

## Ultrasonication-Assisted Spray Ionization Mass Spectrometry for On-Line Monitoring of Organic Reactions

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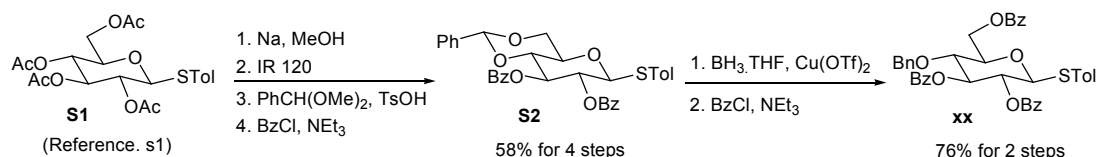
### Electronic Supporting Information

#### Experimental

##### Reagents and Materials

Methanol and hydrofluoric acid were obtained from Tedia (Fairfield, OH); acetonitrile and sodium hydroxide (NaOH) were purchased from Riedel de Haën (Seelze, Germany). The fused-silica capillary (50- $\mu\text{m}$  i.d.  $\times$  365- $\mu\text{m}$  o.d.) was obtained from Polymicro Technologies (Phoenix, AZ). All solvents for reactions were ACS grade and dried or distilled following standard procedures before used. Dichloromethane ( $\text{CH}_2\text{Cl}_2$ ) was bought from Mallinckrodt (Philipsburg, NJ, USA), acetonitrile ( $\text{CH}_3\text{CN}$ ) was bought from J. T. Baker (Philipsburg, NJ, USA). Methanol and ethyl acetate (EtOAc) were bought from local vendor ECHO (Miaoli, Taiwan) and hexane was bought from Haltermann (Hamburg, Germany). Reagents of chemical reactions were purchased from oversea vendors and used without further purification. Sodium (Na) was bought from TCI (Tokyo, Japan), amberlite IR-120- $\text{H}^+$  from Sigma-Aldrich (St. Louis, MO, USA), benzaldehyde dimethyl acetal from Alfa-Aesar (Heysham, MA, USA), *p*-toluenyl sulfonic acid monohydrate (TsOH) from Alfa-Aesar (Ward Hill, MA, USA), triethyl amine ( $\text{NEt}_3$ ) from TEDIA (Fairfield, OH, USA), benzoyl chloride (BzCl) from Lancaster (Morecambe, England), 1 M borane in THF from Acros (NJ, USA), and copper triflate ( $\text{Cu}(\text{OTf})_2$ ) from STREM (New Bury Port, MA, USA). Thin layer chromatography plates (60F-254 E) for monitoring reactions and silica gel (60, particle size 63–200  $\mu\text{m}$ ) for purification of compounds were purchased from E. Merck (Darmstadt, Germany).

