Synthesis of 2-Thioaldoses via BF_3-Promoted Cycloaddition of β-Methoxyvinyl Sulfides with 2,3-*O*-Isopropylidene Derivatives of *aldehydo*-Aldoses

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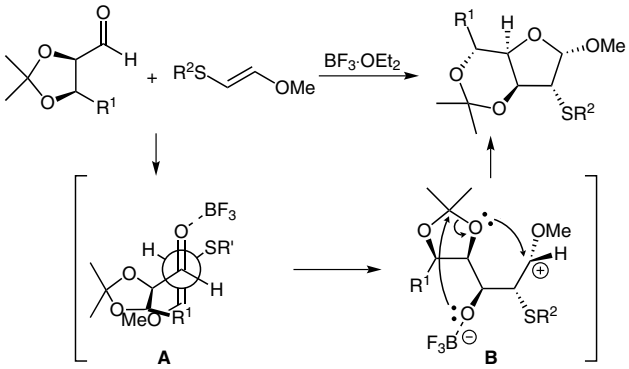
Abstract: A highly stereoselective approach to the synthesis of 2-thioaldose derivatives via BF_3-promoted cycloaddition of β-methoxyvinyl sulfides with 2,3-*O*-isopropylidene derivatives of *aldehydo*-aldoses is described.

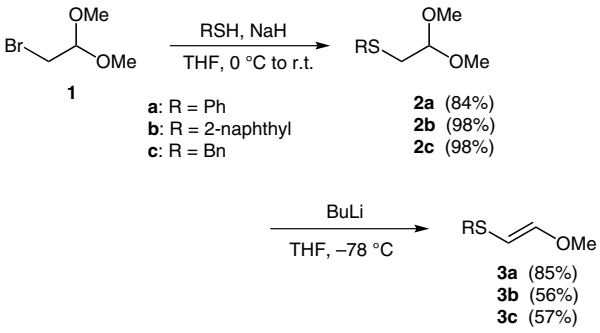
Key words: aldehydes, boron, carbohydrates, cycloaddition, sulfur

There are several sulfur-containing sugars found in nature.[1] Among them, angucycline class of compounds, BE-7585A[2] and rhodonocardins,[3] are the only reported natural products containing a 2-thioglucose. However, in the field of synthetic organic chemistry, 2-thioaldoses have been of much interest for decades and a wide range of synthetic studies has been reported.[4] For instance, some oligomers of saccharides with sulfur in the glycosidic linkage have been synthesized as potential glycosidase inhibitors[5] or potentially stable immunogens.[6] 2-Thioaldose derivatives have also been used as synthetic equivalents of 2-deoxyglycosyl donors in the stereocontrolled synthesis of 2-deoxyglycosides.[7,8] In this strategy, the sulfur-containing group controls the glycosylation stereochemistry by acting as a neighboring participation group, and is then removed by reductive desulfurization after the glycoside formation, stereoselectively furnishing the corresponding 2-deoxyglycosides. In these synthetic studies, 2-thioaldoses are usually prepared by an S_N2 displacement reaction involving a sulfur-containing nucleophile at C-2[9] or by *anti*-addition of an electrophilic sulfur species to the double bonds of glycals in the presence of alcohols.[10] It is anticipated that an alternative approach, via carbon elongation reactions, would be useful for obtaining a variety of 2-thioaldose derivatives, but to the best of our knowledge, such an approach to the synthesis of 2-thioaldoses has not been reported to date. We previously reported a novel method for the two-carbon elongation of aldose derivatives based on [2+3]-type cycloaddition reactions of 1-alkenyl ethers with 2,3-*O*-isopropylidene derivatives of *aldehydo*-aldoses.[11] This synthetic strategy enabled stereocontrolled installation of two stereogenic centers at C-2 and C-3 in a single step, and the synthesis of several 2-subsituted or 2,2-disubstituted 2-deoxy-D-*gluco*-hexose derivatives was achieved in a highly stereoselective manner. As part of a study to examine the use of these cycloaddition products as synthetic intermediates, we now report the synthesis of 2-thioaldoses using the strategy outlined in Scheme 1. We envisioned that a range of 2-(aryl- or alkylthio)aldofuranoses could be readily accessed via the cycloaddition of β-methoxyvinyl sulfides with 2,3-*O*-isopropylidene-*aldehydo*-aldose derivatives.

