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Synthesis of 2-deoxy cyclic and linear oligosaccharides by oligomerization of monomers

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ABSTRACT

Cyclic and linear oligosaccharides constituted with 2-deoxy sugar units are synthesized by an oligomerization reaction involving activated thioglycoside monomers, consisting of a 2-deoxy sugar unit. The oligomerization promoter plays an important role in the formation of either the cyclic- or the linear oligosaccharides. Encapsulation abilities of a 2-deoxy cyclic hexamer with *p*-nitrophenol, by a ^{1}H NMR method, showed complexation of the guest molecule with the host molecule.

1. Introduction

1,2-Unsaturated sugars, namely glycals, are a rich source to obtain 2-deoxy sugars through chemical modifications.[1] A methodology involving the reaction of glycals with EtSH, in the presence of catalytic amount of $(NH_4)_2Ce(NO_3)_6$, was identified previously by us to provide activated 2-deoxy thioglycosides.[2] The activated 2-deoxy thioglycosides were used to prepare a range of alkyl- and aryl 2-deoxy sugars and 2-deoxy disaccharides.[3,4] Continuing our synthetic efforts to involve 2-deoxy thioglycosides, it was desired to prepare 2-deoxy oligosaccharides, in both the linear and cyclic forms. When the 2-deoxy sugar unit corresponds to an *arabino*-hexopyranosyl unit, the resulting oligosaccharides would correspond to either maltooligosaccharide analogues, in the case of the linear oligosaccharides, or cyclomaltooligosaccharides (cyclodextrin) analogues, in the case of the cyclic oligosaccharides. This report concerns the synthesis of the malto- and the cyclomaltooligosaccharide analogues, synthesized through oligomerizations of appropriately designed AB-type monomers.

2. Results and discussion

We had previously identified that 1,2-unsaturated glycals can be converted to 2-deoxy-1-thioglycosides.[2] The activated 2-deoxy-1-thioglycosides predominantly lead to a glycosylated product in the α-anomeric configuration, with both glycosyl and aglycosyl acceptors.[3,4] For the synthesis of the oligosaccharides constituted with 2-deoxy glycoside units, identification of an appropriately protected AB-type monomer was an important requirement. A disaccharide monomer **4** was identified as a suitable monomer for the oligomerization protocol. In the early attempts, the monosaccharide monomers were observed to be ineffective. Design of a disaccharide monomer for the oligomerization was thus undertaken, and continued attempts led to realizing the methyl ether as a suitable protecting group for the monomer. The disaccharide monomer **4** was obtained by a synthetic manipulation of the 2-deoxy-1-thiomaltoside derivative **1**[4] (Scheme 1). The protecting group manipulations on **1** leading to **4** were accomplished in good yields in the individual steps. The AB-type monomer **4** presents an active thioglycoside moiety at the reducing end and the acceptor functionality at C-4 of the non-reducing end.

The oligomerization was conducted using two thiophilic activators, namely (i) NIS/TfOH and (ii) NIS/AgOTf. The reaction was conducted in CH_2Cl_2 at 0 °C for 1 h and at room temperature for 12 h, then quenched with Et_3N and worked up (Scheme 2). MALDI-TOF mass spectrometric analysis of the crude reaction mixture revealed the presence of the cyclic tetrasaccharide **5** and the cyclic hexasaccharide **6**, in addition to the linear di- and tetrasaccharides **7** and **8**. Better yields of **5** (40%) and **6** (25%) were isolated, when the monomer concentration was 25 mM. The HPLC profile of the reaction conducted at this concentration is shown in Figure 1.

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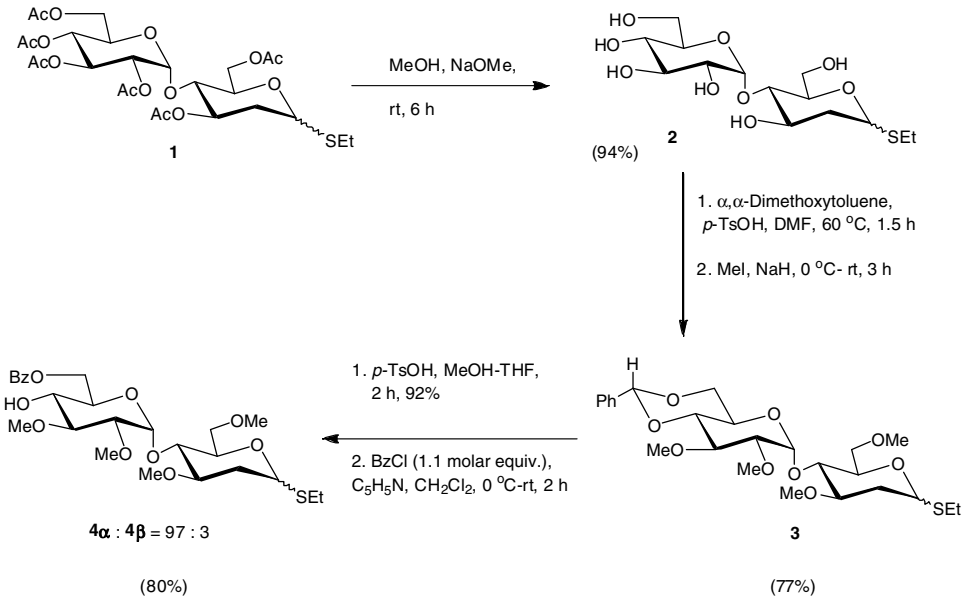
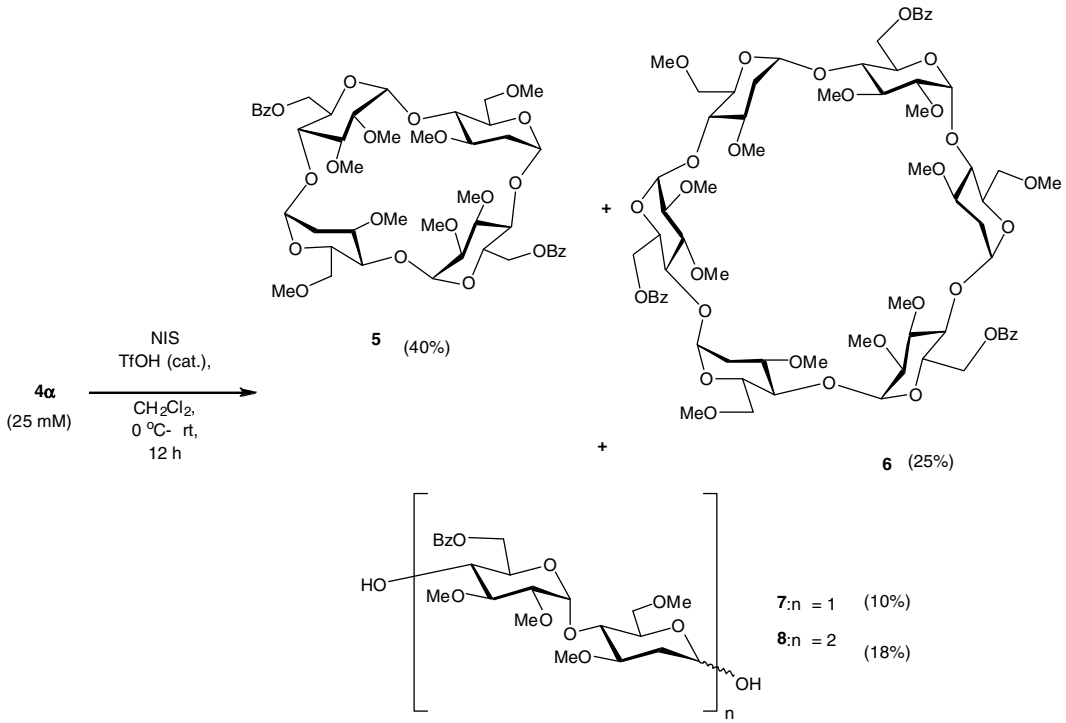


Scheme 1. Synthesis of AB-type monomer **4**.



Scheme 2. Oligomerization of monomer **4α** in the presence of NIS/TfOH.

Attempts were made previously with benzyl ether protecting groups on the disaccharide monomer. The disaccharide monomer **13** was obtained from hexa-*O*-acetyl-maltal **9**[5] (Scheme 3), and monomer **15** was achieved by synthetic manipulation of the 2-deoxy-1-thiomaltoside derivative **2** (Scheme 4). Oligomerization with this monomer **13** led to only a trace amount of the cyclic tetrasaccharide **16**, hydrolyzed monomer **17,** and linear tetrasaccharide **18**. Further, an ester protecting group on monomer **15** was also attempted. However, only the hydrolyzed monomer **19** and the linear tetrasaccharide **20** were obtained with this protecting group on the monomer (Scheme 5).

The symmetrical structures of **5** and **6** were ascertained from their respective NMR spectra. In the ^{1}H NMR spectrum of **6** (Fig. 2), the H-1 resonance of the 2-deoxy sugar moiety was observed at 4.82 ppm (app.d, *J* 3.6 Hz), whereas the H-1 nuclei of the glucose moiety resonated at 5.91 ppm (d, *J* 3.9 Hz). In the ^{13}C NMR spectrum, the C-1 nuclei of the 2-deoxy sugar moiety appeared at 95.6 ppm and that of the glucose moiety was observed at 98.7 ppm. The C-2 nuclei of the 2-deoxy sugar moiety resonated at 36.5 ppm.

Similar ^{1}H and ^{13}C NMR profiles were observed for the cyclic tetrasaccharide **5**. The MALDI-TOF mass spectral analyses showed molecular ion peak of **5** and **6** (Fig. 3), as [M+Na^{+}] adducts.

