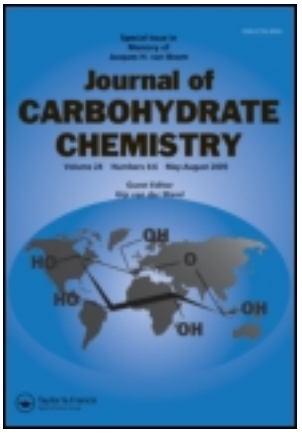

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Synthesis of Interglycosidically *S*-Linked 1-Thio-Oligosaccharides Under Microwave Irradiation

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Microwave irradiation (MWI) has accelerated the synthesis of *S*-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)thiouronium bromide **(2a)**, whose reaction with 2,3,4,6-tetra-*O*-acetyl-*α*-D-glucopyranosyl bromide **(1a)** in the presence of Et_3N afforded stereoselectively the acetylated *β*,*β*-1-thiotrehalose **4a**. Similarly, the respective D-galactopyranosyl **4b** and 2-acetylamino-2-deoxy-D-glucopyranosyl **4c** analog as well as 4,4′-di-*O*-(2,3,4,6-tetra-*O*-acetyl-*β*-D-galactopyranosyl) **4d** and 4,4′-di-*O*-(2,3,4,6-tetra-*O*-acetyl-*α*-D-glucopyranosyl) **4e** derivatives of 2,2′,3,3′,6,6′-hexa-*O*-acetyl *β*,*β*-1-thiotrehalose were prepared.

Keywords Microwave, Thio-oligosaccharides, Thiotrehaloses, Glycosyl isothiouronium salt, Glycosyl halide

INTRODUCTION

Thioglycosides are considered an important class of carbohydrate derivatives.[1–4] There is increasing interest in using them as glycosyl donors,[5] and they are promising candidates for carbohydrate mimics, potential thera-

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peutics, and enzyme inhibitors.[6] The interest in their enzyme inhibition[1,2] is due to their stability to the action of glycosidases, which is more promising than that of the corresponding *O*-glycosides. Thus, they can inhibit enzymatic hydrolysis, which may be a versatile approach to map the active site of glycosyl hydrolases. The thioanalog of oligosaccharides have gained a recent continuous development not only devoted to their synthesis but also for biochemical and x-ray studies.[1,2,7–9] 1,1-Thio-α,α-trehalose and α-D-glucopyranosyl-1-thio-α-D-mannopyranoside have been found to be inhibitors for cockchafer trehalase.[10] Moreover, thiosucrose inhibits levansucrase from *Bacillus subtilis* and yeast invertase.[11] Although the β,β-thiotrehalose was synthesized[12] in 1917, the α,α-thiotrehalose was synthesized[13] 60 years later, in 1978. Since then a number of their analog have been prepared and various conditions utilized.[14–23]

RESULTS AND DISCUSSION

Recently there has been a growing interest in employing microwave irradiation (MWI) for the synthesis of organic compounds.[24–27] This technique is based on the empirical observation that some organic reactions proceed much faster and with higher yields under MWI compared to conventional heating. Continuing our work[27] on accelerating organic reactions under MWI, we have developed a convenient, efficient, and practical one-pot method for the synthesis of β,β-thio-oligosaccharides.

The β,β-thiotrehaloses have been conventionally prepared from the reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide with either potassium sulfide or 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose.[12,16] The former can be catalyzed by the presence of quaternary alkylammonium[14] or phosphonium[15] salts.

In the present work, the readily available *S*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-thiouronium bromide[4] **(2a**) has been used under MWI as a source for generating the respective thiol at the anomeric center to act as a nucleophile that upon reaction with the anomeric electrophile, generated from **1a**, would give the respective thiotrehalose. Thus, the precursor **2a** was prepared by MWI of a solution of **1a** and thiourea in acetone for 3 min. Then the electrophilic thiol was generated, in situ, by MWI of **2a** in a mixture with **1a** in the presence of triethylamine as a catalyst to give 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (acetyl derivative of β,β-1-thiotrehalose) **(4a)** within 3 min in a higher yield than that resulting from the conventional method.[15] The galacto and 2-acetylamino-2-deoxy analog **4b** and **4c** were also obtained from the reaction of **1b** with **2b** and **1c** with **2c**, respectively, under similar conditions (Fig. 1).