β-Methoxyvinyl sulfides **3a**–**c** were prepared as the *trans* form by a two-step reaction of bromoacetaldehyde dimethyl acetal with benzenethiol, 2-naphthalenethiol, and benzyl mercaptan, according to the literature method[12] with minor modifications (Scheme 2).



Scheme 1 Scheme for synthesis of 2-thioaldose using BF_3-promoted cycloaddition reaction



Scheme 2 Preparation of β-methoxyvinyl sulfides **3a**–**c**

With β-methoxyvinyl sulfides **3a**–**c** in hand, the cyclization reaction was then investigated using 2,3;4,5-di-*O*-isopropylidene-*aldehydo*-D-arabinose (**4**). The reaction was carried out using 1.5 equivalents of **3a**–**c** in the presence of 1.2 equivalents of $BF_3{\cdot}OEt_2$ at –78 °C in CH_2Cl_2, affording the desired furanoside derivatives **5a**–**c**[13,14] with high diastereoselectivities (>95%). The vinyl sulfides employed in this study underwent cycloaddition to give ad-

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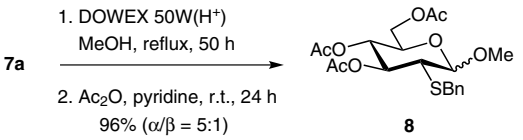
ducts in good yields and diastereoselectivities, regardless of the steric and electronic properties of the substituents on the sulfur (Table 1, entries 1–3). The newly formed stereogenic centers, C-1, C-2, and C-3, were proved to have 1,2-*cis*–2,3-*trans*–3,4-*cis* relationships, using NMR spectroscopy (vide infra).

Encouraged by the above results, we next embarked on the synthesis of 2-thioglucose. Starting from 2,3-*O*-isopropylidene derivatives of *aldehydo*-D-erythrose, the addition of β-methoxyvinyl sulfides **3** to the carbonyl group, followed by cyclization, proceeded in a similar stereochemical fashion, affording 2-thio-D-glucofuranoside derivatives stereoselectively. We investigated the reactions of aldehydes **6a** and **6b**, derived from D-erythrose, with vinyl sulfide **3c** under the same reaction conditions. As a result, the desired cycloadducts **7a** and **7b**[15] were again respectively obtained as the sole diastereomers, although the yield of **7a** was somewhat lower, probably due to instability of the silyl-protecting group under the reaction conditions (Table 2).

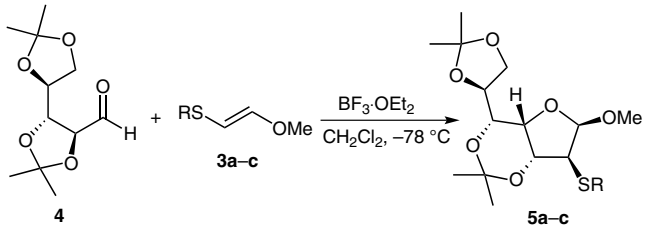
The furanoside **7a** was converted into the corresponding methyl pyranoside **8**[16] in good yield as an inseparable 5:1 (α/β) mixture (Scheme 3) by treatment with an ion-exchange resin (DOWEX-50W, H^+-form) in absolute methanol under reflux, followed by treatment with acetic anhydride in pyridine. The anomeric configuration of the major isomer was confirmed as α-*gluco* by the ^{1}H NMR *J* values of the C-2 axial proton (3.2 Hz and 11.5 Hz).