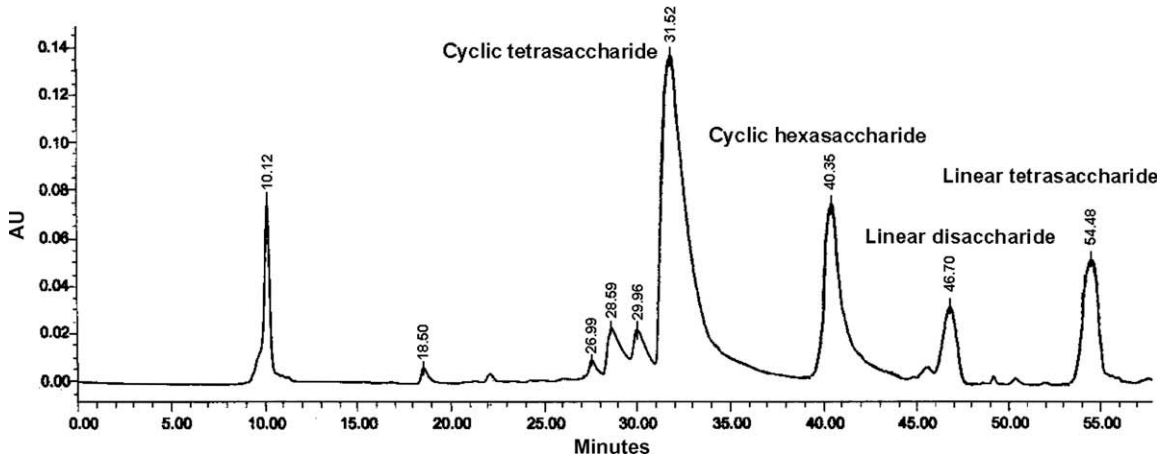
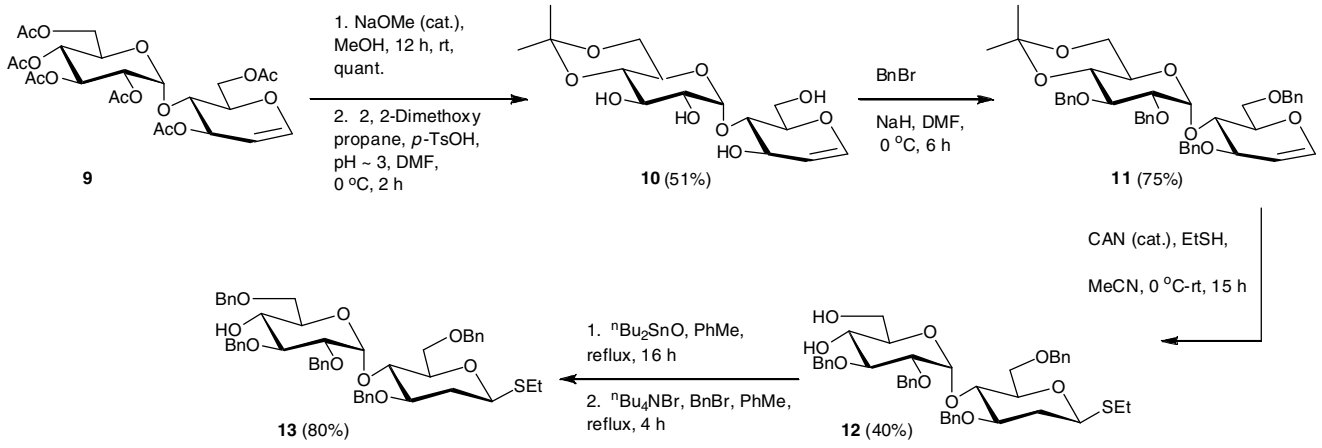
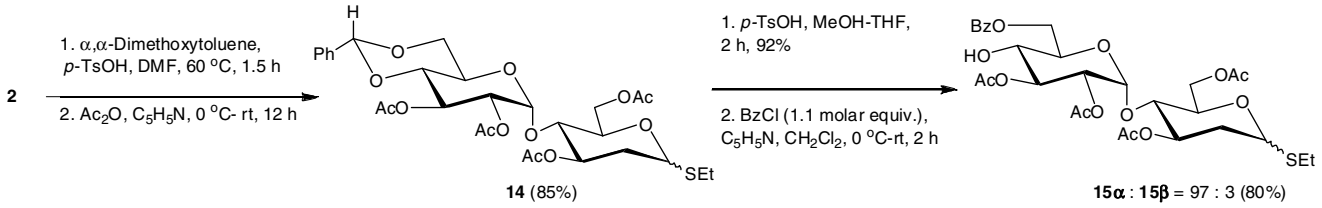


Figure 1. HPLC profile of the crude reaction mixture (Phenomenex column (5 μ SiO_2), (EtOAc–MeOH) (260 nm).



Scheme 3. Synthesis of AB-type monomer **13**.

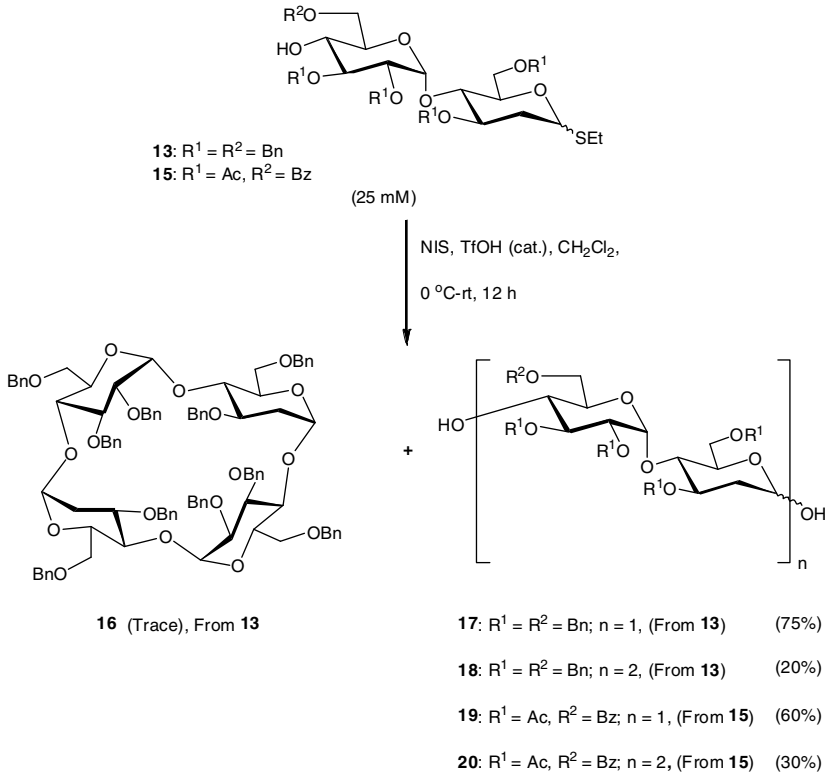


Scheme 4. Synthesis of AB-type monomer **15**.

The alternative thiophilic activator was also utilized for the oligomerization reaction. Reaction of the monomer **4** was carried out in the presence of NIS/AgOTf in a manner similar to the previous NIS/TfOH reaction (Scheme 6).

After 12 h, monitoring the reaction showed that the products of the reaction were not similar to that resulting from the NIS/TfOH promoter. Subsequent acetylation of the reaction mixture was performed. The MALDI-TOF mass spectral (Fig. 4) analysis showed that the products were essentially linear oligosaccharides, consisting of di- to eicosasaccharides. Series of the newly formed linear oligosaccharides correspond to the 2-deoxy analogues of maltooligosaccharides. Purification of the oligosaccharides by GPC provided only the hexasaccharide as a pure product. The remaining oligosaccharides could not be obtained individually, even after repeated GPC purifications.

The methylated cyclodextrins are useful for enhanced encapsulation of small molecules.[6] A preliminary inclusion study was thus undertaken with the benzoate-deprotected **6**, obtained using NaOMe/MeOH, with *p*-nitrophenol (*p*NP), by the ^{1}H NMR titration method, in D_2O and in the presence of NaOD and KCl. ^{1}H NMR resonances of the benzoate-deprotected **6** appeared complex, reflecting a possible reduced symmetry.[7] Reduced symmetry was presumed due to conformational flexibility of benzoate-deprotected **6**. It is known that the modification of the secondary hydroxyl groups of an α- or β-CD introduces more conformational flexibility in the molecule and deviates the shape of the cavity. Conformational stability to the cyclic oligosaccharides arises from the intramolecular hydrogen-bonding network between the hydroxyl groups present at the secondary face. The removal of the hydrogen-bonding network by substitution on the free hydroxyl



Scheme 5. Oligomerization of monomers **13** and **15** in the presence of NIS/TfOH.

group results distortion in the structures, which is reflected in the line broadening, as well as in the appearance of several signals in the ^{1}H NMR spectra.[7] In the case of 2-deoxy cyclic oligosaccharides, absence of a hydroxyl group at C-2 leads to a more flexible structure and a loss in the rigidity relative to that of the normal cyclic oligosaccharide. On the other hand, when *p*NP complexes to benzoate-deprotected **6**, the spectrum appeared well defined, thereby indicating a more symmetrical structure for the complex. Upfield shifts for the anomeric protons and other sugar ring protons were observed, upon the host–guest complexation. The anomeric H-1^D and H-1^G showed an upfield shift of 0.03 ppm and 0.01 ppm, respectively. A maximum upfield shift of 0.11 ppm was observed in the case of H-3^G. The H-2^D and H-3^D also exhibited 0.02 ppm upfield shift. A downfield shift of 0.07 ppm was observed for H-5^G. The spectral overlapping between the H-5^D signal and one of the –OMe resonances restricted the chemical shift

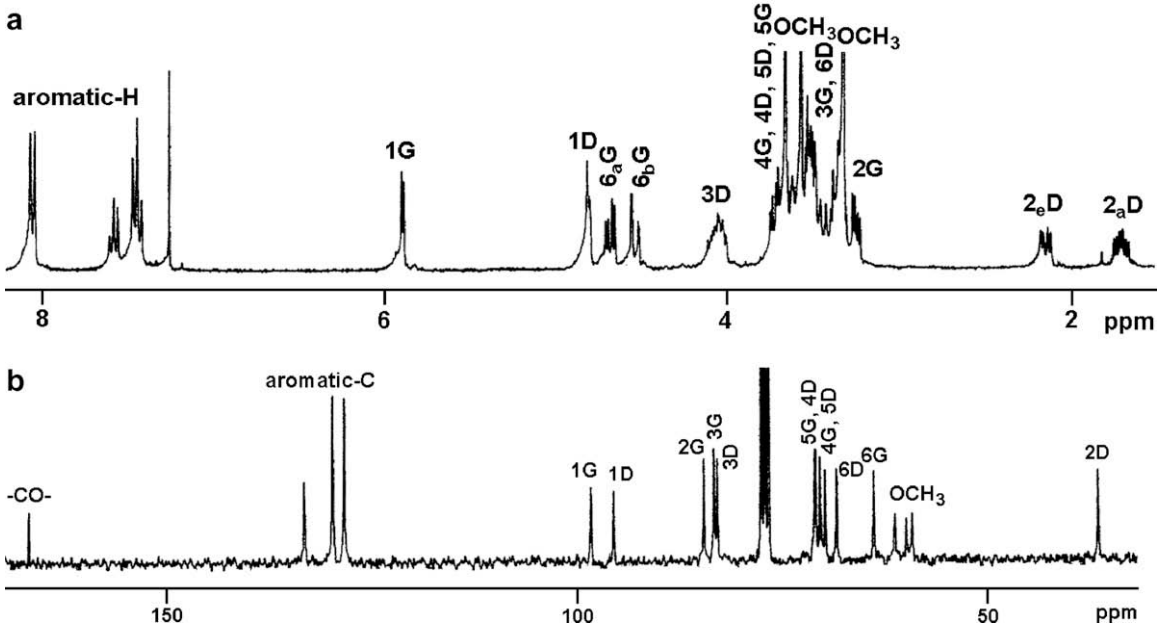


Figure 2. (a) ^{1}H NMR ($CDCl_3$, 300 MHz) and (b) ^{13}C NMR ($CDCl_3$, 75 MHz) spectra of the cyclic hexasaccharide (**6**). D = 2-deoxy sugar and G = glucopyranosyl residues.