Similarly, the reaction was extended to the disaccharides, whereby the isothiouronium derivatives **2d** and **2e** were prepared from the respective

bromides **1d** and **1e** by reaction with thiourea under MWI. Further reaction of **1d** with **2d** and **1e** with **2e** in the presence of Et_3N under MWI gave 4,4′-di-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl) 2,2′,3,3′,6,6′-hexa-*O*-acetyl-β,β-1-thiotrehalose (**4d)** and 4,4′-di-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl) 2,2′,3,3′,6,6′-hexa-*O*-acetyl-β,β-1-thiotrehalose **(4e)**, respectively. The structures of the products were confirmed by their spectral data. The β-anomeric configuration in the products was readily deduced from their ^{1}H NMR spectra; H-1 appeared as a doublet with $J_{1,2}$ value 10.2 Hz, and ^{13}C-1 appeared at δ_C 80.7 in compound **4a**. Moreover, the DEPT, HMQC, and DQF COSY correlations assisted in assigning the spectra; the symmetrical nature of such oligosaccharides are apparent in their spectra. Similarly, the spectra of **4b–e** showed high coupling constant values between H-1 or H-1a and H-2 or H-2a, respectively, indicating β-orientation at such anomeric positions. Moreover, the orientation of the glycosidic linkage within the lactosyl and maltosyl moieties was confirmed by the coupling of H-1b with H-2b with values 9.0 and 3.8 Hz, respectively for the β-and α-orientations. Their carbons appeared at δ_C 101.1 and 95.6, respectively .

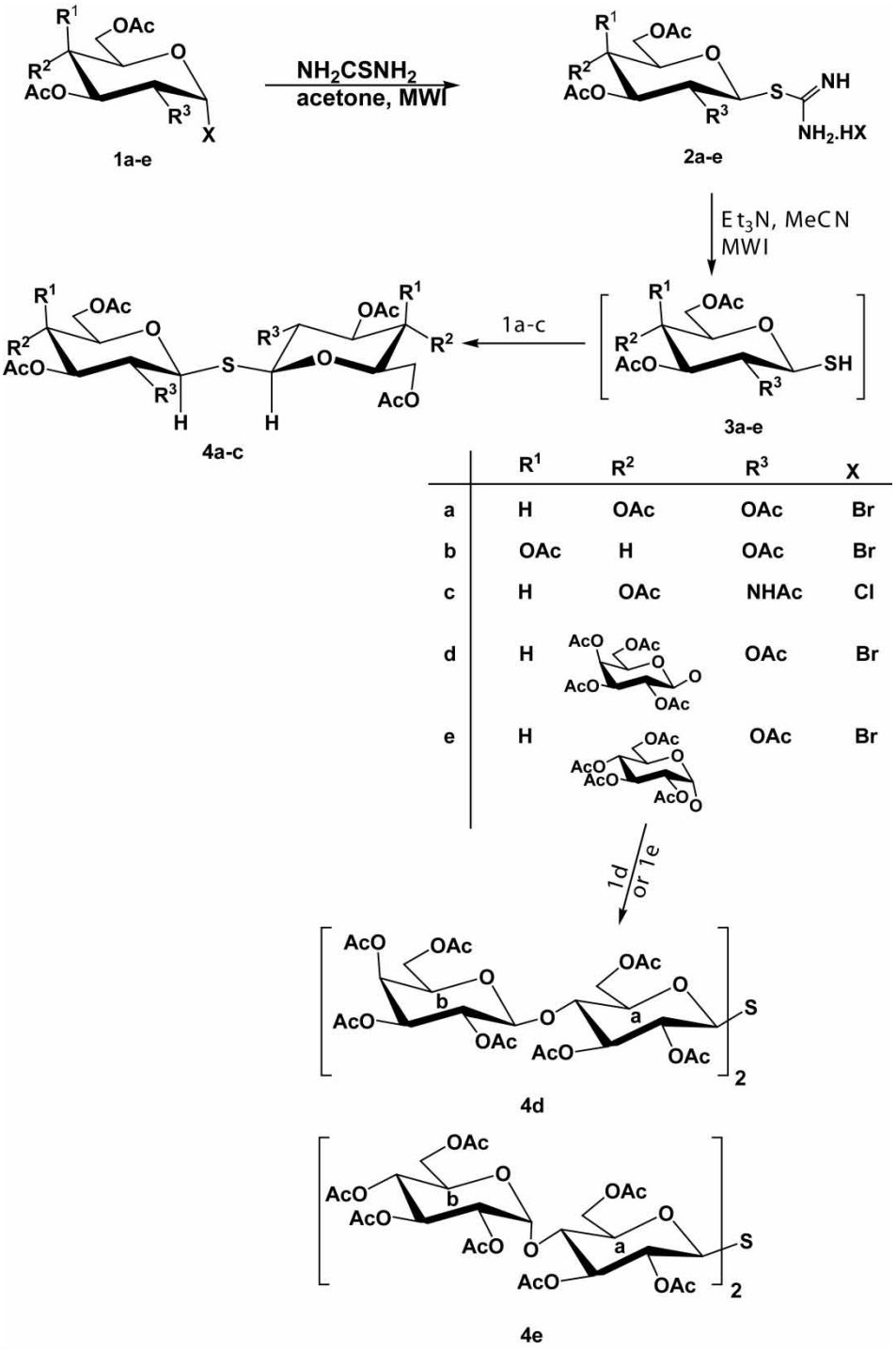
In conclusion, a practical one-pot stereoselective synthesis of the nonreducing thio-oligosaccharides has been achieved by using MWI technology in higher yields than by conventional methods in addition to the quick termination of the reaction. The reactions were clean, and pure products have been readily obtained without chromatography. Moreover, the *S*-glycosyl isothiouronium salts have been also readily prepared under MWI.

