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Thiosugars VI: A Simple Stereoselective Approach to (1→3)-3-S-Thiodisaccharides from Levoglucosenone

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Summary. A new stereoselective synthesis of (1→3)-3-S-thiodisaccharides is described. Levoglucosenone-derived chiral building blocks produced by the selenium-mediated iodination at C-3 afforded 3-iodoketones in moderate yield. Iodine displacement with sulfur nucleophiles (1-thiols) resulted in 3-thiodisaccharides. Following reduction of the C-2 keto function constituted a new two-step general approach to these biologically important thiosugars.

Keywords. Thiosugars; Levoglucosenone; S_N2 Displacement; (1 → 3)-3-S-Thiodisaccharides.

Introduction

In continuation of our program on C-glycosyl compounds [1] and C-disaccharides [2] as non-hydrolyzable epitopes, we focused our attention on the development of new strategies for the synthesis of (1→4), (1→2), and (1→3)-S-thiodisaccharides [3, 4]. Thiodisaccharides [5] containing sulfur in the glycosidic linkage have been synthesized previously by a variety of methods [6–14], including S_N2-type reactions involving the action of a thiolate anion and a glycosyl halide, *i.e.* the displacement of a leaving group by 1-thio-glucopyranose.

Taking into account that existing synthetic methods of thiodisaccharide synthesis are multistep [6–17] and overall low-yield approaches, an urgent need for shorter and more convergent syntheses exists. Moreover, the biological relevance and therapeutic potential of thiosugars [5], including antitumor activity of (1→2)-S-linked thiodisaccharides on selected cell culture systems [9], make them attractive new biological targets and constitutes the rationale for their synthesis.

In our efforts towards preparing thiodisaccharides [3, 4], we employed the new chiral building blocks **1–6** derived from levoglucosenone [19–21] (1,6-anhydro-3,4-dideoxy-β-*D*-glycero-hex-3-enopyranos-2-ulose). These new 'synthons' are

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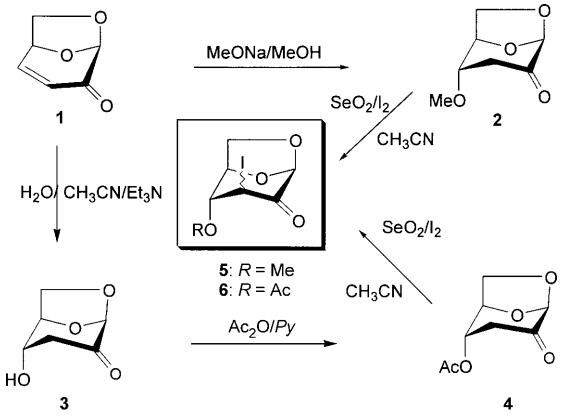


Scheme 1

extremely attractive and versatile building blocks because of their high functionality and conformational rigidity (Scheme 1).

The 1,6-anhydro bridge in **1**–**6** 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 the molecules. Therefore, these 'synthons' have already been used in the synthesis of various natural products and their intermediates [22–24].

Results and Discussion

The new approach presented here features ongoing studies on the utility of the new, convenient chiral 'synthons' **5** and **6** produced from levoglucosenone [19–21]. *Michael* addition of methanol to levoglucosenone under basic conditions proceeds easily with the direct formation of adduct **2** [25]. Analogous addition of water afforded adduct **3** [19] which by conventional *in situ* acetylation furnished the acetyl derivative **4**. Direct α-iodination of **2** and **4** using iodine/selenium dioxide [26] led to the isolation of a diastereoisomeric mixture (1:1) of the 3-iodoketones **5** and **6** in 72% yield.

Taking into account that 3-iodoketone **5** will require additional deprotection of the C-4 methyl group after coupling reaction with thiols, the 3-iodoketone **6** was chosen as a more versatile and reactive substrate in the stereoselective displacement reaction with glycosyl thiols **7** [27] and **8** [28–30].

The reaction of **6** with thiols **7** [27] and **8** [28–30] proceeded smoothly with the formation of β-(1→3)-3-S-thiodisaccharides **9** and **10** in 60–72% yield. Proton–proton couplings in the ^{1}H NMR spectra of **9** and **10** confirmed that only the 3-equatorial products was obtained as the single product in both cases. This stereospecificity has been observed previously in levoglucosenone conjugate addition [3, 4] and proceeds by the attack of incoming nucleophile at the iodine face opposite the 1,6-anhydro ring.

