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Stereoselective synthesis of thioxylooligosaccharides from *S*-glycosyl isothiourea precursors

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Abstract—A stereoselective synthesis of thioxylo-di-, -tri-, -tetra- and -penta-saccharides from *S*-glycosyl isothiourea precursors is described. The synthesis was performed starting from 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl isothiouronium bromide using a triethylamine promoted reaction with 1,2,3-tri-*O*-benzoyl-4-*O*-trifluoromethanesulphonyl-β-L-arabinopyranose. The resulting 4-thioxylobiose was then converted into the corresponding isothiouronium bromide and used for the synthesis of 4,4′-dithioxylotriose. Higher homologues of the series and their α-methyl glycosides were also prepared. © 2001 Elsevier Science Ltd. All rights reserved.

Thio-linked oligosaccharides have recently drawn attention owing to their potential as competitive inhibitors for *exo*- and particularly for *endo*-glycosidases. Due to a close similarity to the natural oligosaccharides and stability to enzymatic cleavage, thiooligosaccharides have proven to be very convenient and versatile tools for biochemical and structural investigations of the carbohydrate processing enzymes.[1]

In recent years, xylanases have attracted considerable research interest because of their large potential application in food and paper pulp industries.[2] Xylanases hydrolyze the β-1,4-linkages between the internal xylose units of xylan, the major constituent of hemicellulose. Syntheses of some derivatives of 4-thioxylobiose and 4,4′-dithioxylotriose have been described.[1,3] However, for an efficient productive binding into the active site of the enzymes, higher oligosaccharides are required.[4]

A systematic synthesis of higher members of this series or of their methyl glycosides has not been carried out due to the difficulties involved in the preparation of suitable intermediates. Here, we present the synthesis of a series of 1,4-thioxylooligosaccharides from *S*-glycosyl isothiourea derivatives using a new efficient approach, recently developed in our laboratory.[5]

S-Glycosyl isothiourea derivatives are known as very convenient precursors for the stereoselective synthesis of thioglycosides due to the fixed 1,2-*trans*-configuration of the thioglycosidic bond, the simplicity of their preparation from corresponding glycosyl bromides and thiourea,[6] and their ability to be readily converted into the target compounds.[5–7]

Although *S*-glycosyl isothiourea derivatives have also been utilized for the preparation of thiooligosaccharides, the syntheses were usually performed employing a two-step procedure, involving cleavage of the *S*-amidino group, followed by isolation of the corresponding 1-thio-aldose and subsequent coupling with an appropriate triflate derivative.[8]

Recently, we described a synthesis of methyl 4-thio-α-cellobioside and methyl 4-thio-α-lactoside derivatives using a one-pot procedure based on the triethylamine promoted reaction of methyl 2,3,6-tri-*O*-benzoyl-4-*O*-trifluoromethanesulphonyl-α-D-galactopyranoside with a corresponding isothiourea derivative in acetonitrile.[5] Successful synthesis of these two compounds prompted us to apply the same approach to the synthesis of thioxylooligosaccharides.

1,2,3-tri-*O*-Benzoyl-4-*O*-trifluoromethanesulphonyl-β-L-arabinopyranose **6** has been chosen as the key monomer for the synthesis of the thioxylooligosaccharides for several reasons. The benzoyloxy group at the anomeric position can be easily substituted affording a glycosyl bromide, which, in turn, can be converted into

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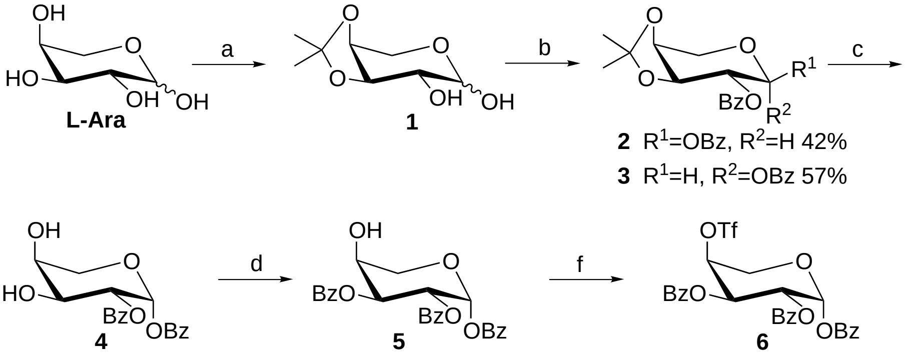
the corresponding isothiouronium bromide. Moreover, due to steric reasons the axial 1-benzoyloxy group decreases the decomposition of triflate **6**, leading to the formation of unsaturated byproducts during the coupling step. The rate of this side reaction strongly depends on the glycosidic bond configuration, and explains the considerably lower yields of corresponding coupling products with an equatorial substituent at C-1.[9] Indeed, the yield of disaccharide **8** was almost double in comparison with the yield of corresponding 4-thioxylobiose derivative prepared from the α-L-analog of compound **6**. For the same reason, the synthesis of thioxylooligosaccharides has been performed utilizing a stepwise approach. It is also important that benzoyl protecting groups can be selectively introduced and easily removed under basic conditions in the final step to give free thiooligosaccharides.

