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Synthesis and Isolation of Diastereomeric Anomeric Sulfoxides from a D-Mannuronate Thioglycoside Building Block

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Abstract: Methyl [*S*-phenyl 4-*O*-acetyl-2,3-di-*O*-benzyl-1-thio-α-D-mannopyranoside (R/S)$_S$-oxide] uronate was synthesised from a thioglycoside mannosyl uronate donor in a 98% yield. By using one equivalent of meta-chloroperbenzoic acid (m-CPBA) as the sulphur oxidant, a smooth conversion to the diastereomeric sulfoxide products was achieved. The product was fully characterized by ^{1}H, ^{13}C and 2D NMR alongside MS analysis.

Keywords: glycosyl sulfoxide; uronate; thioglycoside oxidation; mannose

1. Introduction

Glycosyl sulfoxides have been successfully used as glycosyl donors within carbohydrate synthesis ever since a report by Kahne and co-workers in which they activated an anomeric sulfoxide with triflic anhydride to glycosylate a deoxycholic ester derivative [1]. Since then, glycosyl sulfoxides' use has continued, along with developments in mechanistically understanding their role in glycosylation reactions [2]. Glycosyl sulfoxides are traditionally formed by the careful oxidation of a parent thioglycoside component to form an *S*-oxide, typically by using meta-chloroperbenzoic acid (m-CPBA) as the oxidant, although other methods, including OXONE®, have recently been developed [3,4]. Whilst the oxidation generally proceeds to yield diastereomeric mixtures, stereoselective sulfoxidations have been reported for particular classes of parent thioglycosides, e.g., α-mannopyranose thioglycosides [5–7].

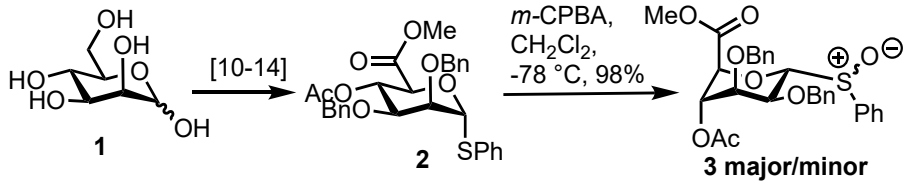
Uronic acids, where the C6 pyranosyl carbon is at the carboxylic acid oxidation level, have also been prepared as glycosyl sulfoxide donors for the synthesis of oligosaccharide targets that contain D-glucuronic acid [8]. As part of a wider project concerning the chemical synthesis of alginate oligosaccharides [9], we required access to a D-mannuronic acid glycosyl sulfoxide building block (**3**) and provide here our record of its synthesis and full characterization from *S*-phenyl thioglycoside (**2**).

2. Results

Starting from D-mannose **1**, we prepared thioglycoside uronate donor **2** by using established procedures (Scheme 1) [10–14]. Briefly, peracetylation of **1** followed by anomeric thioglycosidation using PhSH/BF_3·Et_2O enabled global deacetylation and 4,6-benzylidenation. The benzyl protection of the remaining hydroxy groups was then followed by 4,6-benzylidene hydrolysis to allow for regioselective C6 oxidation of the corresponding mannuronic acid. Finally, methylation of the carboxylic acid and 4-OH protection with acetate delivered thioglycoside donor **2**.

We next pursued the preparation of glycosyl sulfoxide **3** by using one equivalent of m-CPBA as the oxidant at −78 °C (Scheme 1). Following the addition of the oxidant, the reaction was slowly allowed

to warm to −30 °C over four hours. Thin layer chromatography (TLC) analysis at this point showed the appearance of two new, lower R_f spots, which were indicative of an oxidised material. Following workup, ^{1}H NMR analysis of the crude residue indicated that a mixture of sulfoxide diastereomers had formed (**3major**:**3minor**, 2:1). The diastereoisomers were separated by column chromatography and analytical data collected for both.



Scheme 1. Synthesis of methyl [*S*-phenyl 4-*O*-acetyl-2,3-di-*O*-benzyl-1-thio-α-D-mannopyranoside $(R/S)_S$-oxide] uronate **3** from thioglycoside **2**.