Scheme 3 Transformation to methyl 2-thio-D-glucopyranoside **8**

Detailed structural and conformational elucidations of the cycloadducts were achieved by NMR spectroscopic analysis. As a result of the fixed bicyclic structure of the furanoside, the coupling constants and NOE effects are very distinctive. Furanosides **5** and **7** both show relatively large coupling constants of $J_{1,2}$ = 5.0–5.5 Hz, indicating *cis* vicinal protons. In addition, furanoside **5** has a typical *trans* vicinal coupling constant, $J_{2,3}$ = 0.0 Hz, indicating that the dihedral angle between 2-H and the axial 3-H is near 90°, whereas furanoside **7** has $J_{2,3}$ = 4.6 Hz, probably as a result of a larger dihedral angle between 2-H and the equatorial 3-H than that in **5**. Moreover, the results of detailed NOE

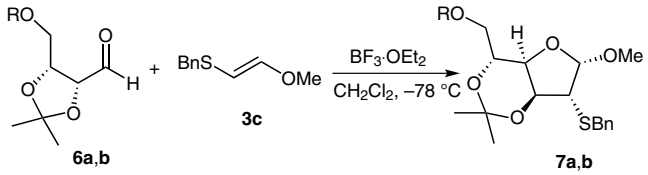
Table 1 Cycloaddition of β-Methoxyvinyl Sulfides **3a**–**c** with Aldehyde **4**

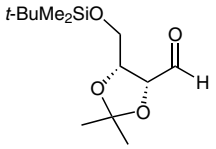
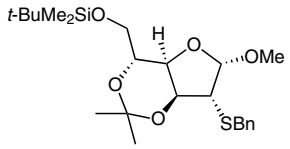
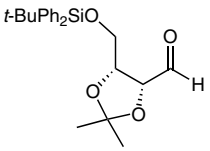
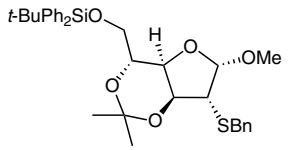


Entry	Sulfide	Reaction time (h)	Product	Yield (%)[a]
1	**3a**	2	**5a**	98
2	**3b**	3	**5b**	84
3	**3c**	2	**5c**	84

[a] Isolated yield.

Table 2 Cycloaddition of β-Methoxyvinyl Sulfide **3c** with Aldehydes **6a** and **6b**



Entry	Aldehyde	Reaction time (h)	Product	Yield (%)[a]
1	**6a** 	2	**7a** 	62
2	**6b** 	2	**7b** 	82

[a] Isolated yield.

studies are in good accordance with this conformational analysis, based on a fixed bicyclic structure, as illustrated in Figure 1.

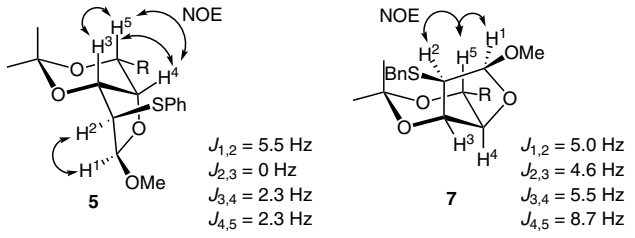


Figure 1 Structural comparison of cycloadducts **5** and **7**

The exclusive formation of a single diastereomer in all the reactions can be explained by the open transition-state model **A**, as depicted in Scheme 1, which serves to minimize steric interactions between the nucleophile R′S and the aldehyde substituents and allows an antiperiplanar arrangement of the C=O and C=C. Subsequent ring closure of the resulting addition intermediate **B** is postulated to occur through the attack of the oxygen at C4 on the oxocarbenium ion with the sterically favorable arrangement of the methoxy substituent, forming the cyclization product.

