-propanesulfinamide (1.38 g, 11.4 mmol) was added under argon to a mixture of 2,3,5-tri-*O*-benzyl-D-xylofuranose<sup>11</sup> (2.4 g, 5.7 mmol) and 4 Å activated molecular sieves (1.5 g) in dry toluene (12 mL). After 10 min of stirring at room temperature (ca. 20 °C),  $\text{Ti}(\text{OEt})_4$  (1.8 mL, 8.6 mmol) was added and the mixture was stirred at 70 °C until no starting material was present (TLC, ca. 22 h). The light-brown solution was diluted with  $\text{CH}_2\text{Cl}_2$  (15 mL) and filtered through Celite<sup>®</sup> (L = 1 cm,  $\varnothing$  = 5 cm), the Celite<sup>®</sup> pad was washed with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  15 mL), and the filtrate was stirred with brine (100 mL) for 5 minutes. The mixture was then again filtered through a second pad of Celite<sup>®</sup> (L = 1 cm,  $\varnothing$  = 5 cm), to remove titanium salts, the solids were washed with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  15 mL) and the phases were separated. The organic phase was

dried (MgSO<sub>4</sub>), filtered through a cotton plug and concentrated. The crude product was chromatographed (6:4→5:5 PE–EA) to provide **1** as yellow oil (1.94 g, 65%). Mixture of anomers ( $\alpha/\beta$  ratio varies).<sup>12</sup> *R<sub>f</sub>* 0.35 and 0.28 (1:1 PE–EA). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.38–7.22 (m, 15H, 3  $\times$  OCH<sub>2</sub>Ph  $\alpha$  + 3  $\times$  OCH<sub>2</sub>Ph  $\beta$ ), 5.36 (dd, 0.6H, <sup>3</sup>*J*<sub>1,2</sub> = 4.1 Hz, <sup>3</sup>*J*<sub>1,NH</sub> = 11.0 Hz, H-1  $\alpha$ ), 5.19 (br d, 0.4H, <sup>3</sup>*J*<sub>1,NH</sub> = 11.1 Hz, H-1  $\beta$ ), 4.77 (d, 0.4H, <sup>3</sup>*J*<sub>1,NH</sub> = 11.2 Hz, NH  $\beta$ ), 4.70 (d, 0.4H, <sup>2</sup>*J* = 11.7 Hz, 0.5  $\times$  OCH<sub>2</sub>Ph  $\beta$ ), 4.61–4.50 (m, 5H, 2  $\times$  OCH<sub>2</sub>Ph  $\alpha$  + 2.5  $\times$  OCH<sub>2</sub>Ph  $\beta$  + NH  $\alpha$ ), 4.46 (d, 0.6H, <sup>2</sup>*J* = 11.9 Hz, 0.5  $\times$  OCH<sub>2</sub>Ph  $\alpha$ ), 4.45–4.39 (m, 1.2H, H-4  $\alpha$  + 0.5  $\times$  OCH<sub>2</sub>Ph  $\alpha$ ), 4.37–4.32 (m, 0.4H, H-4  $\beta$ ), 4.25–4.22 (m, 0.4H, H-2  $\beta$ ), 4.04–4.00 (m, 1H, H-3  $\alpha$  + H-3  $\beta$ ), 3.89–3.86 (m, 0.6H, H-2  $\alpha$ ), 3.79–3.66 (m, 2.0H, H-5b  $\beta$  + H-5b'  $\beta$  + H-5b  $\alpha$  + H-5b'  $\alpha$ ), 1.17 (s, 5.4H, C(CH<sub>3</sub>)<sub>2</sub>  $\alpha$ ), 1.10 (s, 3.6H, C(CH<sub>3</sub>)<sub>2</sub>  $\beta$ ). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta$  138.3 (C-Ar  $\alpha$ ), 138.0 (C-Ar  $\beta$ ), 137.9 (C-Ar  $\alpha$ ), 137.5 (C-Ar  $\beta$ ), 137.2 (C-Ar  $\alpha$ ), 137.2 (C-Ar  $\beta$ ), 128.7–127.7 (CH-Ar  $\alpha$  + CH-Ar  $\beta$ ), 91.7 (C-1  $\beta$ ), 87.0 (C-1  $\alpha$ ), 85.7 (C-2  $\beta$ ), 81.6 (C-2  $\alpha$ ), 80.9 (C-3  $\beta$ ), 80.3 (C-3  $\alpha$ ), 80.2 (C-4  $\beta$ ), 78.2 (C-4  $\alpha$ ), 73.6 (OCH<sub>2</sub>Ph  $\beta$ ), 73.5 (OCH<sub>2</sub>Ph  $\alpha$ ), 72.6 (OCH<sub>2</sub>Ph  $\alpha$ ), 72.6 (OCH<sub>2</sub>Ph  $\alpha$ ), 72.6 (OCH<sub>2</sub>Ph  $\beta$ ), 72.2 (OCH<sub>2</sub>Ph  $\beta$ ), 68.6 (C-5  $\beta$ ), 67.7 (C-5  $\alpha$ ), 56.2 (C(CH<sub>3</sub>)<sub>2</sub>  $\alpha$ ), 56.1 (C(CH<sub>3</sub>)<sub>2</sub>  $\beta$ ), 22.6 (C(CH<sub>3</sub>)<sub>2</sub>  $\alpha$ ), 22.5 (C(CH<sub>3</sub>)<sub>2</sub>  $\beta$ ). IR (neat):  $\nu_{max}$  = 3030, 2866, 1454, 1363, 1207, 1061, 1027, 733 cm<sup>-1</sup>. HRMS (ESI): *m/z* calcd. for C<sub>30</sub>H<sub>38</sub>NO<sub>5</sub>S [M + H]<sup>+</sup> 524.2465; found: 524.2461.<sup>13</sup>

When the mixture ( $\alpha/\beta$ ) was characterized by NMR spectroscopy as a solution in CDCl<sub>3</sub>, traces of the open chain imine were also detected. Signals that were confidently assigned are reported below. (Signals for the imine were sometime not observed even after keeping **1** for one week as a solution in CDCl<sub>3</sub>).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.0 (s, 0.03H, H-1), 5.81 (d, 0.03H, *J* = 7.8 Hz), 5.10 (d, 0.04H, <sup>2</sup>*J* = 11.2 Hz, 0.5  $\times$  OCH<sub>2</sub>Ph), 5.01 (d, 0.03H, <sup>2</sup>*J* = 11.2 Hz, 0.5  $\times$  OCH<sub>2</sub>Ph), 3.43–3.31 (m, 0.07H, H-5a + H-5b), 2.61 (br d, 0.03H, <sup>3</sup>*J*<sub>4,OH</sub> = 3.9 Hz, OH). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta$  159.6 (C-1), 132.4 (CH-Ar), 73.8 (OCH<sub>2</sub>Ph), 73.4 (OCH<sub>2</sub>Ph), 72.8 (OCH<sub>2</sub>Ph), 57.9 (C).

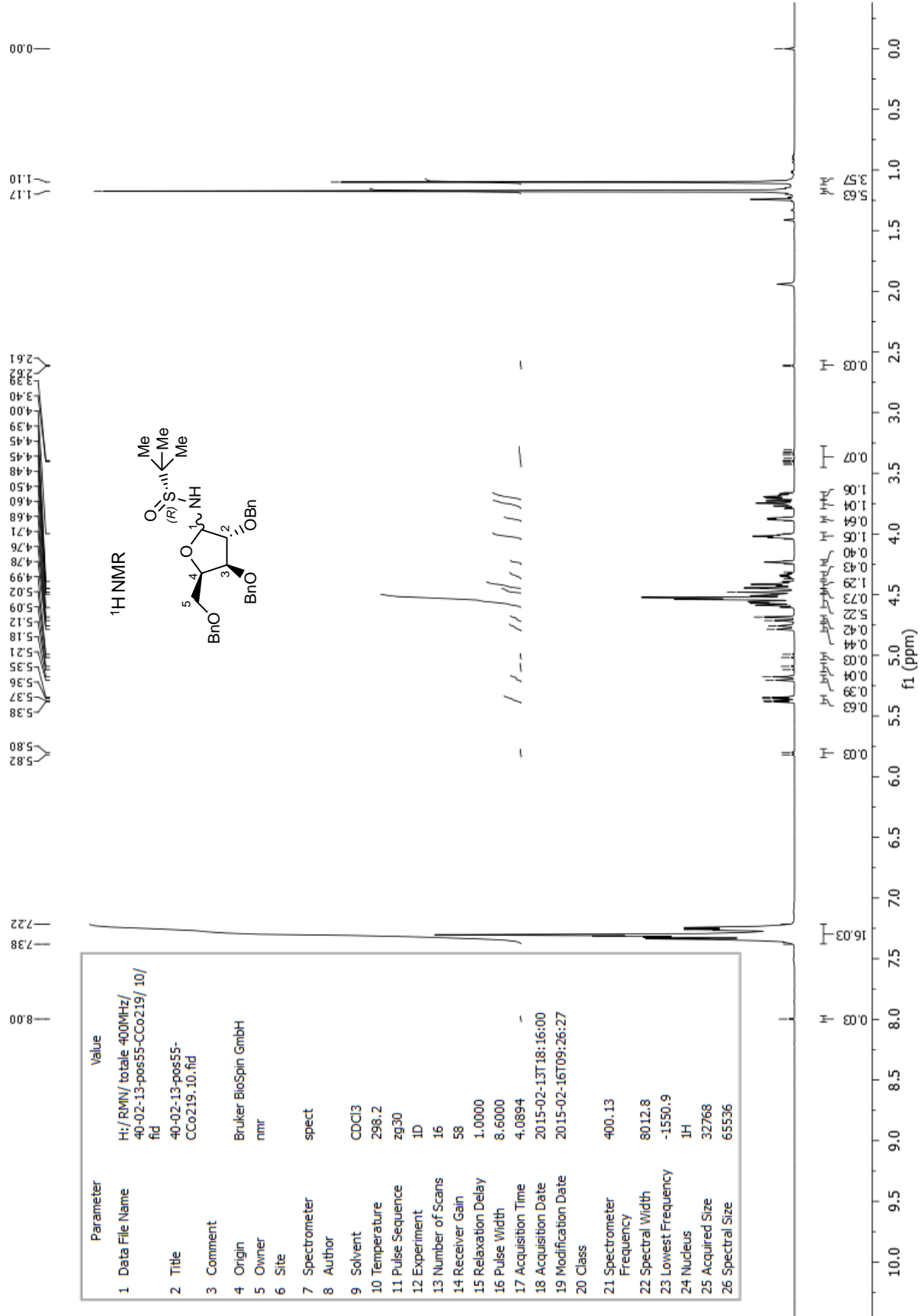
**(S<sub>R</sub>)-N-tert-Butanesulfinyl-5-O-tert-butyltrimethylsilyl-2,3-O-isopropylidene- $\alpha,\beta$ -D-ribofuranosylamine (2)**

(*R*)-2-Methyl-2-propanesulfinamide (80 mg, 0.66 mmol) was added under argon to a stirred mixture of 5-*O*-tert-butyltrimethylsilyl-2,3-*O*-isopropylidene- $\alpha,\beta$ -D-ribofuranose (100 mg, 0.33 mmol) and 4 Å activated molecular sieves (0.2 g) in 1,2-dichloroethane (1 mL). After 10 min,

Cs<sub>2</sub>CO<sub>3</sub> (156 mg, 0.50 mmol) was added and the stirring was continued at 60 °C until no starting material was present (TLC, 17–30 h). The yellow solution was filtered through Celite® (L = 1 cm, Ø = 3 cm), the solids were washed with CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and the filtrate was concentrated. The crude product was chromatographed (7:3 PE–EA) to provide anomeric mixture of **2** ( $\alpha/\beta$  ratio varies) as white amorphous solid (88 mg, 65%).<sup>12</sup> R<sub>f</sub> 0.40 (SiO<sub>2</sub>, PE:EA 6:4). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  5.35 (dd, 0.7H, <sup>3</sup>J<sub>1,2</sub> = 4.0 Hz, <sup>3</sup>J<sub>1,NH</sub> = 11.5 Hz, H-1  $\alpha$ ), 5.24 (br 'd', 0.3H, <sup>3</sup>J<sub>1,NH</sub> = 10.0 Hz, H-1  $\beta$ ), 4.92 (d, 0.3H, <sup>3</sup>J<sub>1,NH</sub> = 9.9 Hz, NH  $\beta$ ), 4.74 (d, 0.7H, J = 6.0 Hz, H-3  $\alpha$ ), 4.66 (br 'd', 0.3H, J = 6.0 Hz, H-3  $\beta$ ), 4.61 (br 'd', 0.3H, J = 6.0 Hz, H-2  $\beta$ ), 4.54 (dd, 0.7H, <sup>3</sup>J<sub>2,1</sub> = 4.1 Hz, <sup>3</sup>J<sub>2,3</sub> = 6.0 Hz, H-2  $\alpha$ ), 4.38 (d, 0.7H, J = 11.5 Hz, NH  $\alpha$ ), 4.23-4.19 (m, 0.3H, H-4  $\beta$ ), 4.13-4.09 (m, 0.7H, H-4  $\alpha$ ), 3.82-3.69 (m, 1.3H, H-5b  $\alpha$  + H-5b  $\beta$  + H-5b'  $\beta$ ), 3.74 (dd, 0.7H, <sup>3</sup>J<sub>5b,4</sub> = 2.3 Hz, <sup>3</sup>J<sub>5b,5b'</sub> = 10.8 Hz, H-5b'  $\alpha$ ), 1.48 (s, 2.1H, C(CH<sub>3</sub>)<sub>2</sub>  $\alpha$ ), 1.47 (s, 0.9H, C(CH<sub>3</sub>)<sub>2</sub>  $\beta$ ), 1.33 (s, 2.1H, C(CH<sub>3</sub>)<sub>2</sub>  $\alpha$ ), 1.30 (s, 0.9H, C(CH<sub>3</sub>)<sub>2</sub>  $\beta$ ), 1.21 (s, 6.3H, C(CH<sub>3</sub>)<sub>3</sub>(SO)  $\alpha$ ), 1.18 (s, 2.7H, C(CH<sub>3</sub>)<sub>3</sub>(SO)  $\beta$ ), 0.90 (s, 2.7H, C(CH<sub>3</sub>)<sub>3</sub>Si  $\beta$ ), 0.86 (s, 6.3H, C(CH<sub>3</sub>)<sub>3</sub>Si  $\alpha$ ), 0.10 (s, 0.9H, CH<sub>3</sub>Si  $\beta$ ), 0.09 (s, 0.9H, CH<sub>3</sub>Si  $\beta$ ), 0.05 (s, 2.1H, CH<sub>3</sub>Si  $\alpha$ ), 0.04 (s, 2.1H, CH<sub>3</sub>Si  $\alpha$ ). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta$  112.7 (C(CH<sub>3</sub>)<sub>2</sub>  $\beta$ ), 112.2 (C(CH<sub>3</sub>)<sub>2</sub>  $\alpha$ ), 93.3 (C-1  $\beta$ ), 89.1 (C-1  $\alpha$ ), 87.6 (C-2  $\beta$ ), 86.1 (C-4  $\beta$ ), 82.5 (C-4  $\alpha$ ), 82.2 (C-3  $\beta$ ), 82.1 (C-3  $\alpha$ ), 80.8 (C-2  $\alpha$ ), 65.6 (C-5  $\alpha$ ), 65.1 (C-5  $\beta$ ), 56.4 (C(CH<sub>3</sub>)<sub>3</sub>(SO)  $\beta$ ), 56.3 (C(CH<sub>3</sub>)<sub>3</sub>(SO)  $\alpha$ ), 26.9 (C(CH<sub>3</sub>)<sub>2</sub>  $\beta$ ), 26.3 (C(CH<sub>3</sub>)<sub>2</sub>  $\alpha$ ), 26.1 (C(CH<sub>3</sub>)<sub>3</sub>Si  $\beta$ ), 25.9 (C(CH<sub>3</sub>)<sub>3</sub>Si  $\alpha$ ), 25.3 (C(CH<sub>3</sub>)<sub>2</sub>  $\beta$ ), 24.8 (C(CH<sub>3</sub>)<sub>2</sub>  $\alpha$ ), 22.6 (C(CH<sub>3</sub>)<sub>3</sub>(SO)  $\beta$ ), 22.6 (C(CH<sub>3</sub>)<sub>3</sub>(SO)  $\alpha$ ), 18.6 (C(CH<sub>3</sub>)<sub>3</sub>Si  $\beta$ ), 18.1 (C(CH<sub>3</sub>)<sub>3</sub>Si  $\alpha$ ), -5.1 (CH<sub>3</sub>Si  $\beta$ ), -5.2 (CH<sub>3</sub>Si  $\beta$ ), -5.4 (CH<sub>3</sub>Si  $\alpha$ ), -5.6 (CH<sub>3</sub>Si  $\alpha$ ). IR (neat):  $\nu_{max}$  = 3240, 2930, 2858, 1463, 1381, 1256, 1211, 1072, 825 cm<sup>-1</sup>. HRMS (ESI): *m/z* calcd. for C<sub>18</sub>H<sub>38</sub>NO<sub>5</sub>SSi [M + H]<sup>+</sup> 408.2234; found: 408.2233.<sup>13</sup>

## ACKNOWLEDGEMENTS

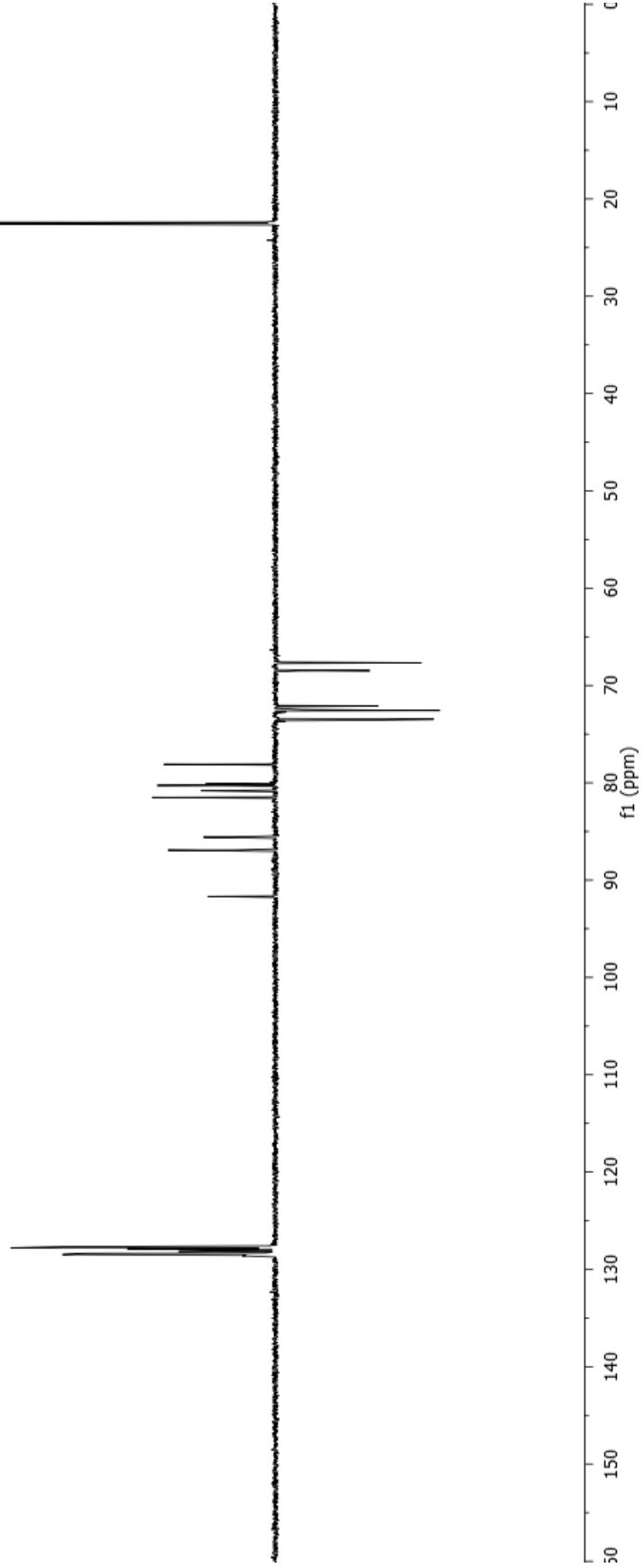
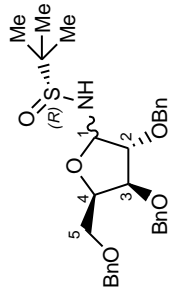