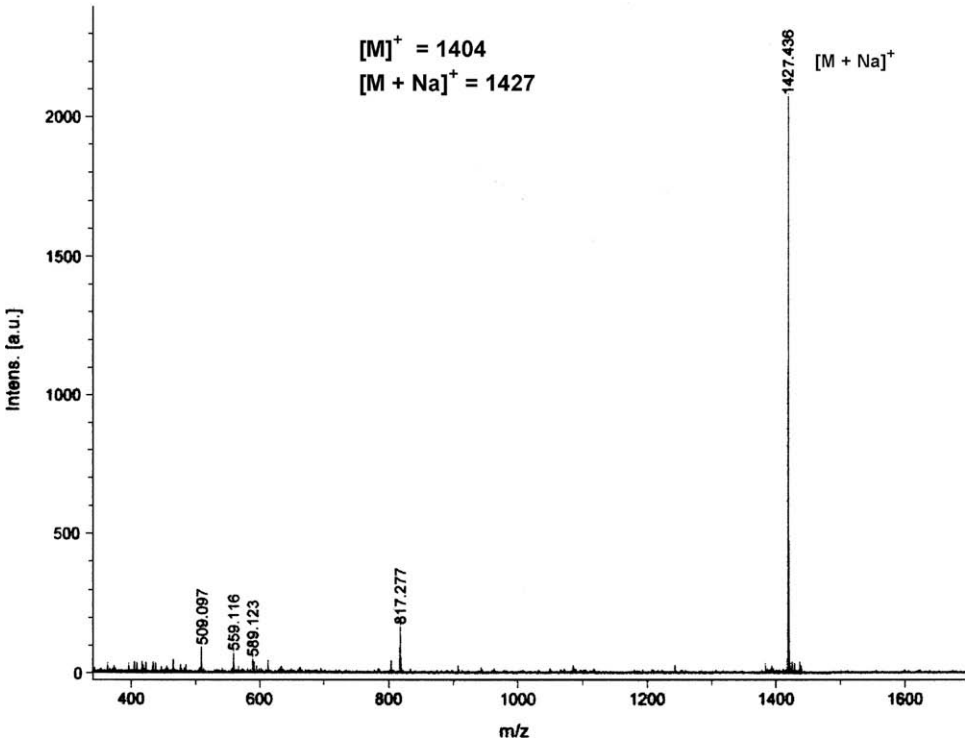
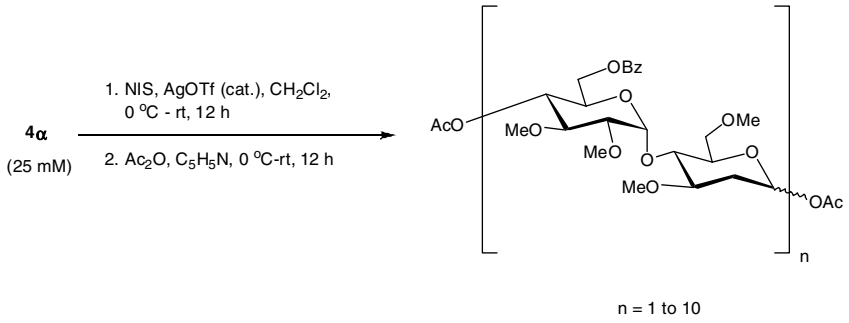


Figure 3. MALDI-TOF mass spectrum of **6**.



Scheme 6. Oligomerization of the monomer **4α** in the presence of NIS/AgOTf.

measurement. The shifts in the resonances of H-3 and H-5, induced by the addition of *p*NP, confirmed the complexation.[8] These spectral shifts were compared with such a study reported for a permethylated α-cyclodextrin (α-MCD).[9,10] Upon complexation of α-MCD with *p*NP, an upfield shift of 0.31 ppm for the H-2 nucleus and a downfield shift of 0.11 ppm for the H-5 nucleus have been observed. From the preliminary studies, it appears that the 2-deoxy cyclic oligosaccharide is unexceptional in the guest complexation behavior, in comparison to the normal cyclic oligosaccharides.

Methods to synthesize cyclic oligosaccharides have been previously reported.[11,12] Ogawa and Takahashi demonstrated the cyclization of linear oligosaccharides to afford the cyclic oligosaccharides.[13] Varied glycosyl donors and glycosyl acceptors in the linear oligosaccharides have been utilized to synthesize several cyclic oligosaccharides.[12,14] In a route advanced by Kochetkov and co-workers,[15] and by Stoddart and co-workers,[16,17] the syntheses of cyclic oligosaccharides were achieved using designed monomers and subjecting them to oligomerizations. This protocol allows syntheses of several cyclodextrin analogues, including achiral cyclodextrins[17] and carbohydrate nanotubes.[18] This advantage to afford more than one cyclic oligomer in one pot is a prominent feature associated with the oligomerization involving an AB-type monomer, and such a feature is observed in the oligomerizations reported herein.

In conclusion, a chemical synthesis of new types of linear and cyclic oligosaccharides, in which the alternative sugar moiety corresponding to a 2-deoxy sugar constituent, is accomplished. The report represents the first instance of a thioglycoside mediating the oligomerizations. The evolution of a coiled geometry of a growing linear polymer is a prerequisite for a cyclization.[19] Propensity for the formation of coiled geometry, combined with adequate glycosylation donor/acceptor properties of the monomer with the methyl groups, might have favored a cyclization under the reaction conditions involving NIS/TfOH in the present study, so as to afford the cyclodextrin analogues. Preliminary study with the cyclic hexamer shows that it functions as a host to an aromatic guest molecule. Having established the new types of linear and cyclic

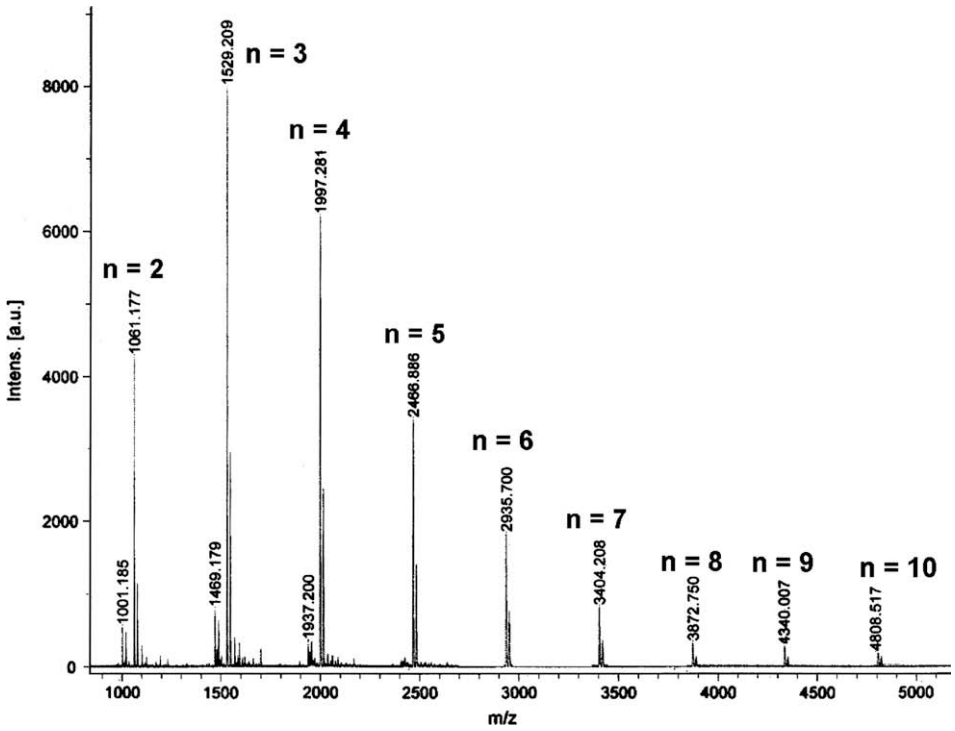


Figure 4. MALDI-TOF mass spectra of the linear oligosaccharides.

oligosaccharides, future studies will involve exploring their structural properties.

3. Experimental

3.1. General methods

Chemicals were purchased from commercial sources, and were used without further purification. Solvents were dried and distilled according to literature procedures. Analytical TLC was performed on commercial E. Merck plates coated with Silica Gel GF_{254} (0.25 mm), with a detection by a UV lamp and/or by charring, following immersion in 5% H_2SO_4/EtOH. Silica gel (100–200 mesh) was used for column chromatography. Optical rotations were recorded on a Jasco Model P-1020 polarimeter at the sodium D line at 24 °C. High-resolution mass spectra were obtained from a Micromass Q-TOF micro™ system, by the electrospray-ionization (ESI) technique. MALDI-TOF mass spectra were recorded on a Bruker instrument using a 2,5-dihydroxybenzoic acid as the matrix. The melting point was recorded on a Buchi Melting Point B-540 system. ^{1}H NMR spectra were recorded on a Bruker 400 and a JEOL JNM-LA 300 FT NMR system (300 MHz), and ^{13}C NMR spectra were recorded on a Bruker 400 (100 MHz) and a JEOL JNM-LA 300 FT NMR system (75 MHz), with residual solvent signal as the internal standard. The following abbreviations were used to designate the multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet; band, several overlapping signals; br, broad.