For the major diastereoisomer, an analysis of the ^{1}H NMR data [5.11 ppm (d (doublet), J = 10.1 Hz, H1)] suggested that the product adopted a $^1C_4$ conformation in solution and the H1–H2 coupling supported a *trans*-diaxial relationship. This observation was further supported by the multiplicity for H4 (dd (doublet of doublets), J = 3.9, 1.4 Hz), which was distinct from the usual *trans*-diaxial coupling observed for $^4C_1$ mannose derivatives (Figure 1). The coupling observed for the minor diastereoisomer was different [5.26 ppm (br d, J = 7.4 Hz, H1)] and more closely matched the J value that was observed for **2** [5.80 ppm (d, J = 7.1 Hz, H1)], thus suggesting that the barrier to interconvert between $^1C_4$ and $^4C_1$ was lower for this diastereoisomer, as evidenced by signal broadening and J value averaging in the ^{1}H NMR spectrum. Diastereomeric sulfoxide **3** is currently being evaluated as a glycosyl donor for the synthesis of mannonate-containing oligosaccharides. Copies of NMR data for the major and minor isomers of **3** are included in the Supplementary Materials.

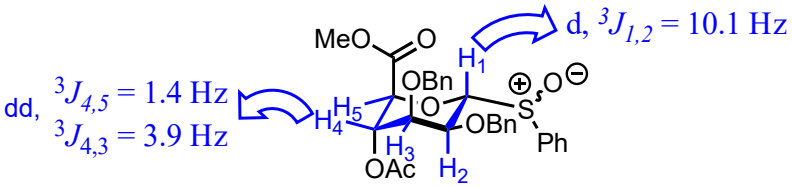


Figure 1. Indication of $^1C_4$ conformation for (**3**) using ^{1}H NMR coupling constant data.

3. Materials and Methods

3.1. General

All reagents and solvents that were available commercially were purchased from Acros Organics™ Belgium, Alfa Aesar™ Ward Hill, MA, Fisher Scientific™ Waltham MA, or Sigma Aldrich™ St. Louis MO. All reactions in non-aqueous solvents were conducted in flame-dried glassware under a nitrogen atmosphere with a magnetic stirring device. Solvents were purified by passing through activated alumina columns, used directly from a PureSolv-MD solvent purification system, and transferred under nitrogen. Reactions requiring low temperatures used the following cooling baths: −78 °C (dry ice). Infrared spectra were neatly recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer; selected absorbencies (ν_{max}) are reported in cm^{-1}. ^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C spectra were recorded at 100 MHz with the use of a Bruker AVIII400 spectrometer. ^{1}H NMR signals were assigned with the aid of gDQCOSY. ^{13}C NMR signals were assigned with the aid of gHSQCAD. Coupling constants are reported in Hertz. Chemical shifts (δ, in ppm) were standardized against the deuterated solvent peak. NMR data were analysed with the Nucleomatica iNMR software. ^{1}H NMR splitting patterns were assigned as follows: s (singlet), br d (broad doublet), d (doublet), t (triplet), dd (doublet of doublets), ddd (doublet of doublet of doublets), or m (multiplet and/or multiple resonances).

Reactions were followed by TLC by using Merck silica gel 60F254 analytical plates (aluminium support) and were developed with the use of standard visualising agents: short wave UV radiation (245 nm) and 5% sulfuric acid in methanol/Δ. Purification via flash column chromatography was conducted by using silica gel 60 (0.043–0.063 mm). Optical activities were recorded on a Rudolph autopol I automatic polarimeter (concentration in g/100mL). MS and HRMS (ESI) were obtained on Waters (Xevo, G2-XS TOF) or Waters Micromass LCT spectrometers by using a methanol mobile phase. High resolution (ESI) spectra were obtained on a Xevo, G2-XS TOF mass spectrometer.

3.2. Methyl [S-phenyl 4-O-acetyl-2,3-di-O-benzyl-1-thio-α-D-mannopyranoside (R/S)$_S$-oxide] uronate **3**

m-CPBA (66 mg, 0.38 mmol, 1.0 equiv.) was added to a stirred solution of **2** (200 mg, 0.38 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) at −78 °C, followed by warming to -30 °C over 4 h, whereupon TLC analysis (EtOAc/hexane, 1/2) indicated that no starting material remained. The reaction was quenched by the addition of a saturated aqueous $NaHCO_3$ solution (25 mL) and the organic layer separated and washed with brine (2 × 25 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure, furnishing crude **3** as a yellow oil. Purification was conducted with the use of silica gel flash column chromatography eluting with EtOAc/hexane (0/100, 20/80, 40/60, 90/10) to afford (**3**) (201 mg, 0.34 mmol, 98%) as two separable diastereoisomers (**3major**:**3minor**, 2:1, 132 mg:69 mg).