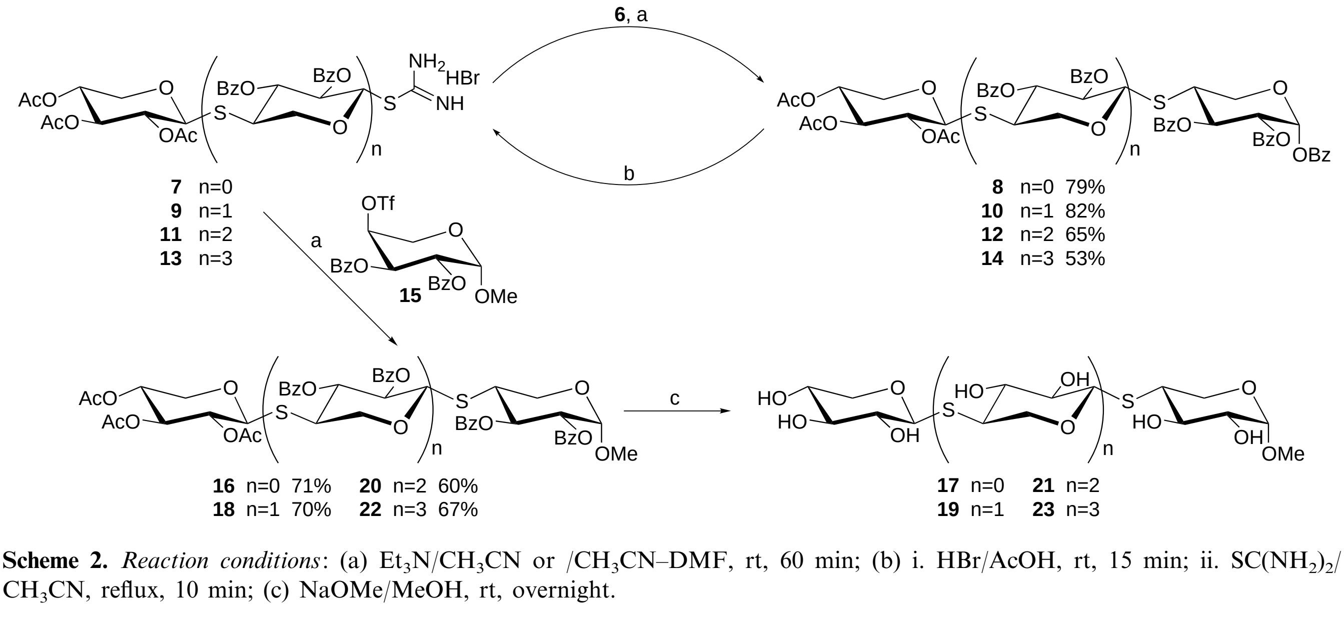
The compound **6** has been prepared (Scheme 1) starting from 3,4-isopropylidene L-arabinopyranose **1**, which can be readily obtained in high yield by acetonation of L-arabinose with 2,2-dimethoxypropane in DMF applying the procedure described for its D-isomer.[10] Benzoylation of this compound afforded both anomers of 1,2-di-*O*-benzoyl-3,4-isopropylidene L-arabinopyranose **2** and **3** in comparable yields. The β-L-anomer **3** was separated as a crystalline material by crystallization from 2-propanol. After the removal of the isopropylidene group by heating in 60% acetic acid for 25 min, the desired 1,2-di-*O*-benzoyl-β-L-arabinopyranose **4** was precipitated from the reaction mixture after dilution with cold water. Selective benzoylation of the OH group at C-3 in pyridine followed by triflation of the resulting tri-*O*-benzoate **5** in CH_2Cl_2 afforded the desired 4-*O*-triflate **6**.

Synthesis of thioxylooligosaccharides has been performed as described in Scheme 2 using a triethylamine promoted reaction of the isothiouronium bromides with triflate **6**.

To a suspension of 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl isothiouronium bromide **7**, prepared from α-acetobromoxylose and thiourea by a 10–15 minute reflux in acetonitrile, compound **6** and triethylamine were added. The reaction mixture was stirred at room temperature for one hour to give the thiodisaccharide **8** in 79% yield after work up.



Scheme 1. *Reaction conditions*: (a) $Me_2C(OMe)_2$, TosOH, DMF, rt, 1 h, 95%; (b) BzCl/Pyr, 0°C–rt, 2 h; (c) AcOH/H_2O (3:2), 95°C, 25 min, 82%; (d) BzCl/Pyr, −20°C, 1 h, 0°C, 2 h, rt, 15 h, 81%; (e) Tf_2O, Pyr/CH_2Cl_2, 0°C–rt, 30 min, 96%.