3.2. HPLC analysis

HPLC purifications of the crude reaction mixtures were performed on a Waters HPLC system with monitoring at λ 260 nm. A Phenomenex HPLC column (250 × 5 mm, 5 μ SiO_2) and elution with a gradient of EtOAc–MeOH from 100% EtOAc to 2% of MeOH for 60 min were employed.

3.3. Ethyl 2-deoxy-4-*O*-(α-D-glucopyranosyl)-1-thio-α,β-D-*arabino*-hexopyranoside (2)

Compound **1**[4] (5.0 g, 8.0 mmol) was admixed with NaOMe (catalytic amount) and MeOH (50 mL), and stirred for 6 h at room temperature. The mixture was then quenched with 1:10 AcOH–MeOH and concentrated. Purification, by column chromatography using a $CHCl_3$–MeOH eluant system, afforded **2** (2.8 g, 94%, α/β 9:1) as a foamy solid. R_f 0.27 (15:85 MeOH–$CHCl_3$); α anomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.34 (app.d, 1H, J 5.4 Hz, H-1^D), 5.22 (d, 1H, J 3.6 Hz, H-1^G), 4.00–3.94 (m, 2H, H-3^D, H-4^D), 3.77–3.73 (band, 2H, H-4^G, H-5^D), 3.68–3.65 (band, 2H, H-6^G_a, H-6^G_b), 3.62–3.57 (m, 3H, H-5^G, H-6^D_a, H-6^D_b), 3.52 (dd, 1H, J 3.6, 9.0 Hz, H-2^G), 3.41 (t, 1H, J 9.0 Hz, H-3^G), 2.54–2.38 (m, 2H, SCH_2), 2.00 (app.dd, 1H, J 4.8, 13.2 Hz, H-2^D_e), 1.90 (ddd, 1H, J 5.4, 11.6, 13.2 Hz, H-2^D_a), 1.09 (t, 3H, J 7.4 Hz, CH_3); characteristic resonances for the β anomer: δ 5.24 (d, 1H, J 4.0 Hz, H-1^G), 2.13 (m, 1H, H-2^D_e), 1.56 (m, 1H, H-2^D_a); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 100.6 (C-1^G), 79.6 (C-1^D), 79.3 (C-2^G), 72.7 (C-3^G), 72.5 (C-3^D), 70.7 (C-5^G), 70.3 (C-4^D), 69.4 (C-4^G), 64.0 (C-5^D), 61.5 (C-6^D), 60.5 (C-6^G), 37.1 (C-2^D), 24.5 (SCH_2), 13.9 (CH_3). HRESIMS *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{26}O_9S$: 393.1195; found: 393.1185.

3.4. Ethyl 4-*O*-(4,6-*O*-benzylidene-2,3-di-*O*-methyl-α-D-glucopyranosyl)-2-deoxy-3,6-di-*O*-methyl-1-thio-α-D-*arabino*-hexopyranoside (3)

A mixture of **2** (4.64 g, 13 mmol), α,α-dimethoxytoluene (2.4 mL, 16 mmol), and *p*-TsOH monohydrate (0.25 g, 1.3 mmol) in DMF (20 mL) was kept at a diminished pressure at 60 ± 5 °C, upon attachment to a rotary evaporator for 1.5 h. The reaction was quenched with Et_3N (1 mL). The solvent was removed, and the crude residue was taken for the next step without further purification.

To a suspension of NaH (60% dispersion in oil, 2.34 g, 58.5 mmol) in THF (15 mL), a solution of above crude residue in

THF (10 mL) was added at 0 °C, over a period of 15 min. After stirring the reaction mixture for another 45 min at 0 °C, MeI (3.6 mL, 57.8 mmol) was added and stirred for 3 h. The reaction mixture was neutralized with 1:50 AcOH–MeOH and diluted with EtOAc (100 mL). After extraction, the organic layer was washed with H_2O (3 × 50 mL), dried (Na_2SO_4), and concentrated. Purification of the crude product afforded **3** (4.96 g, 77%, after two steps), as a colorless gum. R_f 0.26 (2:3 EtOAc–pet ether); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50–7.35 (band, 5H, aromatic), 5.84 (d, 1H, *J* 3.6 Hz, H-1^G), 5.55 (s, 1H, PhCH), 5.47 (app.d, 1H, *J* 4.2 Hz, H-1^D), 4.31–4.29 (m, 1H, H-5^G), 4.20–4.18 (m, 1H, H-4^G), 3.94 (t, 1H, *J* 9.0 Hz, H-4^D), 3.85 (dd, 1H, *J* 2.0, 10.0 Hz, H-6^G_a), 3.81–3.75 (m, 2H, H-6^G_b, H-3^D), 3.74–3.72 (band, 2H, H-3^G, H-5^D), 3.64 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 3.49–3.44 (band, 5H, H-6^D_a, H-6^D_b, OCH_3), 3.34 (s, 3H, OCH_3), 3.30 (dd, 1H, *J* 3.6, 9.0 Hz, H-2^G), 2.65–2.50 (m, 2H, SCH_2), 2.32 (app.dd, 1H, *J* 4.8, 13.2 Hz, H-2^D_e), 1.96 (ddd, 1H, *J* 4.2, 11.6, 13.2 Hz, H-2^D_a), 1.27 (t, 3H, *J* 7.2 Hz, CH_3); characteristic resonances for the β anomer: δ 4.86 (app.dd, 1H, *J* 11.5 Hz, H-1^D); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.4, 127.8, 127.1, 125.1 (aromatic), 100.3 (PhCH), 95.2 (C-1^G), 81.0 (C-3^G), 80.4 (C-2^G), 79.4 (C-1^D), 79.2 (C-3^D), 78.3 (C-5^G), 70.4 (C-4^D), 70.0 (C-4^G), 68.5 (C-5^D), 68.1 (C-6^D), 61.8 (C-6^G), 60.0, 58.2, 57.6, 54.7 (OCH_3), 33.5 (C-2^D), 23.9 (SCH_2), 13.9 (CH_3). HRESIMS *m/z*: $[M+Na]^+$ calcd for $C_{25}H_{38}O_9S$: 537.2134; found: 537.2130.

3.5. Ethyl 4-*O*-(6-*O*-benzoyl-2,3-di-*O*-methyl-α-D-glucopyranosyl)-2-deoxy-3,6-di-*O*-methyl-1-thio-α,β-D-*arabino*-hexopyranoside (4)

To a solution of **3** (4.56 g, 9 mmol) in 1:1 THF–MeOH (40 mL), *p*-TsOH·H_2O (1.9 g, 10 mmol) was added. After 3 h, the reaction mixture was quenched with Et_3N (3 mL), concentrated, and purified (SiO_2, 100–200 mesh) to afford the benzylidene-group deprotected **3** (3.48 g, 92%, α/β 9:1) as a gum. R_f 0.21 (4:96 MeOH–$CHCl_3$).

To a mixture of BzCl (0.6 mL, 5.2 mmol) and pyridine (0.76 mL, 9.4 mmol) in CH_2Cl_2 (15 mL), the above intermediate (2.02 g, 4.7 mmol) in CH_2Cl_2 (15 mL) was added dropwise at 0 °C. After 24 h, the reaction mixture was diluted with CH_2Cl_2 (75 mL), washed with ice-cold HCl (5%, 3 × 50 mL) solution, satd aq $NaHCO_3$ solution (2 × 50 mL), and water (2 × 50 mL). The extract was dried (Na_2SO_4) and concentrated. Purification of the crude product afforded **4** (2.01 g, 80%, α/β 9:1) as a pale yellow gum.

Compound **4α**: R_f 0.36 (1:1 EtOAc–pet ether); $[\alpha]_D^{24}$ +168.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07–7.42 (band, 5H, aromatic), 5.86 (d, 1H, *J* 3.6 Hz, H-1^G), 5.47 (app.d, 1H, *J* 4.2 Hz, H-1^D), 4.80 (dd, 1H, *J* 3.5, 12.1 Hz, H-6^G_a), 4.45 (dd, 1H, *J* 1.9, 12.1 Hz, H-6^G_b), 4.20–4.17 (m, 1H, H-4^G), 3.93 (t, 1H, *J* 9.0 Hz, H-4^D), 3.82–3.77 (band, 3H, H-5′, H-3, H-5^D), 3.68 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3), 3.49–3.43 (band, 3H, H-3^G, H-6^D_a, H-6^D_b), 3.37 (s, 3H, OCH_3), 3.32 (s, 3H, OCH_3), 3.23 (dd, 1H, *J* 3.6, 9.0 Hz, H-2^G), 3.02 (br s, 1H, OH), 2.65–2.50 (m, 2H, SCH_2), 2.30 (app.dd, 1H, *J* 4.8, 13.2 Hz, H-2^D_e), 1.94 (ddd, 1H, *J* 4.2, 11.7, 13.2 Hz, H-2^D_a), 1.27 (t, 3H, *J* 7.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.2 (CO), 133.2, 129.9, 129.7, 128.4 (aromatic), 95.6 (C-1^G), 81.9 (C-3^G), 81.8 (C-2^G), 80.3 (C-1^D), 80.2 (C-3^D), 71.6 (C-5^G), 71.0 (C-4^D), 70.0 (C-4^G), 69.8 (C-5^D), 69.7 (C-6^D), 63.5 (C-6^G), 61.3, 59.0, 58.0, 55.7 (OCH_3), 34.5 (C-2^D), 24.9 (SCH_2), 14.8 (CH_3). HRESIMS *m/z*: $[M+Na]^+$ calcd for $C_{25}H_{38}O_{10}S$: 553.2083; found: 553.2059.