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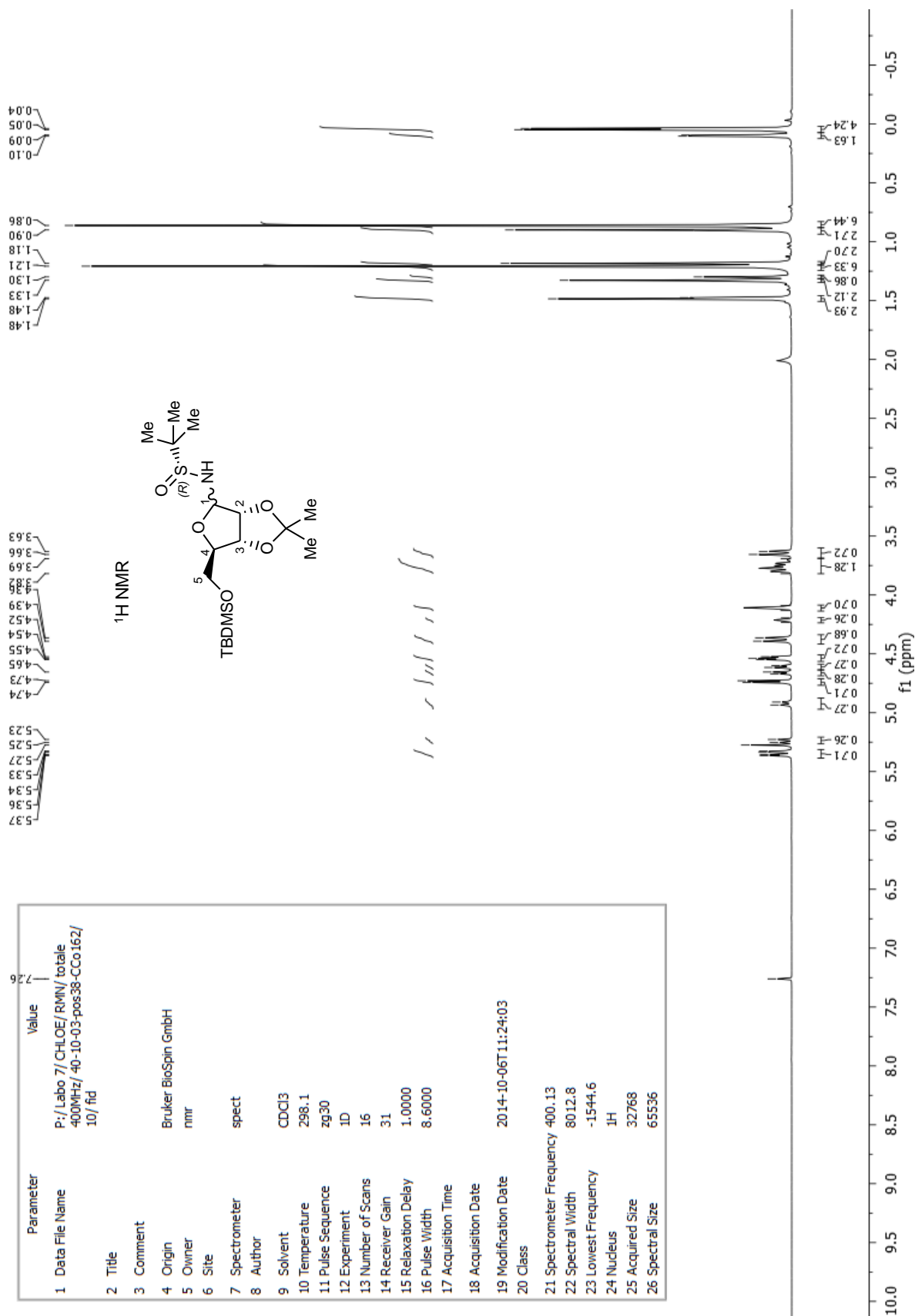




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DEPT NMR

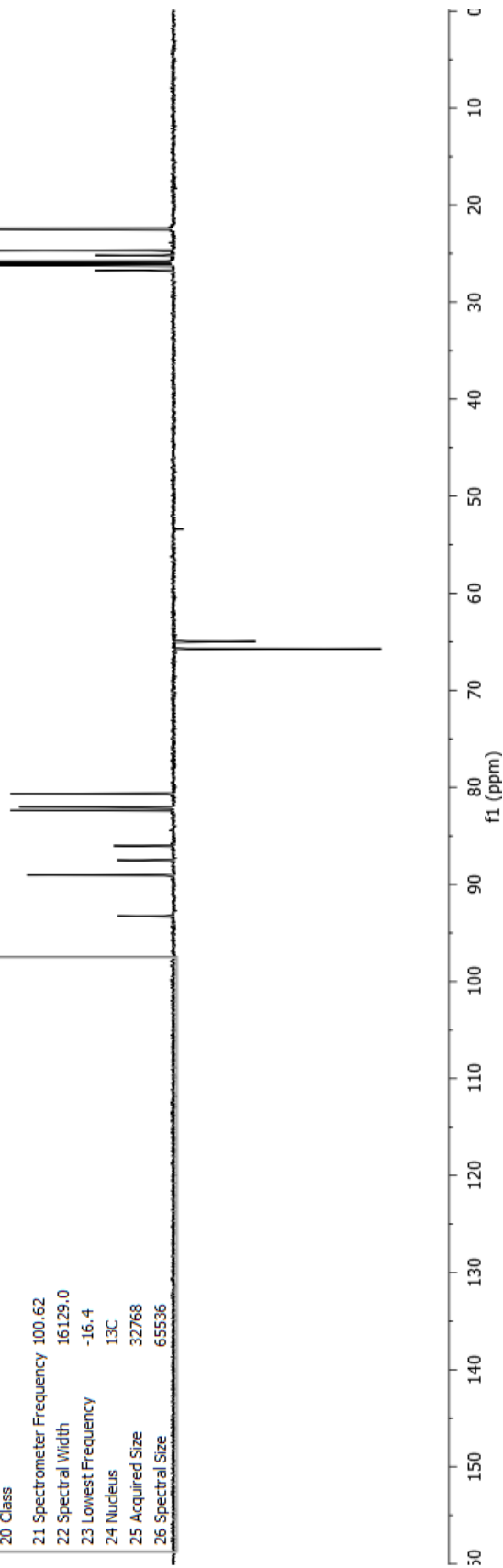
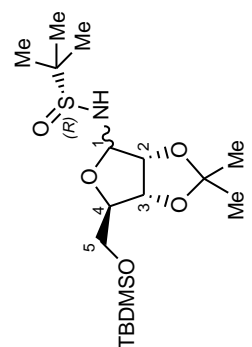






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DEPTNMR



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  9. Unpublished results.
  10. *N*-benzyl-, *N*-Cbz-, *N*-alkyl- and *N*-*tert*-butanesulfinyl-*N*-glycosides commonly epimerize in solution, going through an open-chain imine intermediate. Addition of nucleophiles to these intermediates, subsequent activation and cyclization give the related iminosugar-*C*-glycosyl compounds stereoselectively. For this purpose, the two anomers ( $\alpha/\beta$ ) of compounds **1** and **2** do not need to be separated although they might be (see ref. 8).
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  12. The signals for anomeric protons were assigned by analogy with the literature. See Nicolaou, K. C.; Snyder, S. C.; Longbottom, D. A.; Nalbandian, A. Z.; Huang, X. *Chem. Eur. J.* **2004**, *10*, 5581–5606.
  13. *N*-*tert*-butanesulfinyl glycosylamines can be handled in air at room temperature, but prolonged storage at room temperature results in decomposition over a period of a few days. For this reason we were not able to obtain correct elemental analytical figures for compounds **1** and **2**.