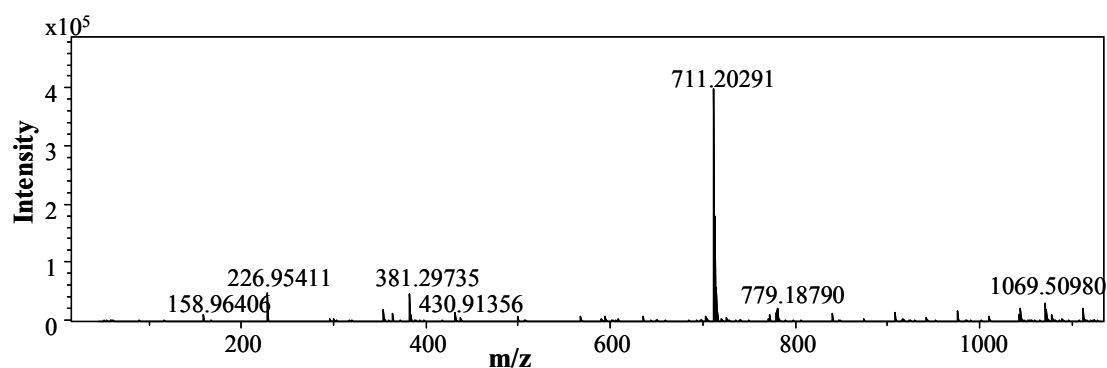
##### Synthesis of Reactant A



Peracetyl thioglucopyranoside **S1** (4 g, 8.8 mmol) was treated with sodium (Na) (ca. 40 mg) in a mixture of dichloromethane ( $\text{CH}_2\text{Cl}_2$ ) (16 mL) and methanol (20 mL) at

RT.<sup>1</sup> Upon complete removal of the acetyl functions, the mixture was neutralized with resin IR-120(H<sup>+</sup>), which was removed by simple filtration. The resulting filtrate was concentrated and dried under vacuum for 3 h. The crude thioglucopyranoside was subsequently suspended in dry acetonitrile (CH<sub>3</sub>CN) (40 mL), and followed by the addition of benzaldehyde dimethyl acetal (1.74 mL, 11.4 mmol) and *p*-toluenyl sulfonic acid monohydrate (168 mg, 0.88 mmol). Upon completion of acetal formation as assessed by TLC, the reaction was quenched by addition of triethylamine (NEt<sub>3</sub>) (ca. 0.3 mL). The quenched reaction mixture was concentrated, and diluted with CH<sub>2</sub>Cl<sub>2</sub> (40 mL), which was washed with satd. NaHCO<sub>3</sub> (20 mL × 1), brine (20 mL × 1), dried (over MgSO<sub>4</sub>), filtered, and concentrated for precipitation in a mixture of CH<sub>2</sub>Cl<sub>2</sub> and hexane to afford the crude 4,6-*O*-benzylidene acetal intermediate as white amorphous solid (2.8 g, 85% from **S1**). The crude 4,6-*O*-benzylidene acetal intermediate (1.8 g, 3.1 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and NEt<sub>3</sub> (3 mL, 21.7 mmol) was treated with drop-wise addition of benzoyl chloride (BzCl) (1.2 mL, 10.2 mmol) at 0 °C under N<sub>2</sub> and the reaction mixture was stirred at RT. Upon completion of benzylation, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL), which was then washed with satd. NaHCO<sub>3</sub> (10 mL × 1), brine (10 mL × 1), dried (over MgSO<sub>4</sub>), filtered, and concentrated for column chromatography purification over Silica gel (Elution: Hexane/EtOAc/CH<sub>2</sub>Cl<sub>2</sub> = 3/0.5/2 to 3/1/2) to afford the 2,3-*O*-dibenzoyl-4,6-*O*-benzylidene thioglucopyranoside **S2** as white amorphous solid (1.9 g, 68%).<sup>2</sup> A mixture of the thioglucopyranoside **S2** (2.5 g, 4.3 mmol) and BH<sub>3</sub>·THF (1 M, 21.5 mL) was treated with copper triflate (233 mg, 6.4 mmol) in at 0 °C under N<sub>2</sub>. Upon completion of reductive cleavage of benzylidene acetal, the cooled mixture was neutralized with addition of NEt<sub>3</sub> (0.5 mL), followed by MeOH. The quenched reaction mixture was concentrated for column chromatography purification over silica gel (Elution: Hexane/EtOAc/CH<sub>2</sub>Cl<sub>2</sub> = 4/1/0.5 to 2/1/0.5) to afford 2,3-*O*-dibenzoyl-4-*O*-benzyl thioglucopyranoside as white amorphous solid (2.1 g, 85%).<sup>3</sup> The 2,3-*O*-dibenzoyl-4-*O*-benzyl thioglucopyranoside (1.2 g, 2.05 mmol) was treated with benzoyl chloride (0.29 mL, 2.47 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (7 mL) and NEt<sub>3</sub> (0.85 mL, 6.2 mmol) at 0 °C under N<sub>2</sub>. Upon completion of benzylation, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (15 mL), which was washed with satd. NaHCO<sub>3</sub> (10 mL × 1), brine (10 mL × 1), dried (over MgSO<sub>4</sub>), filtered, and concentrated for column chromatography purification over silica gel (Elution: Hexane/EtOAc/CH<sub>2</sub>Cl<sub>2</sub> = 5/1/0.5 to 2/1/0.5) to afford the target 2,3,6-*O*-tribenzoyl-4-*O*-benzyl

