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Thio-sugars. Part 5: From D-glucal to 3-deoxy-(1→2)-2-*S*-thiodisaccharides through isolevoglucosenone — a simple approach

Zbigniew J. Witczak,* Hong Chen and Peter Kaplon

Department of Pharmaceutical Sciences, School of Pharmacy, University of Connecticut, 372 Fairfield Rd. U-92, Storrs, CT 06269-2092, USA

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Abstract

A new synthesis of isolevoglucosenone and its stereoselective functionalization into 3-deoxy-(1-2)-2-*S*-thiodisaccharides is described. The base-catalyzed conjugate addition of 1-thiosugars to isolevoglucosenone followed by the reduction of the C-4 keto function constitute a new two-step general approach to these classes of biologically important thio-sugars.

1. Introduction

In our efforts towards preparing thiodisaccharides,[1,2] we employed enones **1** and **2**. Both enones, levoglucosenone[1–4] (1,6-anhydro-3,4-dideoxy-β-D-*glycero*-hex-3-enopyranos-2-ulose, **1**) and isomeric isolevoglucosenone[5–13] (1,6-anhydro-2,3-dideoxy-β-D-*glycero*-hex-2-enopyranos-4-ulose, **2**), are, synthetically, extremely attractive versatile chiral building blocks because of their high functionality and conformational bicyclic rigidity, as depicted in Fig. 1.

The 1,6-anhydro bridge in both enones **1** and **2** eliminates the need for protecting groups at the anomeric carbon and the C-6-OH. Moreover, the bridge fixes the conformation of the system and sterically hinders the β-D-face of both molecules. Therefore, both enones have already been used in the synthesis of various natural products and their intermediates.[10,11] However, isolevoglucosenone **2** is considerably less accessible than levoglucosenone **1** and relatively unstable,[13] decomposing over several months while in storage at −25°C. Levoglucosenone **1** was also used for the synthesis of isolevoglucosenone **2** in ca. ~25% overall yield.[13]

As our need for larger quantities of enones **1** and **2** increased, we have been constantly exploring methods that would make them more readily available for exploratory studies and multistep syntheses.

* Corresponding author. Fax: (860)-742-2400; e-mail: zwitczak@usa.net

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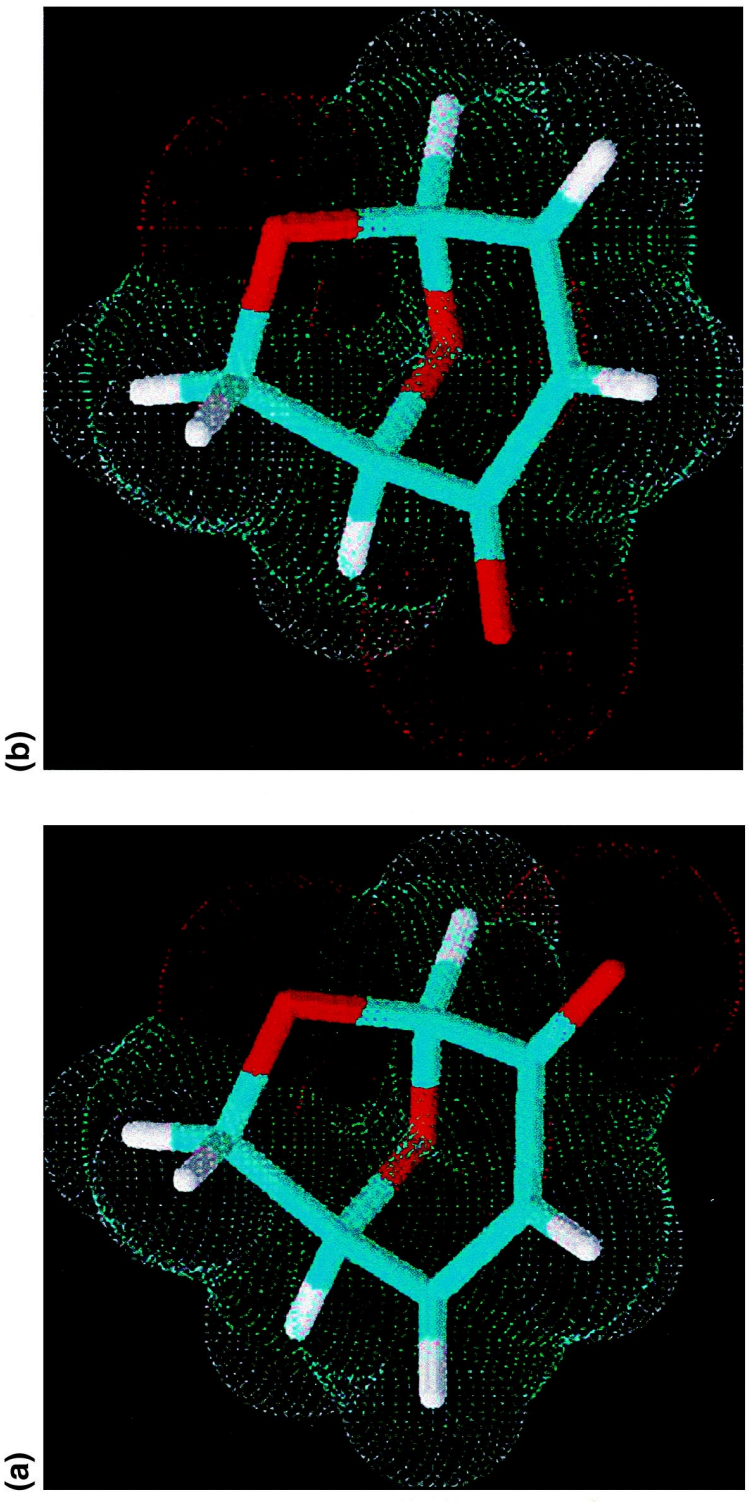