EXPERIMENTAL

General Methods

Melting points were determined on a Mel-temp apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX 600 MHz, Jeol spectrometer (500 MHz) and a Bruker Advance 300 MHz spectrometer. The chemical shifts are expressed on the δ-scale using Me_4Si as a standard, and coupling-constant values are given in Hz. The assignments of ^{1}H NMR spectra were based on chemical-shift correlation DQFCOSY spectra, while the assignment of ^{13}C NMR spectra were based on heteronuclear multiple quantum coherence (HMQC) experiments. TLC was preformed on Merck Silica Gel 60F254 with detection by charring in sulfuric acid and by UV light. Irradiation was achieved using a domestic microwave oven EM-230 M (800-watt output power). Microanalyses were performed in the Microanalysis Unit at the Faculty of Science, Cairo University.

Glycosyl isothiouronium salts (2a–e): General Procedure. A mixture of the glycosyl halide **1a–e** (1.0 mmol) and thiourea (1.0 mmol) in dry acetone



	R1	R2	R3	X
a	H	OAc	OAc	Br
b	OAc	H	OAc	Br
c	H	OAc	NHAc	Cl
d	H		OAc	Br
e	H		OAc	Br

Figure 1: Synthesis of thiotrehaloses.

(5 mL) was irradiated for 3 min in a domestic microwave oven EM-230 M (800-watt output power). The reaction mixture was left to cool at rt to afford products of **2a–e**.

***2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl isothiouronium bromide* (2a).** mp 203–205°C, lit[4] mp 205°C; yield 90%.

***2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl isothiouronium bromide* (2b).** mp 168–170°C, lit[28] mp 169.5°C; yield 88%

***2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl isothiouronium chloride* (2c).** 180–182°C, lit[29] mp 179–181°C, yield 89%.

***2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl-(1 → 4)-2,3,6-tri-O-acetyl-β-D-glucopyranosyl isothiouronium bromide* (2d).** Syrup,[31] yield 83%; ^{1}H NMR (500 MHz, DMSO-d_6): 1.92, 1.95, 1.98, 2.04 (5s, 21H, 7 × CH_3CO), 3.94–3.99 (m, 2H, H-5a, H-4a), 4.09–4.13 (m, 4H, H-5b, H-6′a, H-6b, H-6′b), 4.41 (dd, 1H, $J_{6a,6'a} = 11.5$ Hz, H-6a), 4.87 (dd, 1H, $J_{3b,4b} = 3.8$ Hz, $J_{3b,2b} = 9.9$ Hz, H-3b), 4.95 (d, 1H, H-1b), 4.98 (dd, 1H, H-2a), 5.19 (t, 1H, $J_{2b,3b} = J_{2b,1b} = 9.9$ Hz, H-2b), 5.23 (d, 1H, $J_{4b,5b} = 3.8$ Hz, H-4b), 5.31 (dd, 1H, $J_{3a,4a} = 9.2$ Hz, $J_{3a,2a} = 9.9$ Hz, H-3a), 5.63 (d, 1H, $J_{1a,2a} = 10.0$ Hz, H-1a), 9.25, 9.00 (2s, 2 × 2H, 2 × NH_2).