thioglucopyranoside as white amorphous solid (1.27 g, 90%);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.16 (d,  $J = 7.5$  Hz, 1H, ArH), 8.11 (d,  $J = 7.5$  Hz, 2H, ArH), 8.00 (t,  $J = 7.8$  Hz, 3H, ArH), 7.70–7.62 (m, 2H, ArH), 7.57–7.48 (m, 5H, ArH), ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.16 (d,  $J = 7.5$  Hz, 1 H,ArH), 8.11 (d,  $J = 7.5$  Hz, 1H, ArH), 8.00 (t,  $J = 7.8$  Hz, 3H, ArH), 7.70–7.64 (m, 2H, ArH), 7.57–7.52 (m, 5H, ArH), 7.43-7.28 (m, 6H, ArH), 7.16-7.14 (m, 5H, ArH), 6.97 (d,  $J = 7.8$  Hz, 2H, ArH), 5.85 (t,  $J = 8.1$  Hz, 1 H), 5.4 (t,  $J = 9.9$  Hz, 1 H), 4.95 (d,  $J = 9.9$  Hz, 1H), 4.79 (d,  $J = 11.7$  2, 76.4, 75.5, 74.8, 70.5, 63.1, 21.1 Hz, 1 H) 4.65–4.55 (m, 3H), 3.97–3.91 (m, 2H), 2.30 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  166.0, 165.6, 165.2, 138.3, 136.6, 133.8, 133.6, 133.1, 130.1, 129.8, 129.7, 129.5, 129.2, 128.4, 128.3, 128.28, 128.2, 128.0, 127.6, 85.8, 77. Mass spectrum was obtained from a Bruker Daltonics micrOTOF II focus: calcd for  $\text{C}_{41}\text{H}_{36}\text{O}_8\text{SNa}$  requires 711.20231; observed:  $m/z = 711.20291$  [ $\text{MNa}$ ] $^+$  (see below).



formula	m/z (theoretical)	error	mSigma
C 41H36O8SNa	711.20231	-0.8 ppm	7.3

### **Fabrication of the Tapered Capillary.**

The tapered fused-silica capillary was fabricated by applying a small weight (50 g) on the lower end of a vertical capillary. The lower part of the capillary was heated and then quickly drawn to form a narrow capillary tip. The capillary tip was immersed in an HF solution (24%) for 10 min after cooling to ambient temperature. The tip was rinsed with methanol and deionized water. The tapered capillary was conditioned prior to analysis by using a pump to rinse it successively with 1 M NaOH (30 min), water (30 min), and methanol/acetonitrile (1/1, v/v) (10 min).