Fig. 1. (a) 1,6-Anhydro-3,4-dideoxy-β-D-*glycero*-hex-3-enopyranos-2-ulose (levoglucosenone); (b) 1,6-anhydro-2,3-dideoxy-β-D-*glycero*-hex-3-enopyranos-4-ulose (isolevoglucosenone)

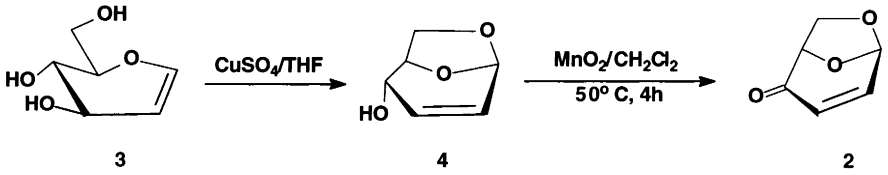
Thus, a convenient and efficient synthetic approach to isolevoglucosenone **2** is extremely important and in demand.

The pioneering work of Achmatowicz et al.[5] on the versatility of furfuryl alcohol and its conversion to various enones, including a racemic mixture of isolevoglucosenone **2**, was the first report of the preparation of isolevoglucosenone and other racemic 2,3-dideoxy-DL-hex-2-enopyranos-4-uloses.[6–9]

Recently, Ogasawara et al.[10,11] developed a new approach to both enones **1** and **2** and their enantiomers, exploring the utility of the non-carbohydrate precursor 2-vinylfuran. Köll and co-workers[12] synthesized isolevoglucosenone from levoglucosenone and from 1,6-anhydro-2,3-isopropylidene-β-D-mannopyranose. Furneaux and co-workers[13] reported the synthesis of isolevoglucosenone **2** directly from levoglucosenone **1** in a five-step sequence. Through the rearrangement of 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enofuranose, Horton and co-workers[14,15] reported a completely different and good yielding approach to isolevoglucosenone. Although overall yields in all of these methods were acceptable, synthesis usually required a large number of steps and the use of air-sensitive reagents such as sodium hydride and aluminum chloride ($AlCl_3$) on a rather large scale.

2. Results and discussion

Studying the formation of the 1,6-anhydro ring, Oberdorfer and co-workers[16,17] recently reported a novel rearrangement of unprotected D-glucal **3** to allyl alcohol **4** under anhydrous conditions and in the presence of anhydrous copper sulfate and molecular sieves. The fact that allyl alcohol **4** could be produced in good yield directly from D-glucal, and could serve as an excellent precursor to target isolevoglucosenone through simple oxidation of the -OH function at C-4, prompted us to explore this potential approach further to produce isolevoglucosenone from glucose in only three steps (Scheme 1). The required 2,3,4-tri-*O*-acetylglucal was produced according to the recently published, one-pot methodology of Koreeda et al.[18] in 93% yield. The deprotection of 1,4,5-tri-*O*-acetyl-D-glucal with an aqueous methanolic solution of triethylamine produced free D-glucal. The key step of Ferrier rearrangement of the unprotected D-glucal was performed according to the published procedure of Oberdorfer[16] in 48% yield. The final oxidation of alkene **6** was performed under various conditions as reported in the Experimental section. The method of choice was, however, oxidation with manganese dioxide with a high 82% yield.



3 4 2

Scheme 1.

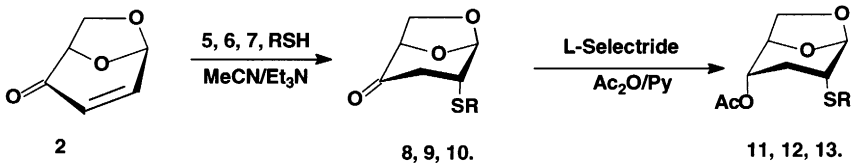
The NMR data clearly confirm the identity of the target isolevoglucosenone. Our reported procedure has significant practical advantages over existing methods and is capable of producing pure (−)-isolevoglucosenone **2** directly from glucose in multigram quantities cheaply, in only three steps, and in 48% overall yield. Its direct synthesis from glucose was also achieved without separation or purification of the intermediates: the oxidation was performed with manganese dioxide and **2** was obtained in ~82% yield (nonoptimized). The HPLC analysis clearly indicates its purity as a homogeneous product.

As noted at the beginning, our recent results[1,2] on Michael addition of sugar thiols to levoglucosenone show complete stereoselective additions due to its rigid bicyclic framework and steric shielding of the

upper face of the pyranose ring by the 1,6-anhydro ring. Because this particular stereoselectivity is highly predictable, it was also observed in the Michael addition of organometallics[19] and other carbon nucleophiles[20,21] to levoglucosenone. This important observation prompted us to expand this study to the exploration of the synthetic utility of isomeric isolevoglucosenone by expecting a similar type of stereoselectively in introducing a sulfur bridge, between two sugar units at C-(1-2) by Michael addition of 1-thio-sugars in the formation of thiodisaccharides.

Thiodisaccharides[22] containing sulfur in the glycosidic linkage have been synthesized previously by a variety of methods,[23–32] including S_N2-type reactions involving the action of a thiolate anion and a glycosyl halide, and the displacement of a leaving group by 1-thio-glucopyranose.

The Michael addition of thiols **5**,[33] **6**,[34,35] and **7**[36] to the enone **2** proceeded smoothly with the formation of β-(1→2)-3-dideoxy-2-thiodisaccharides **8**, **9**, and **10** in 63–70% yield. The proton–proton coupling in the ^{1}H NMR spectra of the conjugate addition products **8**–**10** confirmed that only the 2-*axial* adducts were always obtained as a single addition product (Scheme 2). This stereoselectivity as observed previously in levoglucosenone conjugate addition[19–21] proceeds by the attack of incoming nucleophile at the alkene face opposite the 1,6-anhydro ring.