***2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl-(1 → 4)-2,3,6-tri-O-acetyl-β-D-glucopyranosyl isothiouronium bromide* (2e).** mp 199–201°C; yield 86%; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 1.91$, 1.94, 1.95, 1.98, 2.01, 2.03, 2.05 (7s, 21H, 7 × CH_3CO), 3.94–3.99 (m, 2H, H-5b, H-4a), 4.17–4.06 (m, 4H, H-5a, H-6b, H-6′a, H-6′b), 4.41 (dd, 1H, $J_{6'a,6a} = 11.4$ Hz, H-6′a), 4.87 (dd, 1H, $J_{2a,1a} = 10.7$ Hz, $J_{2a,3a} = 8.4$ Hz, H-2a), 4.94 (dd, 1H, $J_{2b,3b} = 10.0$ Hz, $J_{2b,1b} = 3.1$ Hz, H-2b), 4.95 (dd, 1H, $J_{4b,3b} = 10.0$ Hz, $J_{4b,5b} = 6.1$ Hz, H-4b), 5.17 (t, 1H, $J_{3b,2b} = J_{3b,4b} = 10.0$ Hz, H-3b), 5.23 (d, 1H, $J_{1b,2b} = 3.1$ Hz, H-1b), 5.30 (dd, 1H, $J_{3a,4a} = 9.2$ Hz, $J_{3a,2a} = 8.4$ Hz, H-3a), 5.68 (d, 1H, $J_{1a,2a} = 10.7$ Hz, H-1a), 9.24, 9.06 (2s, 2 × 2H, 2 × NH_2).

Anal. Calcd for $C_{27}H_{39}BrN_2O_{17}S$ (775.57): C, 41.81, H, 5.07, N, 3.61. Found: C, 40.12, H, 5.39, N, 3.48.

Acetylated β,β-1-thiotrehaloses (4a–e): General Procedure. A suspension of the glycosyl isothiouronium salts **2a–e** (1.1 mmol) and the respective glycosyl halide (1.0 mmol) in acetonitrile (5 mL) and triethylamine (5 mmol) were placed in a domestic microwave oven and irradiated for 3 min. Methylene chloride (30 mL) was added to the reaction mixture and the solution was washed with water (3 × 10 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was crystallized from methanol to afford pure products of **4a–e**.

***2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside* (4a).** mp 173–175°C, lit[15] mp 174–175°C; yield 63%; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 2.00$, 2.01, 2.02, 2.03 (4s, 24H, 8 × CH_3CO), 3.60 (ddd, 2H, $J_{5,4} = 9.6$ Hz, $J_{5,6'} = 4.9$ Hz, $J_{5,6} = 2.3$ Hz, 2 × H-5), 4.12 (dd, 2H, $J_{6,5} = 2.3$ Hz, $J_{6,6'} = 12.4$ Hz, 2 × H-6), 4.23 (dd, 2H,

$J_{6',5} = 4.9$ Hz, $J_{6',6} = 12.4$ Hz, 2 × H-6′), 4.81 (d, 2H, $J_{1,2} = 10.2$ Hz, 2 × H-1), 5.03 (dd, 2H, $J_{2,1} = 10.2$ Hz, $J_{2,3} = 9.6$ Hz, 2 × H-2), 5.06 (dd, 2H, $J_{4,3} = 9.6$ Hz, $J_{4,5} = 9.6$ Hz, 2 × H-4), 5.19 (t, 2H, $J_{3,2} = 9.6$ Hz, $J_{3,4} = 9.6$ Hz, 2 × H-3); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 20.4$, 20.5, 20.6, 20.7 (8 × CH_3CO), 62.1 (2 × C-6), 68.1 (2 × C-4), 70.1 (2 × C-2), 73.8 (2 × C-3), 76.2 (2 × C-5), 80.7 (2 × C-1), 169.2, 169.3, 170.1, 170.5 (8 × CO).