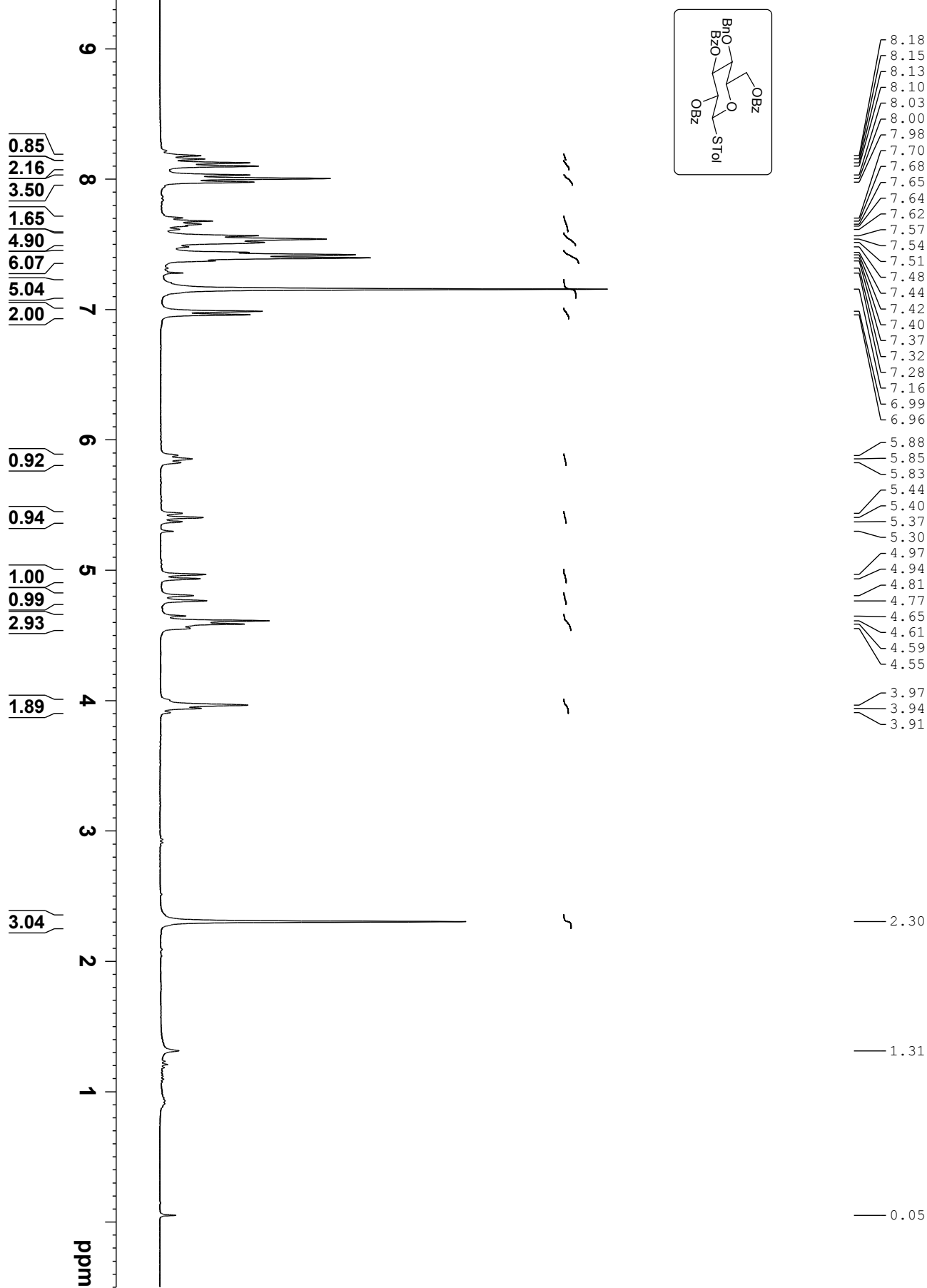
### **Setup of UASI MS**

UASI experiments were performed using an ultrasonicator (160 W) (volume: 2.5 L, frequency: 42 kHz), generally filled with 2.1 L of water. After rinse and activation, the tapered capillary (length, 40 cm; tip diameter: ca.  $10 \pm 3 \mu\text{m}$ ) was filled with sample solution before placing into the aqueous sample solution within a vial that was positioned in an ultrasonicator. The tapered capillary outlet was close to (ca. 5 mm) the inlet of an ion trap mass spectrometer. The heated transfer glass-capillary in the ion trap mass spectrometer was maintained at 150 °C with a dry gas flow of 5 L/min. The voltages on the MS capillary inlet were set at -1500 V for the spectra recorded in positive ion mode. The on-line nanospray mode was employed during UASI MS analysis. When the power of the ultrasonicator was switched on, UASI signals were readily acquired by the ion trap mass spectrometer.