2 **8, 9, 10.** **11, 12, 13.**

5, 8, 11. R = 2,3,4,6-tetra-O-acetyl-D-glucopyranosyl-
6, 9, 12. R = 2,3,4,6-tetra-O-acetyl-D-galactopyranosyl-
7, 10, 13. R = 2,3,4-tri-O-acetyl-L-fucopyranosyl-

Scheme 2.

The sterically hindered 1,6-anhydro bridge in isolevoglucosenone is, therefore, assumed to effectively prevent an attack from the upper side of the molecule which could give an access to the alternative formation of the 2-*equatorial* addition product.

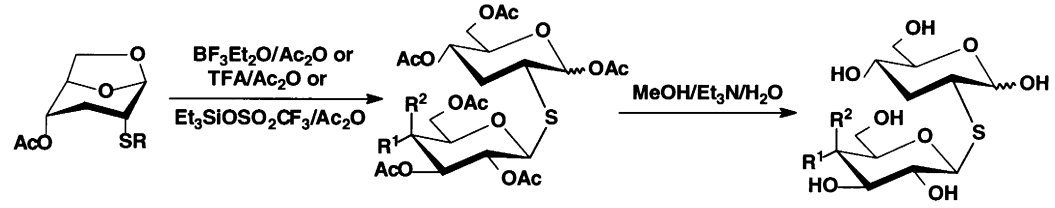
Indeed, the proton–proton coupling in the ^{1}H NMR spectrum of the conjugate addition products **8**, **9**, and **10** confirmed the D-*erythro* stereochemistry with coupling constants $J_{1,2}$=0.5 Hz. This coupling indicates that the substituent at C-2 is *axial* with a quasiequatorial relationship between H-1 and H-3, as seen in compounds **8**, **9**, and **10**. The ^{1}H NMR spectra of the adducts did not show signals corresponding to the potential D-*threo*-isomer, clearly demonstrating that the stereochemistry of the addition of thiols **5**, **6**, and **7** to enone **2** is completely controlled by the steric bulk of the 1,6-anhydro bridge. The ^{13}C NMR spectra of all adducts **8**, **9**, and **10** showed no alkene signals, and the C-3 signal appeared upfield at ca. 37.0–38.4 ppm, respectively.

Ketones **8**, **9**, and **10** offer potential in the synthesis of precursors of certain amino sugars as reported by us earlier[1,2] through conventional oximation and highly stereoselective reduction of the acetamido function. Accessible in a single-step process from isolevoglucosenone and formed in a completely stereospecific manner, **8**, **9**, and **10** are potentially useful for syntheses of 4-amino sugars having three stereogenic centers in the D-*ribo* configuration.

The reduction of the C-4 keto function of ketones **8**, **9**, and **10** with L-Selectride®, followed by in situ conventional acetylation, proceeded stereoselectively with the formation of the D-*ribo*-isomers **11**, **12**, and **13** in 79% yield. Only trace amounts of the corresponding D-*xylo*-isomers **11a**, **12a**, and **13a** were detected by ^{1}H NMR spectroscopy. Additionally, lack of coupling between H-4 and H-5 and coupling constants of reduction products **11**, **12**, and **13**, $J_{3a,4}$=7.2–7.6 Hz and $J_{3e,4}$=4.82 Hz, indicate the axial

disposition of the new substituent at C-4. Unlike levoglucosenone **1**, where the ketone reduction was predictably controlled[37] by the 1,6-anhydro bridge, the analogous reduction of **8**, **9**, and **10** was expected to be dominated by the relative steric contribution of the bulky axial substituent at C-2, as well as the 1,6-anhydro bridge. This is in full agreement with earlier observations by Horton and co-workers[14,15] of high stereoselectivity and yet another classical example of the preferential attack of the reducing agent from the top face on this bicyclic molecule.

Moreover, the ^{1}H and ^{13}C NMR spectra of **11**, **12**, and **13** firmly support their assignments as the D-*ribo*-configuration. Particularly, the coupling constants between equatorially disposed H-2 and the axially disposed H-3, $J_{2,3}$=4.7 Hz, are of great diagnostic value. On the other hand, the more polar equatorial alcohols **11a**, **12a**, and **13a** with the β-*xylo*-configuration (isolated in only ~3% yield) displayed a coupling of $J_{3a,4}$=10.4 Hz, as anticipated for the diaxial disposition of H-3a and H-4 (Scheme 3).



Scheme 3.

The cleavage of the 1,6-anhydro ring in **11**, **12**, and **13** was examined under various reaction conditions. Acetolysis using trifluoroacetic acid and acetic anhydride afforded an anomeric mixture of heptaacetates **14** and **15** in good yield (62%). Acetolysis, under similar conditions, such as acetic anhydride and a catalytic amount of boron trifluoride etherate ($BF_3 \cdot Et_2O$), also gave a good yield (58%). However, chromatographic purification of the crude material was required. Compound **13** undergoes almost total decomposition under the above reaction conditions. The development of alternative deprotection approaches, particularly for acid sensitive fucose derivatives, is underway.

The method of choice was acetolysis using an acetic anhydride solution and a catalytic amount of trifluoromethanesulfonate, performed according to the convenient protocol of Fraser-Reid et al.[38] This resulted in the formation of an anomeric mixture of heptaacetates **14** and **15** (α:β, 1:5) in 91% yield. The presence of the deoxy group at C-3 clearly indicates the strong influence of the 1,6-anhydro ring on the cleavage, and requires a prolonged reaction, up to the 12 h, as compared with the literature data reported.[38] Separation of the anomers proved impossible because of their almost identical R_f values. However, the ^{1}H NMR and ^{13}C NMR spectra and mass spectral data for the mixture firmly established their identity.

Final deprotection of heptaacetates **14** and **15** was performed with an aqueous methanolic solution of triethylamine (4:1:5 MeOH:Et_3N:H_2O) at room temperature for 6 h which produced new thiodisaccharides, 2-*S*-(β-D-glucopyranosyl)-2-thio-D-3-deoxyglucopyranose **16** and 2-*S*-(β-D-galactopyranosyl)-2-thio-D-3-deoxyglucopyranose **17**, in 89% yield.