Scheme 2. *Reaction conditions*: (a) Et_3N/CH_3CN or /CH_3CN–DMF, rt, 60 min; (b) i. HBr/AcOH, rt, 15 min; ii. $SC(NH_2)_2$/CH_3CN, reflux, 10 min; (c) NaOMe/MeOH, rt, overnight.

Due to possible decomposition of triflates **6** and **15** under the basic conditions by elimination of the triflate group as described above, 10–40% molar excess of these compounds was used in the coupling reactions.

Compound **8** was easily converted into a glycosyl bromide by 15 minute treatment with hydrogen bromide in acetic acid/CH$_2$Cl$_2$ using a standard protocol.[11] A 15 minute reflux of the resulting bromide and thiourea in acetonitrile afforded isothiourea derivative **9**.

Reaction of compound **9** with triethylamine and triflate **6** in acetonitrile gave thiotrisaccharide **10** in 82% yield. The compound was then converted into isothiouronium bromide **11** according to the reaction sequence described for **9**, and treated with Et$_3$N and **6** to give thioxylotetrasaccharide **12** in 65% yield. Due to the low solubility of compound **11** in acetonitrile, the reaction was carried out in an acetonitrile–DMF mixture. To reduce oxidation of the 1-thio group, the reaction was performed in the presence of dithiothreitol (DTT) (1 equivalent).

Conversion of **12** into isothiourea derivative **13** followed by reaction with Et$_3$N, DTT and **6** in DMF/acetonitrile afforded thioxylopentasaccharide **14** in 53% yield (Scheme 2).

Similarly, reaction of isothiouronium bromides **7**, **9**, **11** and **13** with methyl 2,3-di-*O*-benzoyl-4-*O*-triflyl-β-L-arabinopyranoside **15** afforded α-methyl glycosides **16** (71% yield), **18**, **20** and **22** in 70, 60 and 67% overall yields, correspondingly, from compounds **8**, **10** and **12**.

The final thioxylooligosaccharides **17**, **19**, **21** and **23** were obtained after removal of the protecting groups from the acylated precursors using a solution of NaOMe in MeOH.[12]

In summary, an efficient approach for the synthesis of 1-4-thioxylooligosaccharides from isothiourea precursors is described. Very mild reaction conditions and short reaction times, high yields of the products in combination with the availability of the reagents used are evidently advantageous for the approach in comparison with all the known methods of 1,2-*trans*-thiooligosaccharide synthesis.[13]

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12. All synthesized compounds gave satisfactory elemental analyses and were characterized by NMR spectroscopy. Assignments in ^{1}H and ^{13}C spectra of final thioxylooligosaccharides were performed using a combination of 1D and 2D homo- and heteronuclear chemical shift correlation techniques including DEPT-135, COSY-45, DQF-COSY, HMQC, COLOC, NOESY and *J*-resolved spectroscopy at 300 MHz Bruker DPX-300. Compound **17**: ^{13}C NMR (D$_2$O, 125 MHz) δ 100.21 (C-1), 84.65 (C-1′), 77.45 (C-3′), 72.98 (C-2), 72.46 (C-2′), 70.14 (C-3), 69.39 (C-4′), 69.14 (C-5′), 62.11 (C-5), 55.52 (OCH$_3$), 45.70 (C-4). Compound **19**: ^{13}C NMR (D$_2$O, 125 MHz) δ 100.19 (C-1), 84.68, 84.56 (C-1′, C-1″), 77.44 (C-3″), 74.36 (C-3′), 73.83 (C-2′), 72.98 (C-2), 72.44 (C-2″), 70.14 (C-3), 70.04 (C-5′), 69.37 (C-4″), 69.12 (C-5″), 62.10 (C-5), 55.53 (OCH$_3$), 45.64, 45.54 (C-4, C-4′). Compound **21**: ^{13}C NMR (D$_2$O, 125 MHz) δ 100.19 (C-1), 84.69, 84.60, 84.56 (C-1′, C-1″, C-1‴), 77.43 (C-3‴), 74.32 (C-3′, C-3″), 73.82 (C-2′, C-2″), 72.96 (C-2), 72.43 (C-2‴), 70.12 (C-3), 70.06 (C-5′, C-5″), 69.37 (C-4‴), 69.13 (C-5‴), 62.11 (C-5), 55.52 (OCH$_3$), 45.64, 45.52, 45.48 (C-4, C-4′, C-4″). Compound **23**: ^{13}C NMR (D$_2$O, 125 MHz) δ 100.19 (C-1), 84.70, 84.60, 84.58, 84.54 (C-1′, C-1″, C-1‴, C-1⁗), 77.43 (C-3⁗), 74.32 (C-3′, C-3″, C-3‴), 73.80 (C-2′, C-2″, C-2‴), 72.95 (C-2), 72.42 (C-2⁗), 70.12 (C-3), 70.08 (C-5′, C-5″, C-5‴), 69.36 (C-4⁗), 69.13 (C-5⁗), 62.12 (C-5), 55.52 (OCH$_3$), 45.63, 45.50, 45.46 (C-4, C-4′, C-4″, C-4‴).
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