The advantage of the stereoselective iodide displacement is the exclusive formation of an S-linkage from the less hindered face of the molecule with inversion of the configuration at C-3. The shielding effect of the 1,6-anhydro bridge in **6** effectively prevents the formation of the 3-axial (*a*) product, thus yielding only

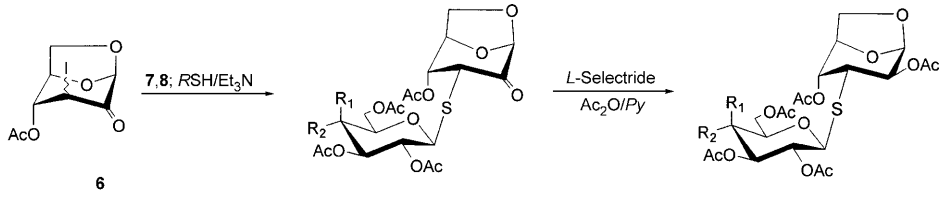
the 3-equatorial (*e*) product. This equatorial attack of the sulfur nucleophiles was expected [12–14], but a new chiral center at C-3 surprisingly stabilizes the molecule, as no epimerization [11, 13] or β-elimination was observed during the coupling reaction. Also, the 4-acetyl protecting group of **6** is sufficiently stable under the above reaction conditions, and no deacetylation or epoxide formation has been observed. This important observation additionally indicates the preferential stereochemistry at C-3 of **6**. The sterically hindered 1,6-anhydro bridge 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 3-axial product.

Indeed, the proton–proton couplings in the ^{1}H NMR spectra of **9** and **10** confirmed the D-allo stereochemistry with coupling constants of $J_{3a,4} = 7.6$ Hz, indicating an equatorial orientation of the substituent at C-3. The ^{1}H NMR spectra of the products did not show signals corresponding to the D-gluco isomer, clearly demonstrating that the stereochemistry of the reaction of thiols **7** and **8** with 3-ketone **6** is completely controlled by the steric bulk of the 1,6-anhydro bridge. The ^{13}C NMR spectra of both **9** and **10** showed no $-CH_2-$ group signal, and the C-3 signal appeared at *ca.* 23.0–23.4 ppm.

The reduction of the C-2 keto function of ketones **9** and **10** with L-Selectride®, followed by conventional *in situ* acetylation, proceeded stereoselectively under formation of the D-altro isomers **12** and **13** in 79% yield. Only a trace amount of the corresponding D-altro isomers **11a** and **12a** were detected by ^{1}H NMR spectroscopy. Additionally, the absence of a coupling between H-4 and H-5 and coupling constants of $J_{1,2} = 8.2$ and $J_{2,3} = 5.2$ Hz for **11** and **12** indicate an equatorial orientation of the new substituent at C-2.

Unlike levoglucosenone, where the C-2 keto group reduction was predictably controlled [31] by the 1,6-anhydro bridge, the analogous reduction of **9** and **10** was expected to be dominated by the relative steric contribution of the bulky equatorial substituent at C-3 as well as by the 1,6-anhydro bridge. This is in full agreement with earlier observations [14, 15] of high stereoselectivity and another classical example of the preferential attack of the reducing agent from the bottom face on this bicyclic molecule. Moreover, the ^{1}H and ^{13}C NMR spectra of **11** and **12** firmly support their assignments to the D-allo configuration. Particularly, the coupling constants between the equatorially disposed H-2 and the axially oriented H-3 are of great diagnostic value ($J_{2,3} = 5$ Hz).

The cleavage of the 1,6-anhydro ring in **11** and **12** was examined under various reaction conditions. Acetolysis using trifluoroacetic acid and acetic anhydride



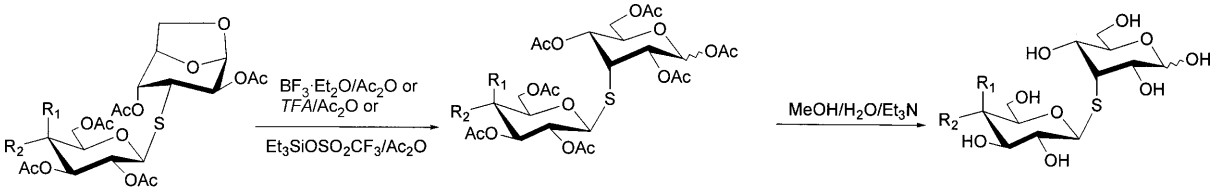
6

7: *R* = 2,3,4,6-tetra-O-acetyl-*D*-glucopyranosyl
8: *R* = 2,3,4,6-tetra-O-acetyl-*D*-galactopyranosyl