Molecular model of selected 2-*S*-(β-D-galactopyranosyl)-2-thio-D-3-deoxyglucopyranose **17** (Fig. 2) clearly confirms the stereogeometry as determined by NMR spectroscopy and the length of the sulfur bridge between C-1–S is 1.8121 Å, whereas at C-2–S it is 1.8104 Å and the dihedral angle for C–S–C bridge is 109.8°. All the measurements are similar to the calculation for the sulfur bridge of

other thiodisaccharides and are substantially different than that of the oxygen counterpart as previously postulated in the literature.[39,40]

3. Conclusion

The conjugate addition of protected 1-thiosugars to isolevoglucosenone, followed by the tandem reaction of C-4 keto group reduction and deprotection, is a new short stereoselective approach to (1→2)-2-*S*-thiodisaccharides. All functionalized new thiodisaccharides are stable glycomimetic compounds of potential biological interest.

4. Experimental

4.1. General methods

Unless otherwise noted, starting materials were obtained from commercial suppliers and used without purification. All melting points were uncorrected and were measured in open capillary tubes. Optical rotations were determined on a Jasco Model DIP-370 polarimeter in $CHCl_3$ solutions. Thin-layer chromatography (TLC) was performed on precoated silica gel $60F_{254}$ plates from E. Merck and visualized by spraying with 10% ethanolic sulfuric acid and subsequent heating. Column chromatography was performed on silica gel 60 (70–230 mesh, Merck No. 34).

^{1}H NMR spectra: NMR samples were prepared in $CDCl_3$ (99.8 atom% D), filtered, freeze-thawed, and sealed in a 5 mm NMR tube. Tetramethylsilane (TMS) was used as an internal chemical shift reference. High-resolution NMR spectra were obtained on a Bruker DMX-500 spectrometer. Mass spectra were obtained either in EI mode at 70 eV or using CI (NH_3).

*4.2. 1,6-Anhydro-2,3-dideoxy-β-*D-erythro-*hex-2-enopyranose **4***

Compound **4** was produced by Oberdorfer and co-workers'[16,17] methodology. R_f=0.59 (EtOAc), mp 60–61.5°C, lit. 58–59°C,[12] $[\alpha]_D$ +318 (*c* 1.0, $CHCl_3$), $[\alpha]_D$ +318 (*c* 1.0, $CHCl_3$): for NMR data see the lit.[8 16,17] For ^{13}C NMR see the lit.[16]

*4.3. 1,6-Anhydro-2,3-dideoxy-β-*D-glycero-*hex-2-enopyranos-4-ulose **2** (isolevoglucosenone)*

(a) The crude allylic alcohol **4** (2.56 g, 20 mmol) was dissolved in dichloromethane (30 mL). Pyridinium dichromate (PDC) (9.63 g, 25.6 mmol) was added to the mixture while stirring at room temperature for 40 h. Filtration through a column of silica/sand/Celite and concentration afforded a brown syrup (1.5 g, 59.5%) which was flash chromatographed using 5:1 *n*-pentane:Et_2O to produce the enone **2** as a pale yellow oil (1.26 g, 50%).

(b) The crude allylic alcohol **4** (2.56 g, 20 mmol) was dissolved in chloroform (30 mL) and manganese dioxide (MnO_2) (29 g, 334 mmol) was added while stirring at room temperature for 6 h. After filtration, the mixture was evaporated to a syrup and flash chromatographed with 5:1 *n*-pentane:Et_2O to give enone **2** (2.06 g, 82%) as a pale yellow oil.

(c) One-pot preparation of **2**:[14,15] to a magnetically stirred suspension of D-glucose monohydrate (10.0 g, 53.7 mmol) in acetic anhydride (36.1 g, 7.0 mmol) 1.0 g of 31% HBr/AcOH was added in portions