In conclusion, we have successfully developed a facile method for the synthesis of 2-thioaldose derivatives using a BF_3-promoted cyclization reaction between β-methoxyvinyl sulfides and 2,3-isopropylidene derivatives of *aldehydo*-aldoses. The reaction proceeded in a highly stereoselective manner to afford the corresponding methyl furanoside derivatives with 1,2-*cis*–2,3-*trans*–3,4-*cis* relationships. The applicability of this approach was demonstrated by the preparation of methyl 2-thioglucopyranoside, in which the newly formed stereogenic centers at C-2 and C-3 were installed in a completely stereocontrolled manner.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(13) **General Procedure for the Cyclization**: To a solution of aldehyde (1.0 mmol) and β-methoxyvinyl sulfide (1.5 mmol) in anhyd CH_2Cl_2 (10 mL) under argon atmosphere was added $BF_3{\cdot}OEt_2$ (1.2 mmol) dropwise at –78 °C. After being stirred for 2–3 h at –78 °C, the reaction mixture was quenched with Et_3N (0.5 mL). The resulting mixture was poured into sat. aq $NaHCO_3$. After the phase separation, the aqueous layer was extracted twice with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane–EtOAc, 19:1 → 9:1) to afford the corresponding cycloadduct.

(14) **Methyl 3,5;6,7-Di-*O*-isopropylidene-2-deoxy-2-phenylthio-β-D-*glycero*-D-*ido*-heptofuranoside (5a)**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.34 (s, 3 H), 1.37 (s, 3 H), 1.39 (s, 3 H), 1.42 (s, 3 H), 3,49 (s, 3 H), 3.88 (dd, *J* = 2.3, 7.8 Hz, 1 H), 3.94 (d, *J* = 5.5 Hz, 1 H), 3.97 (d, *J* = 5.0 Hz, 1 H), 4.07 (dd, *J* = 6.0, 8.7 Hz, 1 H), 4.22 (t, *J* = 2.3 Hz, 1 H), 4.27 (d, *J* = 2.3 Hz, 1 H), 4.31–4.36 (m, 1 H), 5.43 (d, *J* = 5.5 Hz, 1 H), 7.16–7.36 (m, 5 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.5, 25.3, 26.9, 29.2, 55.4, 56.3, 66.7, 69.5, 69.7, 74.6, 77.1, 98.4, 103.5, 109.1, 125.9, 128.5, 129.0, 136.1.

Methyl 3,5;6,7-Di-*O*-isopropylidene-2-deoxy-2-(2-naphthylthio)-β-D-*glycero*-D-*ido*-heptofuranoside (5b): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.33 (s, 3 H), 1.37 (s, 3 H), 1.42 (2 × s, 6 H), 3.51 (s, 3 H), 3.89 (d, *J* = 7.3 Hz, 1 H), 3.96 (dd, *J* = 5.0, 8.7 Hz, 1 H), 4.07–4.10 (m, 2 H), 4.24 (s, 1 H), 4.33–4.37 (m, 2 H), 5.47 (d, *J* = 5.5 Hz, 1 H), 7.41–7.49 (m, 3 H), 7.71–7.84 (m, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.6, 25.3, 26.9, 29.3, 55.4, 56.3, 66.7, 69.6, 69.7, 74.6, 77.1, 98.4, 103.5, 109.1, 125.6, 125.9, 126.6, 126.7, 127.0, 127.7, 128.4, 131.5, 133.8, 133.9.

Methyl 3,5;6,7-Di-*O*-isopropylidene-2-deoxy-2-benzylthio-β-D-*glycero*-D-*ido*-heptofuranoside (5c): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.32 (s, 3 H), 1.34 (s, 3 H), 1.35 (s, 3 H), 1.40 (s, 3 H), 3.35 (d, *J* = 5.5 Hz, 1 H), 3.41 (s, 3 H), 3.76 (d, *J* = 13.0 Hz, 1 H), 3.78 (d, *J* = 13.0 Hz, 1 H), 3.85(dd, *J* = 2.3, 7.3 Hz, 1 H), 3.93 (dd, *J* = 5.0, 8.7 Hz, 1 H), 4.03–4.05 (m, 1 H), 4.06 (t, *J* = 2.3 Hz, 1 H), 4.11 (d, *J* = 2.3 Hz, 1 H), 4.28 (dd, *J* = 5.0, 6.0, 7.3 Hz, 1 H), 5.21 (d, *J* = 5.5 Hz, 1 H), 7.22–7.33 (m, 5 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.6, 25.3, 26.9, 29.2, 37.1, 54.5, 56.1, 66.7, 69.4, 69.6, 74.6, 77.2, 98.1, 103.7, 109.0, 127.1, 128.5, 129.1, 137.9.