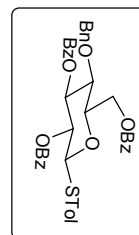
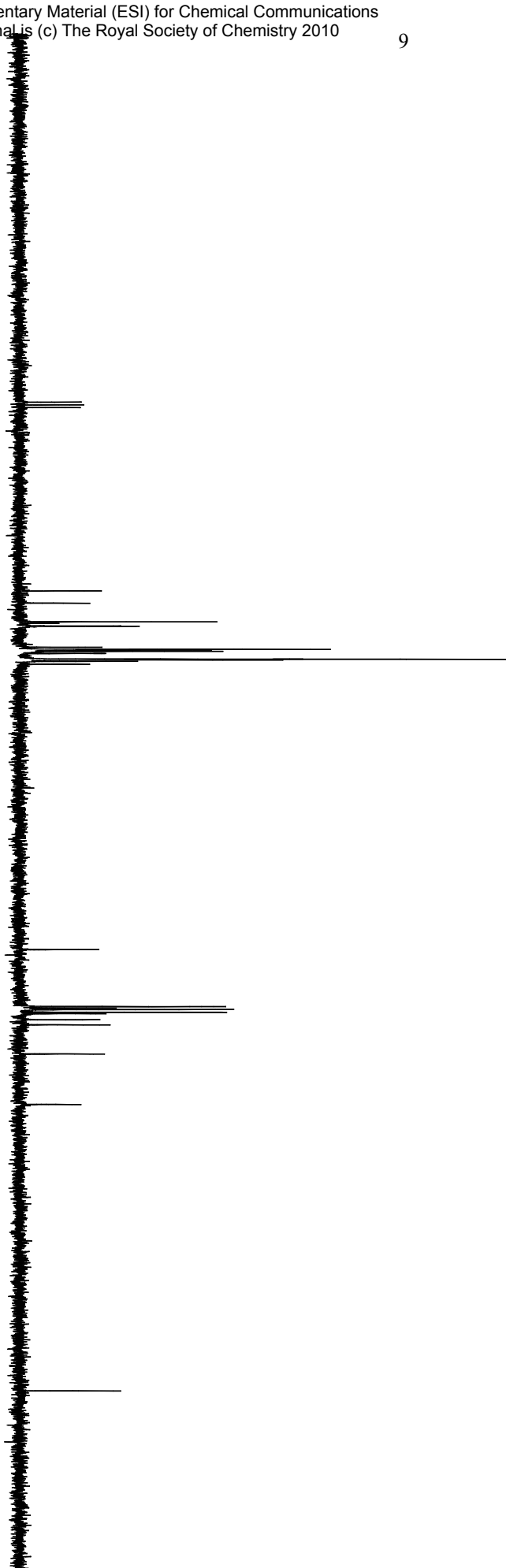
**Instrumentation.** All mass spectra were obtained using an Esquire 2000 ion trap mass spectrometer (Bruker Daltonics, Germany). When the commercial spray emitter was used for ESI, the spray voltage applied on the MS capillary inlet was set at -4 kV, the flow rate for sample infusion was set at 4  $\mu\text{L}/\text{min}$ , the pressure of the nebulizer gas was set at 10 psi, and the temperature of the heated transfer capillary was maintained at 300 °C with a dry gas flow (5 L/min).

### **References**

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210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



166.00  
165.60  
165.21

138.34  
136.55  
133.80  
133.59  
133.14  
130.08  
129.77  
129.66  
129.48  
129.16  
128.35  
128.32  
128.28  
128.22  
128.02  
127.59

85.78  
77.43  
77.20  
77.00  
76.58  
76.38  
75.50  
74.75  
70.48  
63.08

21.10