***2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-galactopyranoside* (4b).** mp 201–203°C; lit[14] mp 199–202°C; yield 65%; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 2.0$, 2.01, 2.09, 2.18 (4s, 24H, 8 × CH_3CO), 3.89–3.93 (m, 2H, 2 × H-5), 4.12 (dd, 2H, $J_{6,5} = 6.5$ Hz, $J_{6,6'} = 11.3$ Hz, 2 × H-6), 4.18 (dd, 2H, $J_{6',5} = 6.7$ Hz, $J_{6',6} = 11.3$ Hz, 2 × H-6′), 4.80 (d, 2H, $J_{1,2} = 10.0$ Hz, 2 × H-1), 5.05 (dd, 2H, $J_{3,4} = 3.3$ Hz, $J_{3,2} = 10.0$ Hz, 2 × H-3), 5.23 (t, 2H, $J_{2,1} = 10.0$ Hz, $J_{2,3} = 10.0$ Hz, 2 × H-2), 5.45 (dd, 2H, $J_{4,3} = 3.3$ Hz, $J_{4,5} = 2.8$ Hz, 2 × H-4), ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 19.8$, 19.88, 19.9, 20.0 (8 × CH_3CO), 60.6 (2 × C-6), 66.4 (2 × C-4), 66.5 (2 × C-2), 71.0 (2 × C-3), 73.9 (2 × C-5), 80.6 (2 × C-1), 168.7, 169.2, 169.4, 169.6 (8 × CO).

***2-Acetamido-2-deoxy-3,4,6-tri-O-acetyl-β-D-glucopyranosyl 2-acetamido-2-deoxy-3,4,6-tri-O-acetyl-1-thio-β-D-glucopyranoside* (4c).** mp 312–314°C; lit[30] mp 314–316°C; yield 62%; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 1.76$ (s, 6H, 2 × $NCOCH_3$), 1.90, 1.96, 2.02 (3s, 18H, 6 × CH_3CO), 3.78 (ddd, 2H, $J_{5,4} = 9.6$ Hz, $J_{5,6'} = 5.1$, $J_{5,6} = 2.1$ Hz, 2 × H-5), 3.92 (dd, 2H, $J_{2,1} = 10.2$ Hz, $J_{2,3} = 9.6$ Hz, 2 × H-2), 4.05 (dd, 2H, $J_{6,5} = 2.1$ Hz, $J_{6,6'} = 12.1$ Hz, 2 × H-6), 4.16 (dd, 2H, $J_{6',5} = 5.1$ Hz, $J_{6',6} = 12.1$ Hz, 2 × H-6′), 4.85 (t, 2H, $J_{4,5} = 9.6$ Hz, $J_{4,3} = 9.6$ Hz, 2 × H-4), 4.92 (d, 2H, $J_{1,2} = 10.2$ Hz, 2 × H-1), 5.08 (t, 2H, $J_{3,2} = 9.6$ Hz, $J_{3,4} = 9.6$ Hz, 2 × H-3); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 20.3$, 20.4, 20.5 (6 × CH_3CO), 22.6 (2 × $NCOCH_3$), 52.0 (2 × C-2), 62.1 (2 × C-6), 68.6 (2 × C-4), 73.7 (2 × C-3), 75.0 (2 × C-5), 80.0 (2 × C-1), 169.3, 169.3, 169.6, 170.1 (8 × CO).

4,4′-Di-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl) 2,2′,3,3′,6,6′-hexa-O-acetyl-β,β-1-thiotrehalose (4d). mp 143–145°C; yield 58%; ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 1.96$–2.18 (14s, 42H, 14 × CH_3CO), 3.58 (ddd, 2H, $J_{5a,\ 4a} = 9.2$ Hz, $J_{5a,\ 6'a} = 5.3$ Hz, $J_{5a,\ 6a} = 3.8$ Hz, 2 × H-5a), 3.78 (dd, 2H, $J_{4a,3a} = 9.9$ Hz, $J_{4a,5a} = 9.2$ Hz, 2 × H-4a), 3.89 (ddd, 2H, $J_{5b,4b} = 7.7$ Hz, $J_{5b,\ 6'b} = 3.1$ Hz, $J_{5b,6b} = 4.6$ Hz, 2 × H-5b), 4.07 (dd, 2H, $J_{6b,5b} = 4.6$ Hz, $J_{6b,\ 6'b} = 11.5$ Hz, 2 × H-6b), 4.13 (dd, 2H, $J_{6'b,5b} = 3.1$ Hz, $J_{6'b,6b} = 11.5$ Hz, 2 × H-6′b), 4.17 (dd, 2H, $J_{6a,5a} = 3.8$ Hz, $J_{6a,\ 6'a} = 12.2$ Hz, 2 × H-6a), 4.46 (d, 2H, $J_{1b,2b} = 9.0$ Hz, 2 × H-1b), 4.57 (dd, 2H, $J_{6'a,5a} = 5.3$ Hz, $J_{6'a,6a} = 12.2$ Hz, 2 × H-6′a), 4.76 (d, 2H, $J_{1a,2a} = 10.0$ Hz, 2 × H-1a), 4.93 (dd, 2H, $J_{2a,1a} = 10.0$ Hz, $J_{2a,3a} = 9.9$ Hz, 2 × H-2a), 4.98 (dd, 2H, $J_{3b,4b} = 3.8$ Hz, $J_{3b,2b} = 9.9$ Hz, 2 × H-3b), 5.11 (dd, 2H, $J_{2b,3b} = 9.9$ Hz, $J_{2b,1b} = 9$ Hz, 2 × H-2b), 5.23 (dd, 2H, $J_{3a,2a} = 9.9$ Hz, $J_{3a,4a} = 9.2$ Hz, 2 × H-3a), 5.34 (dd, 2H, $J_{4b,5b} = 7.7$ Hz, $J_{4b,3b} = 3.8$ Hz, 2 × H-4b). ^{13}C NMR (150.9 MHz,