Compound **4β**: R_f 0.16 (1:1 EtOAc–pet ether); $[\alpha]_D^{24}$ +31.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07–7.43 (band, 5H, aromatic), 5.84 (d, 1H, *J* 3.6 Hz, H-1^G), 4.77 (dd, 1H, *J* 2.0, 12.1 Hz, H-6^G_a), 4.53 (app.d, 1H, *J* 11.4 Hz, H-1^D), 4.44 (dd, 1H, *J* 1.6, 12.1 Hz, H-6^G_b), 3.89–3.85 (m, 2H, H-5^G, H-4^D), 3.71 (app.dd, 1H, *J* 3.9, 11.0 Hz, H-5^D), 3.66 (s, 3H, OCH_3), 3.65-3.57 (band, 2H, H-4^G, H-3^D), 3.52 (s, 3H, OCH_3), 3.49–3.40 (band, 3H, H-3′, H-6^D_a, H-6^D_b), 3.36 (s, 3H, OCH_3), 3.34 (s, 3H, OCH_3), 3.21 (dd, 1H, *J* 3.6, 9.1 Hz, H-2^G), 2.77–2.70 (m, 2H, SCH_2), 2.62 (br s, 1H, OH), 2.39 (app.dd, 1H, *J* 4.8, 12.6 Hz, H-2^D_e), 1.62 (ddd, 1H, *J* 11.4, 11.8, 12.6 Hz, H-2^D_a), 1.29 (t, 3H, *J* 7.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.2 (CO), 133.2, 129.8, 129.6, 128.4 (aromatic), 95.7 (C-1^G), 83.2 (C-3^D), 82.0 (C-3^G), 81.8 (C-2^G), 79.6 (C-1^D), 78.2 (C-6^D), 71.9 (C-4^D), 71.5 (C-5^G), 70.1 (C-4^G), 69.8 (C-5^D), 63.6 (C-6^G), 61.3, 59.3, 58.3, 55.5 (OCH_3), 35.6 (C-2^D), 24.7 (SCH_2), 14.9 (CH_3). HRESIMS *m/z*: $[M+Na]^+$ calcd for $C_{25}H_{38}O_{10}S$: 553.2083; found: 553.2062.

3.6. Cyclo[(1→4)-6-*O*-benzoyl-2,3-di-*O*-methyl-α-D-glucopyranosyl-(1→4)-2-deoxy-3,6-di-*O*-methyl-α-D-*arabino*-hexopyranosyl]dioside (5) and cyclo[(1→4)-6-*O*-benzoyl-2,3-di-*O*-methyl-α-D-glucopyranosyl-(1→4)-2-deoxy-3,6-di-*O*-methyl-α-D-*arabino*-hexopyranosyl]trioside[20] (6)

Monomer **4α** (0.4 g, 0.75 mmol) was dissolved in C_6H_6 (10 mL) and freeze-dried. A solution of *N*-iodosuccinimide (0.19 g, 0.83 mmol) in CH_2Cl_2 (28 mL) was introduced, cooled to 0 °C, and TfOH (7 μL, 0.08 mmol) in CH_2Cl_2 (2 mL) was added. After 12 h, the reaction was quenched with Et_3N (200 μL), diluted with CH_2Cl_2 (50 mL), washed with $Na_2S_2O_3$ (5% w/v, 2 × 50 mL), H_2O (2 × 50 mL), dried (Na_2SO_4), and concentrated. The crude reaction mixture was subjected to HPLC to afford **5** (0.140 g, 40%), **6** (0.088 g, 25%), **7** (0.037 g, 10%), and **8** (0.064 g, 18%) as colorless foamy solids.

Compound **5**: t_R 31.52 min (EtOAc to 2:98 MeOH–EtOAc in 60 min, 1.0 mL min^{-1}); $[\alpha]_D^{24}$ +93.4 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.08–8.05 (m, 4H, aromatic-H), 7.59–7.41 (m, 6H, aromatic), 5.89 (d, 2H, *J* 3.6 Hz, H-1^G), 4.86 (app.d, 2H, *J* 3.3 Hz, H-1^D), 4.80 (dd, 2H, *J* 3.5, 12.0 Hz, H-6^G_a), 4.45 (dd, 2H, *J* 2.1, 12.0 Hz, H-6^G_b), 4.13 (t, 2H, *J* 9.3 Hz, H-4^G), 3.96 (t, 2H, *J* 9.0 Hz, H-4^D), 3.90–3.74 (band, 6H, H-3^D, H-5^D, H-5^G), 3.67 (s, 6H, OCH_3), 3.52 (s, 6H, OCH_3), 3.50–3.42 (m, 6H, H-3^G, H-6^D_a, H-6^D_b), 3.38 (s, 6H, OCH_3), 3.33 (s, 6H, OCH_3), 3.23 (dd, 2H, *J* 3.6, 9.0 Hz, H-2^G), 2.29 (app.dd, 2H, *J* 5.1, 12.5 Hz, H-2^D_e), 1.58 (ddd, 2H, *J* 3.3, 9.8, 12.5 Hz, H-2^D_a); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.2 (CO), 133.2, 129.9, 128.4 (aromatic-C), 98.4 (C-1^G), 95.6 (C-1^D), 82.1 (C-2^G), 81.9 (C-3^G), 79.7 (C-3^D), 71.3 (C-5^G), 71.2 (C-4^D), 70.1 (C-5^D), 69.9 (C-4^G), 69.4 (C-6^D), 63.6 (C-6^G), 61.3, 59.2, 59.0, 57.9 (OCH_3), 34.0 (C-2^D). MALDI-TOFMS: *m/z*: $[M+Na]^+$ calcd for $C_{46}H_{64}O_{20}$: 959; found: 959.

Compound **6**: t_R 40.35 min (EtOAc to 2:98 MeOH–EtOAc in 60 min, 1.0 mL min^{-1}); $[\alpha]_D^{24}$ +87.4 (*c* 1.2 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.07–8.05 (m, 6H, aromatic-H), 7.62–7.43 (m, 9H, aromatic), 5.91 (d, 3H, *J* 3.9 Hz, H-1^G), 4.82 (app.d, 3H, *J* 3.6 Hz, H-1^D), 4.69 (dd, 3H, *J* 4.5, 12.0 Hz, H-6^G_a), 4.54 (dd, 3H, *J* 2.1, 12.0 Hz, H-6^G_b), 4.06 (ddd, 3H, *J* 5.4, 9.0, 10.2 Hz, H-3^D), 3.75–3.57 (band, 30H, H-4^G, H-4^D, H-5^G, H-5^D, OCH_3), 3.55–3.46 (m, 9H, H-3^G, H-6^D_a, H-6^D_b), 3.33–3.30 (band, 18H, OCH_3), 3.25 (dd, 3H, *J* 3.9, 9.3 Hz, H-2^G), 2.15 (app.dd, 3H, *J* 5.4, 12.5 Hz, H-2^D_e), 1.69 (ddd, 3H, *J* 3.6, 10.2, 12.5 Hz, H-2^D_a); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.8 (CO), 133.3, 129.8, 129.7, 128.4 (aromatic-C), 98.7 (C-1^G), 95.6 (C-1^D), 84.5 (C-2^G), 83.3 (C-3^G), 82.9 (C-3^D), 71.0 (C-5^G), 70.9 (C-4^D), 70.4 (C-4^G), 69.7 (C-5^D), 68.4 (C-6^D), 63.8 (C-6^G), 61.3, 61.2, 59.9, 59.1 (OCH_3), 36.5 (C-2^D). MALDI-TOFMS: *m/z* $[M+Na]^+$ calcd for $C_{69}H_{96}O_{30}$: 1427; found: 1427.

3.7. 6-*O*-Benzoyl-2,3-di-*O*-methyl-α-D-glucopyranosyl-(1→4)-2-deoxy-3,6-di-*O*-methyl-α,β-D-*arabino*-hexopyranose (7)

t_R 46.70 min (EtOAc to 2:98 MeOH–EtOAc in 60 min, 1.0 mL min^{-1}); α/β 4:1, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06 (d, 2H, *J* 7.8 Hz, aromatic-H), 7.58–7.55 (m, 1H, aromatic-H), 7.45–7.42 (m, 2H, aromatic-H), 5.84 (d, 1H, *J* 3.7 Hz, H-1^G), 5.42 (br s, 1H, H-1^D), 4.76 (dd, 1H, *J* 3.7, 12.0 Hz, H-6^G_a), 4.47 (app.d, 1H, *J* 12.0 Hz, H-6^G_b), 4.11–4.09 (m, 1H, H-4^G), 3.99–3.94 (m, 1H, H-3^D),

3.87–3.82 (m, 2H, H-5^{G}, H-5^{D}), 3.73 (dd, 1H, *J* 4.0, 10.3 Hz, H-6$^{D}_{a}$) 3.67–3.63 (band, 4H, H-6$^{D}_{b}$, OCH_3), 3.52 (br s, 3H, OCH_3), 3.47–3.44 (m, 2H, H-3^{G}; H-4^{D}), 3.36 (br s, 3H, OCH_3), 3.34 (br s, 3H, OCH_3), 3.23 (dd, 1H, *J* 3.7, 9.0 Hz, H-2^{G}), 3.18 (br s, 1H, OH), 3.11 (br s, 1H, OH), 2.31 (app.dd, 1H, *J* 4.7, 12.9 Hz, H-2$^{D}_{e}$), 1.58–1.51 (m, 1H, H-2$^{D}_{a}$); characteristic resonances for the β anomer: δ 5.81 (d, 1H, *J* 3.7 Hz, H-1^{G}), 4.82-4.81 (m, 1H, H-3^{D}), 2.46–2.42 (m, 1H, H-2$^{D}_{e}$), 1.47–1.41 (m, 1H, H-2$^{D}_{a}$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.1 (CO), 133.2, 129.8, 129.6, 128.4 (aromatic-C), 95.7 (C-1^{G}α), 95.6 (C-1^{G}β), 94.1 (C-1^{D}β), 91.9 (C-1^{D}α), 84.5 (C-2^{G}), 82.0, 81.8, 81.7, 81.5, 79.0, 73.9, 72.0, 71.6, 71.5, 71.4, 70.2, 70.1, 69.8, 69.4, 63.5, 61.3 (C-3^{D}α/β to C-6^{D}α/β, C-2^{G}α/β to C-6^{G}α/β), 59.1, 59.0, 58.3, 58.1, 55.5, 55.4 (OCH_3), 36.6 (C-2^{D}β), 34.0 (C-2^{D}α). MALDI-TOFMS: *m/z* [M+Na]$^+$ calcd for $C_{23}H_{34}O_{11}$: 509; found: 509.