9: R^1 = H, R^2 = OAc
10: R^1 = OAc, R^2 = H

11: R^1 = H, R^2 = OAc
12: R^1 = OAc, R^2 = H

Scheme 2



11: R^1 = H, R^2 = OAc
12: R^1 = OAc, R^2 = H

13: R^1 = H, R^2 = OAc
14: R^1 = OAc, R^2 = H

15: R^1 = H, R^2 = OH
16: R^1 = OH, R^2 = H

Scheme 3

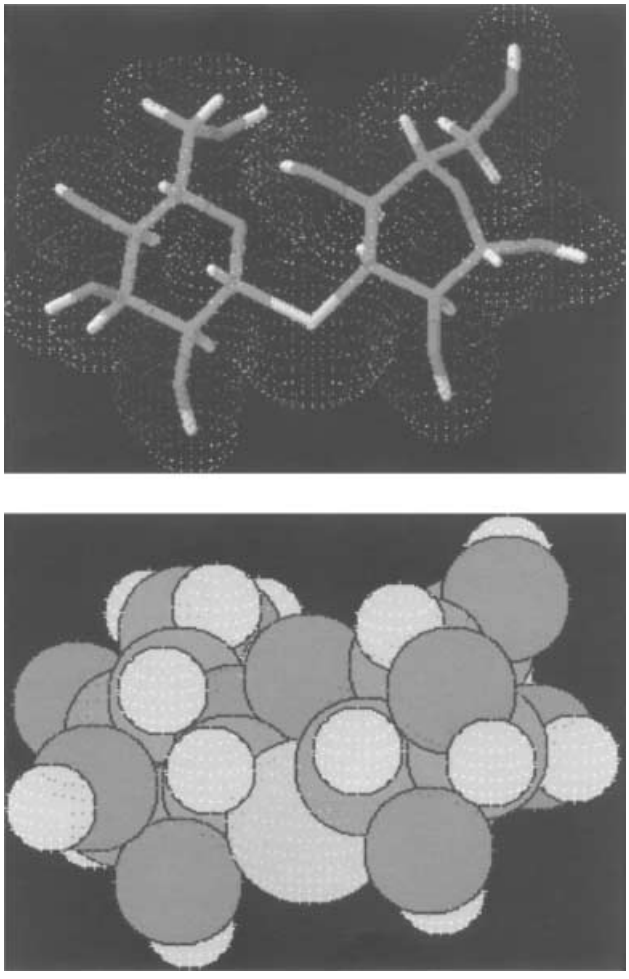


Fig. 1. 3-S-β-*D*-Galactopyranosyl-3-thio-*D*-allopyranose

afforded an anomeric mixture of octaacetates **13** and **14** in good yield (62%). Employing acetic anhydride and a catalytic amount of borontrifluoride etherate also gave acceptable results (68%). However, chromatographic purification of the crude material was required.

The method of choice was acetolysis using acetic anhydride solution and a catalytic amount of trifluoromethanesulfonate and proceeding according to the convenient protocol of *Fraser-Reid* [32]. This resulted in the formation of an anomeric mixture of octaacetates **13** and **14** (α:β = 1:5) in 89% yield. The presence of the sulfur bridge at C-3 clearly indicates the strong influence of the 1,6-anhydro ring on the cleavage; a prolonged reaction time (up to the 12 h) as compared with the literature data reported [32] is required. Separation of the anomers proved impossible because of their almost identical R_f values. However, the ^{1}H and ^{13}C NMR spectra and mass spectroscopic data for the mixture firmly established their identity.

Final deprotection of octaacetates **13** and **14** was performed with an aqueous methanolic solution of triethylamine (MeOH:Et_3N:H_2O = 4:1:5) at room temperature for 8 h, resulting in the new thiodisacharides 3-S-(β-D-glucopyranosyl)-3-thio-D-allopyranose (**15**) and 3-S-(β-D-galactopyranosyl)-3-thio-*D*-allopyranose **16** in 89% yield.

A molecular model of **16** (Fig. 1; generated by ACD Chemsketch 4.0, 3D software program) clearly confirms the structure as determined by NMR spectroscopy. The length of the C-1–S bond amounts to 1.8132 Å, whereas the C-3–S distance is 1.8086 Å; the dihedral and torsional angles for the C–S–C bridge are 107.887 and 61.305°, respectively. Calculations for the sulfur bridge of other thiodisaccharides give similar results and differ substantially from those of their oxygen counterparts as previously postulated in the literature [33, 34].