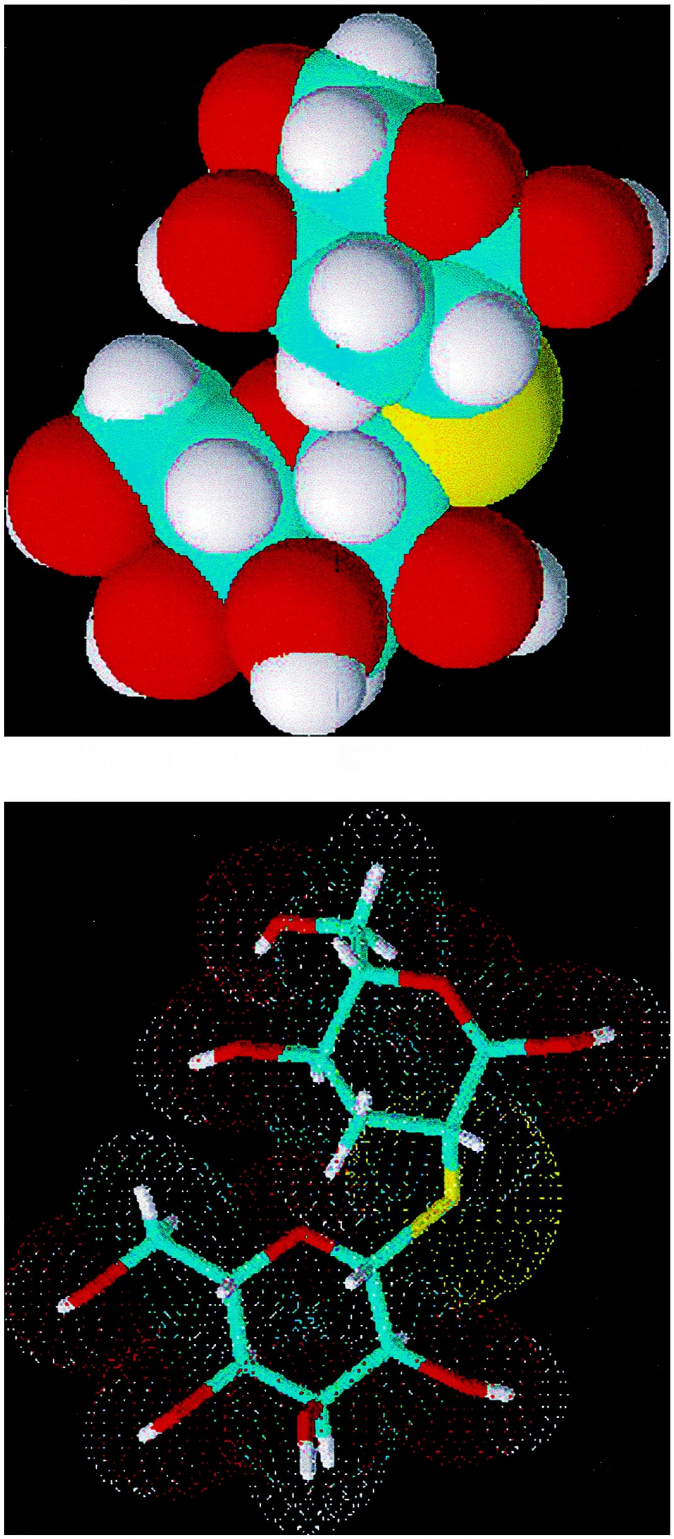


Fig. 2. 2-*S*-β-Glucopyranosyl-2-thio-D-3-deoxyglucopyranose

while maintaining the mixture at room temperature. After 1 h, the clear solution was treated with an additional amount (74 g) of 31% HBr/AcOH and the resulting solution was stirred overnight at room temperature. Anhydrous sodium acetate (30 g) was then added to neutralize the excess of HBr, and the resulting solution was immediately added in portions to an aqueous suspension of copper sulfate (2.6 g) and zinc (102 g), in 100 ml of water and acetic acid (150 mL) containing sodium acetate trihydrate (125 g). The mixture was vigorously stirred at room temperature for 2 h. The inorganic solid was filtered off and washed with ethyl acetate (700 mL) and water (1 L). The inorganic solid must be wet all the time to deactivate the zinc! The organic layer of the filtrate after separation was washed with a saturated aqueous solution of $NaHCO_3$ (1 L) and brine (500 mL), and dried with anhydrous sodium sulfate. The solvent was evaporated on a rotary evaporator to a syrup (14.5 g, 95.4%). Then the colorless syrup was dissolved in 150 mL of aqueous methanolic solution of triethylamine, 4:5:1 MeOH:H_2O:Et_3N, and stirred at room temperature until TLC indicated the completion of the reaction (5–8 h). The solution was evaporated to a syrup (7.39 g), dried overnight in a vacuum over P_2O_5, and dissolved in dry tetrahydrofuran (THF) (140 mL). Anhydrous copper sulfate (59.4 g, 372 mmol) and 4 Å molecular sieves (5.0 g) were added, and the mixture was refluxed while vigorously stirred for 6 h. After filtration of the inorganic material and washing with anhydrous THF (20 mL), the combined filtrate was evaporated to a syrup (3.23 g, 50% yield). The resulting syrup was dissolved in dry chloroform (175 mL) and manganese oxide (35 g, 402 mmol) was added in portions while stirring vigorously for 6 h. The progress of the oxidation was monitored by TLC. After filtering the inorganic material, the solution was evaporated on a rotary evaporator to form a brown syrup (2.7 g), which was flash chromatographed by elution with 5:1 *n*-pentane:Et_2O. The fraction of R_f=0.48 was collected and evaporated to a syrup. The chromatographic purification gave enone **2** (2.45 g, 82% yield) as a pale yellow oil. Enone **2** could be obtained as an analytically pure colorless syrup after a second chromatographic purification using 5:1 *n*-pentane:Et_2O ($[\alpha]_D$ +319.6 (*c* 1.0, $CHCl_3$); lit. $[\alpha]_D$ +321 (*c* 1.0, $CHCl_3$)).[11] The ^{1}H NMR and ^{13}C NMR spectra of **2** were identical with those published in the literature.[13–15]

*4.4. General method for the preparation of 3-deoxy-(1→2)-*S*-thiodisaccharides **8**–**10***

To a solution of isolevoglucosenone[13–15] **2** (126 mg, 0.1 mmol) in acetonitrile (10 mL) a solution of 1-thio-sugar **5**,[33] **6**,[34,35] or **7**[36] (125 mg, 0.34 mmol) in 5 mL of acetonitrile was added dropwise. The reaction mixture was stirred at room temperature for 24 h. After evaporation of the solvent, the syrupy residue was purified by column chromatography on silica gel. The fraction eluted with 20% ethyl acetate in hexane (v/v) gave pure syrupy products, which crystallized from ether–hexane.

*4.4.1. 1,6-Anhydro-3-deoxy-2-*S*-(2,3,4,6-tetra-*O*-acetyl-β-glucopyranosyl)-*D*-glycero-hexopyranos-4-ulose **8***

Yield (436 mg, 89%), mp 157–158.5°C; R_f=0.59 (1:4 hexane:EtOAc); $[\alpha]^{30}$ −124.21 (*c* 0.84, $CHCl_3$); HRMS $(M)^+$ *m/z*: calcd for $C_{20}H_{26}O_{12}S$: 490.47. Found: 490.11. The ^{1}H NMR and ^{13}C NMR spectra of **8** are listed in Tables 1 and 2, respectively.

*4.4.2. 1,6-Anhydro-3-deoxy-2-*S*-(2,3,4,6-tetra-*O*-acetyl-β-galactopyranosyl)-*D*-glycero-hexopyranos-4-ulose **9***

Yield (385 mg, 78.5%), mp 151–152.5°C; R_f=0.41 (1:4 hexane:EtOAc); $[\alpha]^{30}$ −122.2 (*c* 0.8, $CHCl_3$); HRMS $(M)^+$ *m/z*: calcd for $C_{20}H_{26}O_{12}S$: 490.47. Found: 490.11. The ^{1}H NMR and ^{13}C NMR spectra of **9** are listed in Tables 1 and 2, respectively.