3.8. 6-*O*-Benzoyl-2,3-di-*O*-methyl-α-D-glucopyranosyl-(1→4)-2-deoxy-3,6-di-*O*-methyl-α-D-*arabino*-hexopyranosyl-(1→4)-6-*O*-benzoyl-2,3-di-*O*-methyl-α-D-glucopyranosyl-(1→4)-2-deoxy-3,6-di-*O*-methyl-α-D-*arabino*-hexopyranose (8)

t_R 54.48 min (EtOAc to 2:98 MeOH–EtOAc in 60 min, 1.0 mL min^{-1}); α anomer: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.12–8.06 (m, 4H, aromatic-H), 7.61–7.41 (m, 6H, aromatic-H), 5.78 (d, 2H, *J* 3.9 Hz, H-1′, H-1‴), 5.14–5.11 (m, 2H, H-1, H-1″), 4.72–4.66 (m, 2H, H-6′$_a$, H-6‴$_a$), 4.56-4.48 (m, 2H, H-6′$_b$, H-6‴$_b$), 4.06-4.03 (m, 4H), 3.95–3.87 (m, 8H), 3.79–3.15 (band, 30H), 2.98 (br s, 1H, OH), 2.89 (br s, 1H, OH), 2.32–2.28 (m, 2H, H-2$_e$, H-2″$_e$), 1.65–1.60 (m, 2H, H-2$_a$, H-2″$_a$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.1, 166.9 (CO), 133.3, 129.8, 129.7, 129.6, 129.5, 128.6, 128.5, 128.4 (aromatic-C), 98.7 (C-1^{G}), 95.9 (C-1^{D}), 84.5, 84.1, 83.1, 82.8, 82.2, 82.0, 81.9, 81.8, 81.7, 79.4, 71.0, 70.1, 68.4, 63.8, 61.2, 59.1, 58.2 (C-3^{D} to C-6^{D}, C-2^{G} to C-6^{G}, OCH_3), 36.5 (C-2^{D}). MALDI-TOFMS: *m/z* [M+Na]$^+$ calcd for $C_{46}H_{66}O_{21}$: 977; found: 977.

3.9. 1,5-Anhydro-2-deoxy-4-*O*-(4,6-*O*-isopropylidene-α-D-glucopyranosyl)-D-*arabino*-hex-1-enitol (10)

Glycal **9**[5] (2.5 g, 4.5 mmol) was admixed with NaOMe (catalytic amount) and MeOH (20 mL), and stirred for 6 h at room temperature. The reaction mixture was quenched with few drops of 1:10 AcOH–MeOH and concentrated. Purification afforded 1,5-anhydro-2-deoxy-4-*O*-(α-D-glucopyranosyl)-D-*arabino*-hex-1-enitol (1.3 g, 96%), as a white foamy solid. R_f 0.14 (1:3 $CH_3OH/CHCl_3$); $[\alpha]_D^{24}$ +90.5 (*c* 2.1, CH_3OH); ^{1}H NMR (D_2O, 300 MHz): δ 6.32 (d, 1H, *J* 6.0 Hz, H-1), 5.31 (dd, 1H, *J* 0.9, 6.0 Hz, H-1′), 4.73–4.69 (m, 1H, H-2), 4.27–4.23 (m, 1H, H-3), 3.96–3.93 (m, 1H, H-4), 3.81–3.71 (band, 5H, H-2′, H-3′, H-4′, H-6′$_a$, H-6′$_b$), 3.61–3.49 (m, 2H, H-6$_a$, H-6$_b$), 3.45–3.40 (m, 1H, H-5), 3.32–3.25 (m, 1H, H-5′); ^{13}C NMR (D_2O, 75 MHz): δ 144.2 (C-1), 103.2 (C-2), 98.3 (C-1′), 77.5, 74.0, 73.3, 72.9, 71.8, 70.6, 69.9, 67.4, 60.9, 60.4 (C-3 to C-6, C-2′ to C-6′). HRESIMS: *m/z* [M+Na]$^+$ calcd for $C_{12}H_{20}O_9$: 331.1005; found: 331.0983.

To a solution of maltal (2.7 g, 9.0 mmol) and 2,2-dimethoxypropane (2.6 mL, 21.0 mmol) in DMF (10 mL) was added at 0 °C *p*-TsOH in portions to adjust the pH of reaction mixture to ∼pH 3.0.[21] The reaction mixture was stirred at 0 °C for 2 h and quenched with Et_3N. After removal of the solvent, purification of the crude reaction mixture afforded glycal **10** (1.6 g, 51%) as a colorless gum. R_f 0.29 (1:9 CH_3OH–$CHCl_3$); $[\alpha]_D^{24}$ +34.4 (*c* 1.6, CH_3OH); ^{1}H NMR (D_2O, 300 MHz): δ 6.32 (dd, 1H, *J* 0.9, 6.0 Hz, H-1), 5.37 (dd, 1H, *J* 1.5, 4.0 Hz, H-1′), 4.71–4.68 (m, 1H, H-2), 4.30–4.26 (m, 1H, H-3), 3.95–3.90 (m, 1H, H-4), 3.79–3.39 (band, 9H, H-2′, H-3′, H-4′, H-5′, H-6′$_a$, H-6′$_b$, H-5, H-6$_a$, H-6$_b$), 1.43 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); ^{13}C NMR (D_2O, 75 MHz): δ 144.5 (C-1), 101.7 (C-2), 99.2 (–$C(CH_3)_2$–), C-1′), 77.6, 74.2, 73.6, 72.8, 70.9, 68.1, 64.6, 60.6 (C-3 to C-6, C-2′ to C-6′), 28.9, 19.1 (CH_3). HRESIMS: *m/z* [M+Na]$^+$ calcd for $C_{15}H_{24}O_9$: 371.1318; found: 371.1311.

3.10. 1,5-Anhydro-3,6-di-*O*-benzyl-4-*O*-(2,3-di-*O*-benzyl-4,6-*O*-isopropylidene-α-D-glucopyranosyl)-2-deoxy-D-*arabino*-hex-1-enitol (11)

To a suspension of NaH (60% dispersion in oil, 2.02 g, 50 mmol) in DMF (25 mL), a solution of glycal **10** (3.4 g, 9.7 mmol) in DMF (10 mL) was added at 0 °C over a period of 15 min. After stirring the reaction mixture for another 45 min at 0 °C, BnBr (5.3 mL, 45 mmol) was added and stirred for 3 h. The reaction mixture was neutralized with 1:10 AcOH–MeOH and diluted with EtOAc (100 mL). After extraction, the organic layer was washed with H_2O (2 × 50 mL), dried (Na_2SO_4), and concentrated. Purification of the crude reaction mixture afforded **11** (5.2 g, 75%), as a pale-yellow low-melting solid. R_f 0.61 (1:4 EtOAc–pet ether); $[\alpha]_D^{24}$ +16.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (D_2O, 300 MHz): δ 7.39–7.24 (band, 20H, aromatic-H), 6.49 (d, 1H, *J* 5.7 Hz, H-1), 5.46 (d, 1H, *J* 4.0 Hz, H-1′), 4.93–4.52 (band, 8H, H-2, $PhCH_2$), 4.44 (d, 1H, *J* 12.0 Hz, $PhCH_2$), 4.32–4.28 (m, 1H, H-3), 4.21–4.19 (m, 1H, H-4), 3.85–3.61 (band, 8H, H-3′, H-4′, H-5′, H-6′$_a$, H-6′$_b$, H-5, H-6$_a$, H-6$_b$), 3.49 (dd, 1H, *J* 4.0, 12.9 Hz, H-2′), 1.48 (s, 3H, CH_3), 1.46 (s, 3H, CH_3); ^{13}C NMR (D_2O, 75 MHz): δ 145.3 (C-1), 139.0, 138.1, 138.0, 137.9, 128.4, 128.2, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3 (aromatic-C), 99.3 (C-2), 99.2 (–$C(CH_3)_2$–), 96.8 (C-1′), 78.8, 78.7, 76.3, 75.3, 74.9, 74.8, 73.4, 73.3, 69.7, 68.7, 68.0, 64.0, 62.4 (C-3 to C-6, C-2′ to C-6′), 29.2, 19.2 (CH_3). HRESIMS: *m/z* [M+Na]$^+$ calcd for $C_{43}H_{48}O_9$: 731.3196; found: 731.3198.

3.11. Ethyl 3,6-di-*O*-benzyl-4-*O*-(2,3-di-*O*-benzyl-α-D-glucopyranosyl)-2-deoxy-1-thio-β-D-*arabino*-hexopyranoside (12)

A mixture of glycal **11** (2.05 g, 2.9 mmol) and ammonium cerium(IV) nitrate (CAN, 0.159 g, 0.29 mmol) in MeCN (20 mL) was stirred at 0 °C for 15 min. A solution of EtSH (2.2 mL, 29 mmol) in MeCN (5 mL) was added dropwise to the reaction mixture, and stirring was continued for 16 h at room temperature. After 16 h, the reaction mixture was extracted with ether, the extract was washed with $NaHCO_3$ solution (5%, 2 × 50 mL), brine (2 × 50 mL), dried (Na_2SO_4), and concentrated. The crude product was subjected to column chromatography to afford 2-deoxy-1-thioglycoside **12** (0.85 g, 40%, β only) as a light-yellow gum. R_f 0.4 (1:2 EtOAc–pet ether, double elution). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35–7.15 (band, 20H, aromatic-H), 5.85 (d, 1H, *J* 3.7 Hz, H-1^{G}), 4.95 (d, 1H, *J* 12.0 Hz, $PhCH_2$), 4.69–4.55 (band, 6H, H-1^{D}, $PhCH_2$), 4.45–4.36 (m, 2H, $PhCH_2$), 3.99 (t, 1H, *J* 9.6 Hz, H-4^{D}), 3.88 (ddd, 1H, *J* 4.8, 9.0, 11.8 Hz, H-3^{D}), 3.80 (dd, 1H, *J* 5.0, 10.3 Hz, H-6$^{D)}_{a}$), 3.74 (dd, 1H, *J* 1.8, 10.3 Hz, H-6$^{D}_{b}$), 3.70–3.63 (band, 4H, H-3^{G}, H-4^{G}, H-5^{G}, H-6$^{G}_{a}$, H-6$^{G}_{b}$), 3.60–3.50 (m, 1H, H-5^{D}), 3.47 (t, 1H, *J* 9.6 Hz, H-4^{G}), 3.41 (dd, 1H, *J* 3.0, 9.6 Hz, H-2^{G}), 2.81–2.66 (m, 2H, SCH_2), 2.44 (ddd, 1H, *J* 1.4, 4.8, 12.1 Hz, H-2$^{D}_{e}$), 1.78 (ddd, 1H, *J* 9.0, 11.8, 12.1 Hz, H-2$^{D}_{a}$), 1.31 (t, 3H, *J* 7.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.6, 138.2, 137.9, 137.8, 128.5, 128.4, 128.3, 127.7, 127.6, 127.5, 126.9 (aromatic-C), 96.3 (C-1^{G}), 81.6, 80.9, 79.4 (C-1^{D}), 79.1, 78.7, 75.1, 73.4, 72.2, 72.1, 71.7, 70.3, 70.0, 69.0, 62.3 (C-3^{D} to C-6^{D}, C-2^{G} to C-6^{G}, $PhCH_2$), 36.6 (C-2^{D}), 24.6 (SCH_2), 15.2 (CH_3). HRESIMS: *m/z* [M+Na]$^+$ calcd for $C_{42}H_{50}O_9S$: 753.3073; found: 753.3035. Anal. Calcd for $C_{42}H_{50}O_9S$: C, 69.04; H, 6.85; S, 4.38. Found: C, 68.71; H, 6.87; S, 4.10.