Conclusions

The S_N2 nucleophilic displacement reaction of 3-iodoketone **6** with protected 1-thiosugars, followed by C-2 keto group reduction and deprotection, constitutes a new short and stereoselective approach to (1→3)-3-S-thiodisacharides. All new functionalized thiodisaccharides are stable glycomimetics of potential biological interest.

Experimental

General

Unless otherwise noted, starting materials were obtained from commercial suppliers and used without purification. All melting points are uncorrected and were measured in open capillary tubes. Optical rotations were determined on a Jasco Model DIP-370 polarimeter in $CHCl_3$. Thin-layer chromatography (TLC) was performed on precoated Silica gel $60F_{254}$ plates from E. Merck; spots were visualized by spraying with 10% ethanolic H_2SO_4 and subsequent heating. Column chromatography was performed on Silica Gel 60 (70–230 mesh, Merck No. 34). NMR samples were prepared in $CDCl_3$ (99.8 at.% D), filtered, freeze-thawed, and sealed in a 5 mm tube. *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 the EI mode at 70 eV or using CI (NH_3). Levoglucosenone was produced according to the published methodology [19–21]. 1,6-Anhydro-4-O-methyl-β-*D*-erythro-hexopyranos-2-ulose (**2**) [25] and 1,6-anhydro-4-hydroxy-β-*D*-erythro-hexopyranos-2-ulose (**3**) [14] were prepared according to literature methods. 2,3,4,6-Tetra-O-acetyl-1-thio-β-*D*-glucopyranose (**7**) [27] and 2,3,4,6-tetra-O-acetyl-1-thio-β-*D*-galactopyranose (**8**) [28, 29] were prepared by reacting the corresponding α- or β-glycosyl halides with

thiourea and the reduction of the isothiouronium salts with potassium pyrosulfite according to the published procedure [30].

4-O-Acetyl-1,6-anhydro-2,3-dideoxy-β-D-erythro-hexopyranos-2-ulose (**4**; $C_8H_{10}O_5$)

Compound **3** (0.1 mmol) was conventionally acetylated at room temperature for 24 h with acetic anhydride (5 cm^3) in pyridine (4 cm^3). The reaction mixture was poured into ice water and extracted with ethyl acetate. The extract was washed and dried. Removal of the solvent on a rotary evaporator (coevaporation with toluene:EtOH = 1:1; 5 × 30 cm^3) 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 a syrupy product which crystallized from ether/hexane.

Yield: 205 mg (83%); m.p.: 108–110.2°C; $R_f = 0.45$ (EtOAc); $[\alpha]_D = +231°$ ($c = 1.0$, $CHCl_3$); for ^1H and ^{13}C NMR data, see Tables 1 and 2.

General method for the preparation of 3-iodoketones **5** *and* **6**

Compounds **5** and **6** were produced by the *Bekaert* [26] methodology as described below. To a solution of **4** (0.1 mol) in 50 cm^3 of CH_3CN, 6.1 g powdered selenium dioxide (55 mmol) and 13.97 g iodine (55 mmol) were added. The mixture was heated at 80°C for 8 h. The red selenium precipitate was removed by filtration through a short silica gel column. The dark-red solution was diluted with 200 cm^3 of H_2O and extracted with CH_2Cl_2. The organic layer was extracted with 100 cm^3 of a 10% solution of $Na_2S_2O_3$ and washed with H_2O. After drying with anhydrous magnesium sulfate, the solvent was removed on a rotary evaporator, and the 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.

1,6-Anhydro-2,3-dideoxy-3-iodo-4-methoxy-β-D-erythro-hexopyranos-2-ulose
(**5**; $C_7H_9IO_4$)

Yield: 205 mg (73%); m.p.: 80–82.5°C; $R_f = 0.51$ (EtOAc); $[\alpha]_D = +301°$ ($c = 1.0$, $CHCl_3$); for ^1H and ^{13}C NMR data, see Tables 1 and 2.

1,6-Anhydro-2,3-dideoxy-3-iodo-4-O-acetyl-β-D-erythro-hexopyranos-2-ulose
(**6**; $C_8H_9IO_5$)

Yield: 235 mg (73%); m.p.: 60–61.5°C; $R_f = 0.59$ (EtOAc); $[\alpha]_D = +318°$ ($c = 1.0$, $CHCl_3$); for ^1H and ^{13}C NMR data, see Tables 1 and 2.