Table 1
^{1}H NMR chemical shifts (δ) and coupling constants (**J** in hertz) for compounds **8–17**[a]

Compound	H-1' $J_{1,2}$	H-2' $J_{2,3}$	H-3' $J_{2,3'}$	H-4' $J_{3,4}$	H-5' $J_{5,6'}$	H-6' $J_{5,6''}$	H-6' $J_{6,6'}$	H-1 $J_{1,2}$	H-2 $J_{2,3}$	H-3a $J_{3a,4}$	H-3e J_{3a3e}	H-4 $J_{3e,4}$	H-5 $J_{5,6ex}$	H-6endo $J_{5,6endo}$	H-6exo $J_{6ex,6en}$	-$COCH_3$
8	4.56d 8.8	5.19dd 9.6	5.23t 9.9	5.04d 9.5	4.82d 5.0	3.66dd	4.2d	5.3d 0.5	3.66d 5.0	2.82dd 7.6	2.60d 16.6		4.9dd 4.9	3.93dd	4.14dd 8.2	2.02-1.98 4s, 4x OAc
9	4.56d 8.8	5.19dd 9.6	5.23t 9.9	5.04d 9.5	4.82d 5.0	3.66dd	4.26	5.3d 0.5	3.66d 5.0	2.12dd 7.6	2.60d 16.6		4.9dd 4.9	3.93dd 1.1	4.14dd 8.2	2.02-2.1, 4s, 4x OAc
10	4.56d 8.8	5.19dd 9.6	5.23t 9.9	5.04d 9.5	4.82d 5.0	1.16d 6.6		5.3d 0.5	3.66d 5.0	2.12dd 7.6	2.60d 16.6		4.9dd 4.9	3.93dd 1.1	4.04dd 8.2	2.02-1.98 3s, 3x OAc
11	4.56d 8.8	5.19dd 9.6	5.23t 9.9	5.04d 9.5	4.82d 5.0	3.66dd	4.2d	5.3d 7.2	3.66d 5.0	3.12dd 7.6	1.90d 16.0	3.56d 4.82	3.56dd 4.8	3.93dd 1.1	4.04dd 8.2	2.02-2.1 5s, 5x OAc
11a	4.66d 7.8	5.33dd 9.8	5.2t 10.2	5.04d 9.3	4.86d 5.0	3.66dd	4.26d	5.36s	3.76d 4.7	2.22dd 7.2	2.14d 16.4	4.52d 10.0	4.42dd 4.0	4.0dd 1.1	4.04dd 7.5	2.02-2.1, 5s, 5x OAc
12	4.56d 8.8	5.19dd 9.6	5.23t 9.9	5.04d 9.5	4.82d 5.0	3.26dd	4.26d	5.3d 7.2	3.66d 5.0	1.96dd 7.5	1.90d 16.0	3.56d 4.82	4.60dd 4.9	3.93dd 1.1	4.04dd 8.2	2.02-2.1, 5s, 5x OAc
12a	4.66d 7.8	5.33dd 9.8	5.2t 10.2	5.04d 9.3	4.86d 5.0	3.66dd 2.3	4.26d	5.36s	3.76d 4.7	2.22dd 7.2	2.14d 16.4	4.52d 10.4	4.42dd 4.0	3.99dd 1.1	4.04dd 7.5	2.02-2.1 5s, 5xOAc
13	4.56d 8.8	5.19dd 9.6	5.23t 9.9	5.04d 9.5	4.82d 5.0	1.16d 6.6		5.3d 7.2	3.66d 5.0	2.12dd 7.6	2.60d 16.6	3.56d 4.8	4.60dd 4.9	3.93dd 1.1	4.04dd 8.2	2.02-2.1 4s, 4x OAc
13a	4.66d 7.8	5.33dd 9.8	5.2t 10.2	5.04d 9.3	4.86d 5.0	1.16d 6.6		5.36s	3.76d 4.7	1.96dd 7.2	1.94d 14.4	3.52d 10.4	4.32dd 4.0	3.99dd 1.1	4.04dd 7.5	2.01-2.1 4s, 4x OAc
14	4.56d 8.8	5.19dd 9.6	5.23t 9.9	5.04d 9.5	4.82d 5.0	3.66dd	4.26d	5.3d 7.2	3.66d 5.0	2.12dd 7.6	1.90d 16.0	3.50d 8.0	4.90dd 2.9	3.93dd 1.1	4.04dd 8.2	2.01-2.1 7s, 7x OAc
15	4.56d 8.8	5.19dd 9.6	5.23t 9.9	5.04d 9.5	4.82d 5.0	3.66dd	4.26d	5.3d 7.2	3.66d 5.0	2.12dd 7.6	1.90d 16.0	3.56d 8.0	4.90dd 2.9	3.93dd 1.1	4.04dd 8.2	2.01-2.1 7s, 7x OAc
16 [b]	4.62d 7.6	5.21dd 9.8	5.26t 10.0	5.08d 9.7	4.84d 5.2	3.75dd 3.8	4.28d	5.3d 7.5	3.58d 5.2	2.19dd 7.4	2.32d 16.0	3.59d 8.1	4.54dd 4.8	3.96dd 1.2	4.06dd 8.4	
17 [b]	4.62d 8.6	5.21dd 9.8	5.26t 10.0	5.08d 9.7	4.84d 5.2	3.7dd 7.8	3.6d 8.0	5.3d 7.5	3.58d 5.2	2.19dd 7.4	2.62d 16.0	3.59d 8.1	3.84dd 4.8	3.76dd 3.8	3.66dd 7.8	

[a] Determined at 500 MHz in $CDCl_3$ with Me_4Si as internal reference.
[b] Determined at 500 MHz in D_2O with TMSPA-Na as internal reference.