$CDCl_3$): $\delta = 20.4–20.8$ (14 × CH_3CO), 60.7 (2 × C-6b), 62.1 (2 × C-6a), 66.5 (2 × C-4b), 69.0 (2 × C-2b), 70.4 (2 × C-2a), 70.5 (2 × C-5b), 70.9 (2 × C-3b), 73.8 (2 × C-3a), 75.7 (2 × C-4a), 76.1 (2 × C-5a), 80.4 (2 × C-1a), 101.1 (2 × C-1b), 169.0, 169.5, 169.6, 170.0, 170.1, 170.2, 170.3 (14 × CO).

Anal. Calcd for $C_{52}H_{70}O_{34}S$ (1271.16): C, 49.13, H, 5.55. Found: C, 49.14, H, 5.79.

4,4′-Di-O-(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl) 2,2′,3,3′,6,6′-hexa-O-acetyl-β,β-1-thiotrehalose (4e). mp 110–112°C; yield 57%; ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 1.99–2.18$ (14s, 42H, 14 × CH_3CO), 3.68–3.73 (m, 2H, 2 × H-5a), 3.93 (m, 2H, 2 × H-5b), 400 (t, 2H, $J_{4a,5a} = J_{4a,3a} = 9.2$ Hz, 2 × H-4a), 4.03 (dd, 2H, $J_{6'a,6a} = 12.0$ Hz, 2 × H-6′a), 4.21 (dd, 2H, $J_{6a,6'a} = 12.0$ Hz, 2 × H-6a), 4.23 (dd, 2H, $J_{6b,6'b} = 12.2$ Hz, $J_{6b,5b} = 3.8$ Hz, 2 × H-6b), 4.78 (dd, 2H, $J_{2b,1b} = 3.8$ Hz, $J_{2b,3b} = 9.9$ Hz, 2 × H-2b), 4.82 (dd, 2H, $J_{2a,1a} = 10.7$ Hz, $J_{2a,3a} = 9.2$ Hz, 2 × H-2a), 4.83 (d, 2H, $J_{1a,2a} = 10.7$ Hz, 2 × H-1a), 5.06 (dd, 2H, $J_{4b,3b} = 9.9$ Hz, $J_{4b,5b} = 9.9$ Hz, 2 × H-4b), 5.28 (t, 2H, $J_{3a,2a} = J_{3a,4a} = 9.2$ Hz, 2 × H-3a), 5.34 (t, 2H, $J_{3b,2b} = J_{3b,4b} = 9.9$ Hz, 2 × H-3b), 5.4 (d, 2H, $J_{1b,2b} = 3.8$ Hz, 2 × H-1b). ^{13}C NMR ($CDCl_3$, 150.9 MHz): $\delta = 20.5–20.8$ (14 × CH_3CO), 61.5 (2 × C-6b), 62.9 (2 × C-6a), 68.0 (2 × C-4b), 72.2 (2 × C-4a), 68.5 (2 × C-3b), 74.9 (2 × C-3a), 70.1 (2 × C-2b), 69.4 (2 × C-5b), 72.4 (2 × C-5a), 73.8 (2 × C-2a), 90.0 (2 × C-1a), 95.6 (2 × C-1b), 169.3, 169.5, 169.8, 170.0, 170.1, 170.3, 170.4 (14 × CO).

Anal. Calcd for $C_{52}H_{70}O_{34}S$ (1271.16): C, 49.13, H, 5.55. Found: C, 48.89, H, 5.80.

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