General method for the preparation of (1→3)-3-S-thiodisacharides **9** *and* **10**

To a solution of 126 mg 3-iodoketone **6** (0.1 mmol) in 10 cm^3 CH_3CN, a solution of 125 mg **7** [26] or **8** [27, 28] (0.34 mmol) in 5 cm^3 of CH_3CN and 2 cm^3 of thiethylamine was added dropwise. The reaction mixture was stirred at room temperature for 24 h; then, pyridine (4 cm^3) and acetic anhydride (5 cm^3) were added, and the mixture was stirred at room temperature overnight, poured into ice water, and extracted with ethyl acetate. The extract was washed and dried. Removal of the solvent *in vacuo* after coevaporation with 5 × 30 cm^3 toluene:EtOH = 1:1 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 **9** and **10** which crystallized from ether/hexane.

Table 1. ^{1}H NMR chemical shifts (ppm) and coupling constants (Hz) for compounds **5**, **6**, and **9–16** (500 MHz, $CDCl_3$, *TMS*)

	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′ $J_{5,6''}$	H-1 $J_{1,2}$	H-2 $J_{2,3}$	H-3a $J_{3a,4}$	H-4 J	H-5 $J_{5,6exo}$	H-6*endo* $J_{5,6endo}$	H-6*exo* $J_{6exo,6endo}$	$COCH_3$
5								5.3 d –		3.12 dd 7.6	3.56 d 8.0	4.50 dd 4.9	3.93 dd 1.1	4.04 dd 8.2	3.82
6								5.3 d –		3.12 dd 7.6	3.56 d 8.0	4.50 dd 4.9	3.93 dd 1.1	4.04 dd 8.2	2.02
9	4.66 d 8.6	5.19 dd 9.6	5.23 t 9.9	5.04 d 9.5	4.82 d 5.0	4.26 dd –	4.26 dd –	5.3 d –		3.12 dd 7.6	3.56 d 8.0	4.90 dd 4.9	3.93 dd 1.1	4.04 dd 8.2	2.02–1.98 5s, 5 × OAc
10	4.66 d 8.6	5.19 dd 9.6	5.23 t 9.9	5.04 d 9.5	4.82 d 5.0	4.26 dd –	4.26 dd –	5.3 d		3.12 dd 7.6	3.56 d 8.0	4.90 dd 4.9	3.93 dd 1.1	4.04 dd 8.2	2.02–2.1, 5s, 5 × OAc
11	4.66 d 8.6	5.19 dd 9.6	5.23 t 9.9	5.04 d 9.5	4.82 d 5.0	4.26 dd –	4.26 dd –	5.3 d 8.2	3.66 d 5.0	3.12 dd 7.6	3.56 d 8.0	4.90 dd 4.9	3.93 dd 1.1	4.04 dd 8.2	2.02–2.1, 6s, 6 × OAc
12	4.66 d 8.6	5.19 dd 9.6	5.23 t 9.9	4.65 d 9.5	4.82 d 5.0	4.26 dd –	4.26 dd	5.4 d 8.2	3.66 d 5.0	3.12 dd 7.6	4.35 d 8.0	4.48 dd 4.9	3.93 dd 1.1	4.04 dd 8.2	2.02–2.1, 6s, 6 × OAc
13	4.66 d 8.6	5.19 dd 9.6	5.23 t 9.9	5.04 d 9.5	4.82 d 5.0	4.26 dd –	4.26 dd –	4.8 d 8.2	3.66 d 5.0	3.12 dd 7.6	3.56 d 8.0	4.90 dd 4.9	3.93 dd 1.1	4.04 dd 8.2	2.01–2.1 8s, 8 × OAc
14	4.6 d 8.6	5.19 dd 9.6	5.23 t 9.9	5.04 d 9.5	4.82 d 5.0	4.26 dd –	4.26 dd –	4.8 d 8.2	3.66 d 5.0	3.12 dd 7.6	3.56 d 8.0	4.90 dd 4.9	3.93 dd 1.1	4.04 dd 8.2	2.01–2.1 8s, 8 × OAc
15[a]	4.86 d 8.2	5.21 dd 9.8	5.26 t 10.0	5.08 d 9.7	4.84 d 5.2	4.28 dd –	4.28 dd –	4.8 d 8.2	3.58 d 5.2	3.19 dd 7.4	3.59 d 8.1	4.84 dd 4.8	3.96 dd 1.2	4.06 dd 8.4	
16[a]	4.86 d 8.2	5.21 dd 9.8	5.26 t 10.0	5.08 d 9.7	4.84 d 5.2	4.28 dd –	4.28 dd –	4.8 d 8.2	3.58 d 5.2	3.19 dd 7.4	3.59 d 8.1	4.84 dd 4.8	3.96 dd 1.2	4.06 dd 8.4	