Table 2
^{13}C NMR chemical shift (ppm) data for compounds **8–17**[a]

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'	-OCO	-Ac
8	99.4	59.2	37.0	211.1	81.0	63.1	102.6	65.2	39.5	70.2	76.9	63.9	4x 171.0	17.6, 17.6, 17.5, 17.4
9	99.6	59.7	37.1	211.1	81.1	62.1	102.6	67.1	38.4	70.6	76.2	65.7	4x 171.1	17.6, 17.5, 17.5, 17.4
10	99.8	59.7	38.4	211.9	81.1	63.1	99.1	67.1	38.4	70.6	76.2	16.8	3x 171.1	17.6, 17.5, 17.4
11	99.6	59.7	37.1	65.7	81.1	63.1	102.6	67.1	38.4	70.6	76.2	65.7	5x 171.1	17.6, 17.5, 17.5, 17.4
12	99.8	59.7	37.1	65.9	81.0	63.1	101.9	65.7	35.7	69.9	75.0	65.8	5x 176.0	5x 17.6
13	99.8	59.7	37.1	64.9	81.0	63.1	99.9	65.7	35.7	69.9	72.0	16.8	4x 176.0	4x 17.6
14	92.8	59.7	37.1	65.9	75.0	63.1	99.9	70.7	35.7	69.9	72.0	61.8	7x 176.0	7x 17.6
15	91.8	75.7	37.6	65.9	75.0	63.1	101.9	67.7	35.7	69.9	75.0	61.0	7x 176.0	7x 17.6
16[b]	91.8	70.4	35.6	66.4	77.7	63.8	102.1	70.0	72.2	69.8	72.4	62.0		
17[b]	91.6	75.4	35.6	66.4	77.7	63.8	102.1	67.0	70.1	66.8	71.4	61.0		

[a] Determined at 125 MHz in $CDCl_3$ with Me_4Si as the internal reference.
[b] Determined at 125 MHz in D_2O with TMSPA-Na as the internal reference.

*4.4.3. 1,6-Anhydro-3-deoxy-2-*S*-(2,3,4-tri-*O*-acetyl-*L*-fucopyranosyl)-*D*-glycero-hexopyranos-4-ulose* ***10***

Yield (360 mg, 73.4%), mp 135–138.5°C; R_f=0.49 (1:4 hexane:EtOAc); $[\alpha]^{30}$ −134 (*c* 0.84, $CHCl_3$); HRMS $(M)^+$ *m/z*: calcd for $C_{18}H_{24}O_{10}S$: 432.44. Found: 432.27. The ^1H NMR and ^{13}C NMR spectra of **10** are listed in Tables 1 and 2, respectively.

*4.5. General method for the reduction of 3-deoxy-(1→2)-*S*-thiodisaccharides* ***8–10***

To a cooled and stirred solution of thiodisaccharides **8**–**9** (210 mg, 0.428 mmol) in THF, L-Selectride® (1 M in THF, 1.0 mL) was added at −78°C under an Ar atmosphere. The reaction mixture was stirred for 3 h, and then pyridine (4 mL) and acetic anhydride (5 mL) were added and stirred at room temperature overnight. The reaction mixture was poured into ice water and extracted with ethyl acetate. The extract was washed and dried. Removal of the solvent in vacuo after coevaporation with 1:1 toluene:ethyl alcohol (5×30 mL) afforded an oily residue that was subjected to column chromatography on silica gel. The fraction eluted with 20% ethyl acetate in hexane (v/v) gave syrupy products **11**–**12.**

*4.6. 4-*O*-Acetyl-1,6-anhydro-3-deoxy-2-*S*-(2,3,4,6-tetra-*O*-acetyl-2-thio-β-glucopyranosyl)-β-*D*-ribo-hexopyranose* ***11*** *and 4-*O*-acetyl-1,6-anhydro-3-deoxy-2-*S*-(2,3,4,6-tetra-*O*-acetyl-4-thio-β-gluco-pyranosyl)-β-*D*-xylo-hexopyranose* ***11a***

Yield **11** (190 mg, 79%), R_f=0.42 (1:4 hexane:EtOAc); $[\alpha]^{30}$ −34.2 (*c* 0.84, $CHCl_3$); and **11a** R_f=0.29 (1:4 hexane:EtOAc) (6 mg, 3%); $[\alpha]^{30}$ −12.1 (*c* 0.84, $CHCl_3$); HRMS $(M)^+$ *m/z*: calcd for $C_{22}H_{30}O_{13}S$: 534.53. Found: 534.14. The ^1H NMR and ^{13}C NMR spectra of **11** and **11a** are listed in Tables 1 and 2, respectively.

*4.7. 4-*O*-Acetyl-1,6-anhydro-3-deoxy-2-*S*-(2,3,4,6-tetra-*O*-acetyl-2-thio-β-galactopyranosyl)-β-*D*-ribo-hexopyranose* ***12*** *and 4-*O*-acetyl-1,6-anhydro-3-deoxy-2-*S*-(2,3,4,6-tetra-*O*-acetyl-4-thio-β-galactopyranosyl)-β-*D*-xylo-hexopyranose* ***12a***

Yield **12** (170 mg, 81.5%), R_f=0.38 (1:4 hexane:EtOAc); $[\alpha]^{30}$ −30.4 (*c* 0.68, $CHCl_3$); and **12a** R_f=0.25 (1:4 hexane:EtOAc) (16 mg, 1%); $[\alpha]^{30}$ −12.1 (*c* 0.68, $CHCl_3$); HRMS $(M)^+$ *m/z*: calcd for $C_{22}H_{30}O_{13}S$: 534.53. Found: 534.14. The ^1H NMR and ^{13}C NMR spectra of **12** and **12a** are listed in Tables 1 and 2, respectively.