(15) **Methyl 6-*O*-*tert*-Butyldimethylsilyl-3,5-*O*-isopropylidene-2-deoxy-2-benzylthio-α-D-glucofuranoside (7a)**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.08 (s, 6 H), 0.91 (s, 9 H), 1.35 (s, 3 H), 1.38 (s, 3 H), 3.20 (t, *J* = 4.6 Hz, 1 H), 3.31 (s, 3 H), 3.61 (ddd, *J* = 2.8, 6.0, 9.2 Hz, 1 H), 3.73 (dd, *J* = 6.0, 11.0 Hz, 1 H), 3.80–3.85 (m, 3 H), 4.09 (dd, *J* = 5.5, 8.7 Hz, 1 H), 4.36 (dd, *J* = 5.0, 5.5 Hz, 1 H), 4.80 (d, *J* = 5.0 Hz, 1 H), 7.23–7.38 (m, 5 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.3, –5.2, 18.4, 24.0, 25.2, 25.8, 36.1, 52.4, 55.2, 63.6, 71.6, 75.5, 78.8, 100.5, 103.5, 127.0, 128.4, 129.1, 138.3.

Methyl 6-*O*-*tert*-Butyldiphenylsilyl-3,5-*O*-isopropylidene-2-deoxy-2-benzylthio-α-D-glucofuranoside (7b): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.04 (s, 9 H), 1.35 (s, 3 H), 1.38 (s, 3 H), 3.19 (t, *J* = 4.6, 1 H), 3.27 (s, 3 H), 3.69 (ddd, *J* = 2.8, 6.0, 9.2 Hz, 1 H), 3.76–3.84 (m, 3 H), 3.86 (dd, *J* = 2.8, 11.0 Hz, 1 H), 4.13 (dd, *J* = 5.5, 8.7 Hz, 1 H), 4.35 (dd, *J* = 5.0, 5.5 Hz, 1 H), 4.77 (d, *J* = 5.0 Hz, 1 H), 7.22–7.42 (m, 11 H), 7.69–7.71 (m, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.3, 24.1, 25.2, 26.7, 36.1, 52.4, 55.2, 64.4, 71.6, 75.6, 78.8, 100.4, 103.5, 127.0, 127.5, 127.5, 128.4, 129.1, 129.5, 133.6, 133.7, 135.6, 135.7, 138.3.

(16) **Methyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-benzylthio-α,β-D-glucopyranoside (8)**: ^{1}H NMR (500 MHz, $CDCl_3$; assigned to the α-anomer): δ = 2.03 (s, 3 H), 2.07 (s, 3 H), 2.08 (s, 3 H), 2.80 (dd, *J* = 3.2, 11.5 Hz, 1 H), 3.35 (s, 3 H), 3.75 (d, *J* = 13.3 Hz, 1 H), 3.81 (dd, *J* = 13.3 Hz, 1 H), 3.98 (ddd, *J* = 2.3, 4.6, 10.1 Hz, 1 H), 4.04 (dd, *J* = 2.3, 12.4 Hz, 1 H), 4.28 (dd, *J* = 4.6, 12.4 Hz, 1 H), 4.64 (d, *J* = 3.2 Hz, 1 H), 4.96 (dd, *J* = 9.2, 10.1 Hz, 1 H), 5.44 (dd, *J* = 9.2, 11.5 Hz, 1 H), 7.23–7.33 (m, 5 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.6, 20.6, 20.7, 20.8, 36.3, 36.8, 48.3, 49.1, 55.5, 57.5, 62.1, 62.1, 67.4, 69.4, 69.7, 71.4, 71.5, 72.3, 100.7, 106.0, 127.1, 127.3, 128.4, 128.6, 128.9, 129.1, 137.8, 169.8, 170.0, 170.6.