3.12. Ethyl 3,6-di-*O*-benzyl-4-*O*-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-2-deoxy-1-thio-β-D-*arabino*-hexopyranoside (13)

A mixture of **12** (0.78 g, 1.1 mmol) and Bu_2SnO (0.32 g, 1.3 mmol) was dissolved in PhMe (20 mL), and was refluxed for 16 h with azeotropic removal of water using a Dean–Stark appara-

tus. The solvents were evaporated to half of the volume, then BnBr (182 μL, 1.5 mmol) and Bu_4NBr (0.36 g, 1.1 mmol) were added. After refluxing for 4 h, the solvents were evaporated, and the crude product was purified to obtain **13** (0.7 g, 80%, β only) as a pale-yellow gum. R_f 0.42 (1:4 EtOAc–PhMe); $[\alpha]_D^{24}$ +8.2 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.31–7.16 (band, 25H, aromatic-H), 5.86 (d, 1H, *J* 3.6 Hz, H-1^G), 4.93 (d, 1H, *J* 12.0 Hz, $PhCH_2$), 4.71–4.36 (band, 10H, H-1^D, $PhCH_2$), 4.00 (t, 1H, *J* 9.6 Hz, H-4^D), 3.89 (ddd, 1H, *J* 5.0, 9.0, 11.8 Hz, H-3^D), 3.80–3.63 (band, 7H, H-3^G, H-4^G, H-5^G, H-6^G_a, H-6^G_b, H-6^D_a, H-6^D_b), 3.59–3.55 (m, 1H, H-5^D), 3.46 (dd, 1H, *J* 3.0, 9.0 Hz, H-2^G), 2.80–2.64 (m, 2H, SCH_2), 2.44 (ddd, 1H, *J* 1.5, 5.0, 12.1 Hz, H-2^D_e), 1.70 (ddd, 1H, *J* 9.5, 11.8, 12.1 Hz, H-2^D_a), 1.26 (t, 3H, *J* 7.6 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.7, 138.4, 137.9, 137.8, 128.7, 128.3, 128.2, 127.8, 127.7, 127.6, 127.5, 127.4, 126.9 (aromatic-C), 96.4 (C-1^G), 81.7, 81.0, 79.5 (C-1^D), 78.9, 75.3, 73.5, 73.3, 72.2, 72.1, 70.9, 70.5, 70.0, 69.5, 69.4 (C-3^D to C-6^D, C-2^G to C-6^G, $PhCH_2$), 36.3 (C-2^D), 24.2 (SCH_2), 15.2 (CH_3). HRESIMS: *m/z* $[M+Na]^+$ calcd for $C_{49}H_{56}O_9S$: 843.3543; found: 843.3555. Anal. Calcd for $C_{49}H_{56}O_9S$: C, 71.70; H, 6.83; S, 3.90. Found: C, 71.70; H, 7.07; S, 3.74.

3.13. Ethyl 3,6-di-*O*-acetyl-4-*O*-(2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranosyl)-2-deoxy-1-thio-α/β-D-*arabino*-hexopyranoside (14)

A mixture of 2-deoxy-1-thioglycoside **2** (3.75 g, 10.0 mmol), α,α-dimethoxytoluene (2.9 mL, 17.0 mmol), and *p*-TsOH monohydrate (0.19 g, 1.0 mmol) in DMF (20 mL) was stirred at diminished pressure with a rotary evaporator for 1.5 h (bath temperature 60 ± 5 °C). The reaction was quenched with Et_3N (1 mL). The solvent was removed, and the residue was taken for the next step without further purification.

To a mixture of Ac_2O (8 mL) in pyridine (13 mL), crude ethyl 4-*O*-(4,6-*O*-benzylidene-α-D-glucopyranosyl)-2-deoxy-1-thio-α/β-D-*arabino*-hexopyranoside in DMF (5 mL) was added dropwise at 0 °C. After 24 h, the reaction mixture was diluted with CH_2Cl_2 (100 mL), washed with ice-cold HCl (5%, 3 × 50 mL) solution, satd $NaHCO_3$ solution (3 × 50 mL), and water (2 × 50 mL). The extract was dried (Na_2SO_4) and concentrated, and purification of the crude residue afforded **14** (5.4 g, 85% after two steps, α/β 9:1), as a white solid.

Compound **14α**: mp 193–195 °C; $[\alpha]_D^{24}$ +158.1 (*c* 1, $CHCl_3$); R_f 0.5 (1:2 EtOAc–pet ether); ^1H NMR ($CDCl_3$, 400 MHz): δ *7.45–7.34* (band, 5H, aromatic-H), 5.53–5.48 (band, 3H, H-1^G, H-3^G, PhCH), 5.36 (app.d, 1H, *J* 4.7 Hz, H-1^D), 5.12 (ddd, 1H, *J* 5.2, 9.7, 11.0 Hz, H-3^D), 4.89 (dd, 1H, *J* 4.1, 10.0 Hz, H-2^G), 4.45–4.33 (band, 3H, H-5^D, H-5^G, H-6^D_b), 4.27 (dd, 1H, *J* 4.8, 10.2 Hz, H-6^D_a), 3.93–3.82 (m, 2H, H-6^G_a, H-6^G_b), 3.73 (t, 1H, *J* 10.0 Hz, H-4^G), 3.63 (t, 1H, *J* 9.7 Hz, H-4^D), 2.65–2.52 (m, 2H, SCH_2), 2.29 (ddd, 1H, *J* 1.2, 5.2, 13.2 Hz, H-2^D_e), 2.10 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 2.03–1.92 (band, 7H, $COCH_3$, H-2^D_a), 1.27 (t, 3H, *J* 7.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6, 170.3, 169.8, 169.6 (CO), 136.8, 129.0, 128.1, 126.2 (aromatic-C), 101.6 (PhCH), 96.4 (C-1^G), 79.1 (C-1^D), 78.9, 76.9, 73.8, 72.9, 70.9, 68.6, 68.5, 63.5, 63.3 (C-3^D to C-6^D, C-2^G to C-6^G), 34.7 (C-2^D), 24.8 (SCH_2), 21.1, 20.7, 20.5 ($COCH_3$), 14.6 (CH_3). HRESIMS: *m/z* $[M+Na]^+$ calcd for $C_{29}H_{38}O_{13}S$: 649.1931; found: 649.1928.

Compound **14β**: $[\alpha]_D^{24}$ +130.9 (*c* 1.4, $CHCl_3$); R_f 0.62 (1:2 EtOAc–pet ether); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.43–7.33 (band, 5H, aromatic-H), 5.51–5.48 (band, 3H, H-1^G, H-3^G, PhCH), 4.97 (ddd, 1H, *J* 3.8, 9.0, 11.0 Hz, H-3^D), 4.90 (dd, 1H, *J* 4.0, 9.6 Hz, H-2^G), 4.64 (dd, 1H, *J* 1.8, 10.2 Hz, H-1^D), 4.42 (dd, 1H, *J* 1.8, 10.2 Hz, H-6^D_b), 4.34–4.25 (m, 2H, H-5, H-6^D_a), 3.91–3.84 (m, 2H, H-6^G_a, H-6^G_b), 3.73 (t, 1H, *J* 9.6 Hz, H-4^G), 3.65-3.60 (band, 2H, H-4^D, H-5^G), 2.78–2.64 (m, 2H, SCH_2), 2.42 (ddd, 1H, *J* 1.8, 3.8, 12.7 Hz, H-2^D_e), 2.11–2.03 (band, 12H, $COCH_3$), 1.64 (ddd, 1H, *J* 10.2, 11.0, 12.7 Hz, H-2^D_a), 1.29 (t, 3H, *J* 7.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.5, 170.3, 170.1, 169.6 (CO), 136.7, 129.0, 128.1, 126.7, 126.1 (aromatic-C), 101.5 (PhCH), 96.4 (C-1^G), 79.3 (C-1^D), 78.8, 76.0, 75.4, 73.3, 70.9, 68.5, 68.4, 63.5 (C-3^D to C-6^D, C-2^G to C-6^G), 36.3 (C-2^D), 25.0 (SCH_2), 21.1, 20.7, 20.5 ($COCH_3$), 14.9 (CH_3). HRESIMS: *m/z* $[M+Na]^+$ calcd for $C_{29}H_{38}O_{13}S$: 649.1931; found: 649.1942.