*4.8. 4-*O*-Acetyl-1,6-anhydro-3-deoxy-2-*S*-(2,3,4-tri-*O*-acetyl-2-thio-α-*L*-fucopyranosyl)-β-*D*-ribo-hexopyranose* ***13*** *and 4-*O*-acetyl-1,6-anhydro-3-deoxy-2-*S*-(2,3,4-tri-*O*-acetyl-4-thio-α-*L*-fuco-pyranosyl)-β-*D*-xylo-hexopyranose* ***13a***

From **10** (200 mg, 46 mmol) the yield of **13** (170 mg, 80%), R_f=0.31 (1:4 hexane:EtOAc); $[\alpha]^{30}$ −130.2 (*c* 0.6, $CHCl_3$); and **13a** R_f=0.28 (1:4 hexane:EtOAc) (8 mg, 4%) $[\alpha]^{30}$ −12.1 (*c* 0.68, $CHCl_3$); HRMS $(M)^+$ *m/z*: calcd for $C_{20}H_{28}O_{11}S$: 476.50. Found 476.28. The ^1H NMR and ^{13}C NMR spectra of **13** and **13a** are listed in Tables 1 and 2, respectively.

4.9. General methods for the hydrolysis of 3-deoxy-(1→2)-S-thiodisaccharides (**11**–**12**)

Thiodisaccharide **11** or **12** (0.2 g, 0.375 mmol) was dissolved in Ac_2O (8.5 mL) and CF_3COOH (6.2 mL), and the mixture was stirred at room temperature for 10 h. After the solvent was evaporated, the resulting brown syrup was chromatographed (2:1 hexane:Et_2OAc) to afford an anomeric mixture of heptaacetate **15**–**16** a as colorless syrup (α:β ratio 1:5) (160 mg, 62%).

Thiodisaccharide **11** or **12** (0.4g, 0.75 mmol) was dissolved in Ac_2O (8.5 mL). Boron trifluoride etherate ($BF_3 \cdot Et_2O$) (0.1 mL) was added, and the mixture was stirred at room temperature for 10 h. After the solvent was evaporated, the resulting brown syrup was chromatographed (2:1 hexane:Et_2OAc) to afford an anomeric mixture of heptaacetate **14**–**15** as a colorless syrup (α:β ratio 1:5) (0.30 g, 58%).

To a cooled solution (0°C) of **11** or **12** (0.5 g, 0.93 mmol) in acetic anhydride (10 mL) stirred under argon, two drops (3 μl) of trimethylsilyl trifluoromethanesulfonate were added. TLC, 1:1 EtOAc:hexane, indicated the completion of the reaction in 12 h. A solution of saturated sodium bicarbonate was added, the mixture was stirred for 30 min, and the aqueous mixture was extracted three times (3×20 mL) with ethyl acetate. The combined extracts were washed with saturated sodium hydrogen carbonate (20 mL) and brine (20 mL), and dried over sodium sulfate. Evaporation of the solvent under reduced pressure yielded an inseparable anomeric mixture (α:β in a ratio ca. 1:6).

4.10. 3-Deoxy-2-S-(2,3,4,6-tetra-O-acetyl-β-glucopyranosyl)-1,2,6-tri-O-acetyl-1-thio-α,β-D-glucopyranose **14**

Yield (0.648 g, 91%) as a colorless syrup, R_f=0.34 and R_f=0.31 (1:4 hexane:EtOAc); $[\alpha]^{30}$ −12.4 (*c* 0.82, $CHCl_3$); HRMS $(M)^+$ *m/z*: calcd for $C_{26}H_{36}O_{16}S$: 636.62. Found: 636.17. The ^1H NMR and ^{13}C NMR spectra of **14** (mainly the β-anomer) are listed in Tables 1 and 2, respectively.

4.11. 3-Deoxy-2-S-(2,3,4,6-tetra-O-acetyl-β-galactopyranosyl)-1,2,6-tri-O-acetyl-1-thio-α,β-D-glucopyranose **15**

Yield (0.641 g, 86%) as a colorless syrup, R_f=0.42 and R_f=0.41 (1:4 hexane-EtOAc); $[\alpha]^{30}$ −12.4 (C 0.82 $CHCI_3$); HRMS $(M)^+$ *m/z*: calcd for $C_{26}H_{36}O_{16}S$: 636.62. Found: 636.17. The ^1H NMR and ^{13}C NMR spectra of **15** (mainly the β-anomer) are listed in Tables 1 and 2, respectively.

4.12. General methods for the deprotection of 3-deoxy-(1→2)-S-thiodisaccharides **14**–**15**

Thiodisaccharides **14**–**15** (0.250 mg, 0.15 mmol) were dissolved in a 15 ml solution of 4:1:5 MeOH:Et_3N:H_2O, and stirred at room temperature. The TLC indicated the completion of the reaction after 6 h. Evaporation of the solvent produced an inseparable anomeric mixture (α:β in a ratio 1:6)

4.13. 2-S-(β-D-Glucopyranosyl)-2-thio-D-3-deoxyglucopyranose **16**

Yield (119 mg, 89%) as a colorless syrup; $[\alpha]^{30}$ −10.26→−16.2 (*c* 0.82, H_2O); HRMS $(M)^+$ *m/z*: calcd for $C_{12}H_{22}O_9S$: 342.36. Found: 342.09. The ^1H NMR and ^{13}C NMR spectra of **16** are listed in Tables 1 and 2, respectively.

4.14. 2-S-(β-D-Galactopyranosyl)-2-thio-D-3-deoxyglucopyranose **17**

Yield (88 mg, 66%) as a colorless syrup; $[\alpha]^{30}$ −12.26→−14 (*c* 0.8, H_2O); HRMS $(M)^+$ *m/z*: calcd for $C_{12}H_{22}O_9S$: 342.36. Found: 342.12. The ^1H NMR and ^{13}C NMR spectra of **17** are listed in Tables 1 and 2, respectively.

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