Analytical data for **3minor**. R_f 0.18 (EtOAc/hexane, 1/2); $[\alpha]_D^{26}$ +100 (c. 1.0, $CHCl_3$); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.63–6.91 (15 H, m, ArH), 5.51 (1 H, dd, J = 5.3, 3.4 Hz, H4), 5.24 (1 H, d, J = 7.4 Hz, H1), 4.57 (1 H, d, J = 3.2, Hz, H5), 4.50 (1 H, d, J = 12.9 Hz, CH_2Ph-attached to C3), 4.47 (1 H, d, J = 12.6 Hz, CH_2Ph-attached to C3), 4.40 (1 H, d, J = 11.8 Hz, CH_2Ph-attached to C2), 4.33 (1 H, d, J = 11.8 Hz, CH_2Ph-attached to C2), 4.05 (1 H, dd, J = 7.5, 2.9 Hz, H2), 3.92 (1 H, dd, J = 5.0, 2.8 Hz, H3), 3.58 (3 H, s, CO_2CH_3), 2.05 (3 H, s, C(O)CH_3); ^{13}C NMR (101 MHz; $CDCl_3$) δ 169.7 (C=O of C(O)CH_3), 168.1 (C=O of CO_2CH_3), 140.7, 137.3, 137.3, 130.7, 128.9, 128.3, 128.2, 127.9, 127.7, 127.7, 124.5, 92.2 (C1), 74.5 (C5), 73.2 (C3), 72.7 (CH_2Ph-attached to C3), 71.2 (CH_2Ph-attached to C2), 70.0 (C2), 69.4 (C4), 52.4 (CO_2CH_3), 20.9 (C(O)CH_3); LRMS (ESI$^+$) *m/z* 539 [(M + H)$^+$, 100%]; HRMS (ESI$^+$) *m/z* Found: (M + H)$^+$ 539.1739 $C_{29}H_{30}O_8S$ requires (M + H)$^+$, 539.1734; IR νmax/cm^{-1} 1735 (s, C=O), 1183 (s, C–O), 1143 (s, C–O), 1074 (s, S=O).

Analytical data for **3major**. R_f 0.10 (EtOAc/hexane, 1/2); $[\alpha]_D^{26}$ −2.3 (c. 1.0, $CHCl_3$); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.79–7.31 (15 H, m, ArH), 5.52 (1 H, dd, J = 3.9, 1.4 Hz, H4), 5.10 (1 H, d, J = 10.1 Hz, H1), 4.73 (1 H, d, J = 11.1 Hz, CH_2Ph-attached to C2 or C3), 4.62 (1 H, d, J = 12.0 Hz, CH_2Ph-attached to C2 or C3), 4.58 (2 H, d, J = 12.0 Hz, CH_2Ph-attached to C2 or C3), 4.57 (1 H, d, J = 11.1 Hz, CH_2Ph-attached to C2 or C3), 4.39 (1 H, d, J = 1.0 Hz, H5), 4.21 (1 H, dd, J = 10.1, 2.7 Hz, H2), 3.92–3.90 (1 H, m, H3), 3.42 (3 H, s, CO_2CH_3), 2.09 (3 H, s, C(O)CH_3); ^{13}C NMR (101 MHz; $CDCl_3$) δ 170.0 (C=O of C(O)CH_3), 167.9 (C=O of CO_2CH_3), 137.0, 137.0, 130.6, 128.6, 128.5, 128.4, 128.4, 128.2, 128.1, 128.0, 125.1, 86.8 (C1), 74.5 (C5), 72.6 (CH_2Ph-attached to C2 or C3), 72.4 (CH_2Ph-attached to C2 or C3), 72.4 (C3), 70.6 (C2), 69.4 (C4), 52.1 (CO_2CH_3), 21.1 (C(O)CH_3); LRMS (ESI$^+$) *m/z* 539 [(M + H)$^+$, 100%]; HRMS (ESI$^+$) *m/z* Found: (M + H)$^+$ 539.1719 $C_{29}H_{30}O_8S$ requires (M + H)$^+$, 539.1734; IR νmax/cm^{-1} 1735 (s, C=O), 1183 (s, C–O), 1143 (s, C–O), 1074 (s, S=O).

Supplementary Materials: The following are available online, Figure S1: ^{1}H NMR spectrum of compound **3major**, Figure S2: ^{13}C NMR spectrum of compound **3major**, Figure S3: ^{1}H NMR spectrum of compound **3minor**, Figure S4: ^{13}C NMR spectrum of compound **3minor**.

Author Contributions: E.D. and G.J.M. conceived and designed the experiments; E.D. performed the experiments and analysed the data; G.J.M. and E.D. wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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