3.14. Ethyl 3,6-di-*O*-acetyl-4-*O*-(2,3-di-*O*-acetyl-6-*O*-benzoyl-α-D-glucopyranosyl)-2-deoxy-1-thio-α/β-D-*arabino*-hexopyranoside (15)

Compound **14** (0.65 g, 1 mmol) was dissolved in 1:1 MeOH–THF (15 mL), and *p*-TsOH (0.18 g, 1.2 mmol) was added. After 3 h, the reaction mixture was quenched with Et_3N (0.5 mL) and concentrated. The crude product was purified by column chromatography (SiO_2, 100–200 mesh) to afford ethyl 3,6-di-*O*-acetyl-4-*O*-(2,3-di-*O*-acetyl-α-D-glucopyranosyl)-2-deoxy-1-thio-α/β-D-*arabino*-hexopyranoside (0.514 g, 92%, α/β 9:1) as a foamy solid. R_f 0.54 (EtOAc). α anomer: ^1H NMR ($CDCl_3$, 400 MHz): δ 5.42 (d, 1H, *J* 4.0 Hz, H-1^G), 5.28 (app.d, 1H, *J* 4.7 Hz, H-1^D), 5.16 (t, 1H, *J* 10.0 Hz, H-3^G), 5.03 (ddd, 1H, *J* 4.0, 8.0, 12.0 Hz, H-3^D), 4.68 (dd, 1H, *J* 4.1, 10.0 Hz, H-2^G), 4.35-4.20 (band, 4H, H-5^D, H-5^G, H-6^D_a, H-6^D_b), 3.84–3.53 (band, 4H, H-4^D, H-4^G, H-6^G_a, H-6^G_b), 3.20–3.11 (br s, 2H, OH), 2.59–2.43 (m, 2H, SCH_2), 2.21–1.77 (band, 14H, H-2^D_a, H-2^D_e, $COCH_3$), 1.20 (t, 3H, *J* 7.4 Hz, CH_3); Characteristic signals for β anomer: δ 5.53 (d, 1H, *J* 4.0 Hz, H-1^G), 4.82–4.74 (m, 1H, H-3^D), 3.33 (t, 1H, *J* 9.0 Hz, H-4^G), 3.22 (t, 1H, *J* 9.0 Hz, H-4^D), 1.42 (ddd, 1H, *J* 9.0, 11.2, 12.1 Hz, H-2^D_a); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.6, 171.4, 170.7, 170.0 (CO), 95.6 (C-1^G), 79.3 (C-1^D), 73.1, 73.0, 72.5, 72.3, 70.3, 70.0, 68.3, 63.6, 62.3 (C-3^D to C-6^D, C-2^G to C-6^G), 34.9 (C-2^D), 24.9 (SCH_2), 21.3, 20.9, 20.6 ($COCH_3$), 14.7 (CH_3). HRESIMS: *m/z* $[M+Na]^+$ calcd for $C_{22}H_{34}O_{13}S$: 561.1618; found: 561.1613.

To a mixture of BzCl (306 μL, 2.6 mmol) and pyridine (600 μL, 7.4 mmol) in CH_2Cl_2 (15 mL), ethyl 3,6-di-*O*-acetyl-4-*O*-(2,3-di-*O*-acetyl-α-D-glucopyranosyl)-2-deoxy-1-thio-α/β-D-*arabino*-hexopyranoside (1.3 g, 2.43 mmol) in CH_2Cl_2 (15 mL) was added dropwise at 0 °C. After 24 h, the reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with ice-cold HCl (5%, 2 × 50 mL) solution, satd $NaHCO_3$ solution (2 × 50 mL), and water (2 × 50 mL). The extract was dried (Na_2SO_4) and concentrated, and purification of the crude product afforded **15** (1.24 g, 80%, α/β 9:1) as an amorphous solid. R_f 0.35 (1:1 EtOAc–pet ether). α anomer: ^1H NMR ($CDCl_3$, 400 MHz): δ 8.07–8.00 (band, 2H, aromatic-H), 7.61–7.43 (band, 3H, aromatic-H), 5.52 (d, 1H, *J* 3.8 Hz, H-1^G), 5.36 (app.d, 1H, *J* 4.8 Hz, H-1^D), 5.31 (t, 1H, *J* 10.0 Hz, H-3^G), 5.13 (ddd, 1H, *J* 5.0, 9.0, 13.3 Hz, H-3^D), 5.05 (dd, 1H, *J* 3.8, 10.0 Hz, H-2^G), 4.81 (dd, 1H, *J* 4.0, 10.5 Hz, H-6^G_a), 4.77 (dd, 1H, *J* 2.7, 10.5 Hz, H-6^G_b), 4.50–4.28 (band, 4H, H-5^D, H-5^G, H-6^D_a, H-6^D_b), 3.97 (d, 1H, *J* 9.5, OH), 3.85 (t, 1H, *J* 9.0 Hz, H-4^D), 3.65-3.61 (m, 1H, H-4^G), 2.65–2.52 (m, 2H, SCH_2), 2.27 (app.dd, 1H, *J* 5.0, 13.2 Hz, H-2^D_e), 2.16–2.00 (band, 13H, H-2^D_a, $COCH_3$), 1.28 (t, 3H, *J* 7.4 Hz, CH_3); Characteristic signals for β anomer: δ 7.97–7.91 (band, 2H, aromatic-H), 7.39–7.33 (band, 3H, aromatic-H), 4.99–4.90 (m, 1H, H-3^D), 4.63 (dd, 1H, *J* 2.0, 10.0 Hz, H-1^D), 4.25–4.17 (m, 2H, H-6^D_a, H-6^D_b), 4.10 (t, 1H, *J* 9.0 Hz, H-4^D), 2.41–2.37 (m, 1H, H-2^D_e), 1.64 (ddd, 1H, *J* 10.0, 11.2, 12.8 Hz, H-2^D_a); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.1, 170.6, 170.5, 169.8, 166.9 (CO), 133.3, 129.7, 129.5, 129.1, 128.4 (aromatic-C), 95.6 (C-1^G), 79.1 (C-1^D), 73.4, 72.9, 71.2, 70.2, 69.0, 68.3, 63.4, 62.8 (C-3^D to C-6^D, C-2^G to C-6^G), 34.7 (C-2^D), 24.7 (SCH_2), 21.0, 20.7, 20.5 ($COCH_3$), 14.6 (CH_3). HRESIMS: *m/z* $[M+Na]^+$ calcd for $C_{29}H_{38}O_{14}S$: 665.1880; found: 665.1874.

3.15. General procedure for oligomerization of 13 and 15

The monomer (1 mmol) was dissolved in C_6H_6 (20 mL) and freeze-dried. A solution of *N*-iodosuccinimide (1.1 mmol) in CH_2Cl_2

(38 mL) was then introduced. The mixture was cooled to 0 °C, and TfOH (0.11 mmol) in CH_2Cl_2 (2 mL) was added. After 12 h, the reaction was quenched with Et_3N, diluted with CH_2Cl_2 (50 mL), washed with $Na_2S_2O_3$ (5% w/v, 3 × 50 mL), and H_2O (3 × 50 mL). The extract was dried (Na_2SO_4) and concentrated.

3.16. Oligomerization reaction using NIS/AgOTf

Monomer **4α** (0.34 g, 0.64 mmol) was dissolved in C_6H_6 (10 mL) and freeze-dried. A solution of *N*-iodosuccinimide (0.172 g, 0.76 mmol) in CH_2Cl_2 (26 mL) was introduced. The mixture was cooled to 0 °C, and AgOTf (0.01 g, 0.08 mmol) was added. After 12 h, the reaction was quenched with Et_3N (200 μL), diluted with CH_2Cl_2 (50 mL), washed with aq $Na_2S_2O_3$ (5% w/v, 2 × 50 mL), and H_2O (2 × 50 mL). The extract was dried (Na_2SO_4) and concentrated. The crude reaction mixture was dissolved in pyridine (6 mL), cooled to 0 °C, and Ac_2O (4 mL) was added. After 12 h, the reaction mixture was quenched by addition of ice, diluted with CH_2Cl_2 (50 mL), washed with ice-cold aq HCl (5%), and aq $NaHCO_3$. The extract was dried (Na_2SO_4) and concentrated. The crude reaction mixture contained di- to eicosasaccharides. Purification by GPC provided only the pure hexasaccharide, while the remaining oligosaccharides could not be obtained individually, even after four times of repeated GPC purifications.

3.17. 4-*O*-acetyl-6-*O*-benzoyl-2,3-di-*O*-methyl-α-D-glucopyranosyl-(1→4)-2-deoxy-3,6-di-*O*-methyl-α-D-*arabino*-hexopyranosyl-(1→4)-6-*O*-benzoyl-2,3-di-*O*-methyl-α-D-glucopyranosyl-(1→4)-2-deoxy-3,6-di-*O*-methyl-α-D-*arabino*-hexopyranosyl-(1→4)-6-*O*-benzoyl-2,3-di-*O*-methyl-α-D-glucopyranosyl-(1→4)-1-*O*-acetyl-2-deoxy-3,6-di-*O*-methyl-α-D-*arabino*-hexopyranose (linear hexasaccharide)

t_R 7.82 min (THF, 1.0 mL min^{-1}); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.09–8.03 (band, 6H, aromatic-H), 7.55–7.41 (band, 9H, aromatic-H), 5.91 (d, 1H, *J* 3.9 Hz, H-1), 5.87 (d, 2H, *J* 3.6 Hz, H-1″, H-1‴), 5.83 (d, 3H, *J* 3.6 Hz, H-1′, H-1‴, H-1′‴′), 4.64-4.54 (m, 3H, H-3, H-3″, H-3‴′), 4.49–4.37 (m, 3H, H-$6'_a$, H-$6'''_a$, H-$6'''''_a$), 4.35–4.25 (m, 3H, H-$6'_b$, $6'''_b$, H-$6'''''_b$), 4.02–3.28 (band, 60H), 2.08–1.98 (m, 9H, $COCH_3$, H-2_e, H-$2''_e$, H-$2''''_e$), 1.59–1.50 (m, 3H, H-2_a, H-$2''_a$, H-$2''''_a$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.6, 169.5, 166.3, 166.2 (CO), 133.0, 132.9, 129.9, 129.7, 128.5, 128.3 (aromatic-C), 98.6, 95.8, 95.7 (C-1 to C-1‴′), 81.7, 81.6, 81.5, 81.4, 80.4 (×2), 80.3, 79.3, 74.4, 74.2, 73.6, 71.4, 71.2, 70.2, 70.1,67.9, 67.7, 66.4, 62.8, 60.7, 59.2, 58.9, 55.5 (C-3/6 to C-2‴′/6‴′, OCH_3), 35.4, 35.2 (C-2, C-2″, C-2‴′), 21.0, 20.9 ($COCH_3$). MALDI-TOFMS: *m/z* $[M+Na]^+$ calcd for $C_{73}H_{102}O_{33}$: 1529; found: 1530.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2008.10.026.

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