[a] D_2O, *TMSPA*-Na

Table 2. ^{13}C NMR chemical shifts (ppm) for compounds **5**, **6**, and **10–16** (125 MHz, $CDCl_3$, *TMS*)

	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	CH_3
5	102.1	207.2	23.0	78.3	85.0	65.7								50.8
6	102.6	207.1	23.1	76.2	85.1	65.7							171.2	17.6
9	104.8	207.7	63.4	71.9	78.1	68.1	83.7	67.1	48.4	70.6	76.2	68.8	5 × 171.1	17.6, 17.5, 17.4
10	104.6	207.7	63.1	71.8	78.1	68.6	83.7	67.1	48.1	70.6	76.2	68.8	5 × 171.1	17.6, 17.5, 17.5, 17.4
11	104.7	73.7	63.1	71.9	78.0	68.1	83.7	65.7	48.7	72.1	75.0	68.8	6 × 176.0	6 × 17.6
12	104.8	73.7	63.1	71.9	78.0	68.6	83.9	65.7	48.7	72.1	72.0	68.8	6 × 176.0	6 × 17.6
13	98.8	73.7	63.1	65.9	78.0	63.1	84.9	70.7	48.7	69.9	72.0	68.8	8 × 176.0	8 × 17.6
14	98.8	73.7	63.1	65.9	75.0	68.1	84.8	70.7	48.7	69.9	75.0	68.0	8 × 176.0	8 × 17.6
15[a]	98.5	74.4	63.7	68.4	75.7	64.8	84.9	75.6	48.2	68.5	75.4	64.8		
16[a]	98.6	74.4	63.7	68.4	75.7	64.8	84.8	77.0	48.1	68.8	72.4	64.8		

[a] D_2O, *TMSPA*-Na

1,6-Anhydro-3-S-(2,3,4,6-tetra-O-acetyl-β-glucopyranosyl)-β-D-glycero-hexopyranos-4-ulose (**9**; $C_{20}H_{26}O_{12}S$)

Yield: 436 mg (89%); m.p.: 157–158.5°C; $R_f = 0.59$ (hexane:EtOAc = 1:4); $[\alpha]^{30} = -120.21°$ ($c = 0.84$, $CHCl_3$); HRMS: $m/z = 490.11$ (calcd.: 490.47); for ^1H and ^{13}C NMR data: see Tables 1 and 2.

1,6-Anhydro-3-S-(2,3,4,6-tetra-O-acetyl-β-galactopyranosyl)-β-D-glycero-hexopyranos-4-ulose (**10**; $C_{20}H_{26}O_{12}S$)

Yield: 385 mg (78.5%); m.p.: 151–152.5°C; $R_f = 0.41$ (hexane:EtOAc = 1:4); $[\alpha]^{30} = -122.2°$ ($c = 0.8$, $CHCl_3$); HRMS: $m/z = 490.11$ (calcd.: 490.47); for ^1H and ^{13}C NMR data, see Tables 1 and 2.

General method for the reduction of (1→3)-3-S-thiodisacharides **9** *and* **10**

To a cooled and stirred solution of 210 mg thiodisaccharides **9** or **10** (0.428 mmol) in *THF*, 1.0 cm^3 *L*-Selectride® (1 *M* in *THF*) was added at −78°C under an Ar atmosphere. The reaction mixture was stirred for 3 h; then, pyridine (4 cm^3) and acetic anhydride (5 cm^3) were added, and stirring at room temperature was continued 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 5×30 cm^3 toluene:EtOH = 1:1 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** and **12**.

4-O-Acetyl-1,6-anhydro-3-S-(2,3,4,6-tetra-O-acetyl-3-thio-β-glucopyranosyl)-β-D-allo-hexo-pyranose (**11**; $C_{24}H_{32}O_{15}S$)

Yield: 190 mg (79%); $R_f = 0.42$ (hexane:EtOAc = 1:4); $[\alpha]^{30} = -34.2°$ ($c = 0.84$, $CHCl_3$); HRMS: $m/z = 592.14$ (calcd.: 592.57); for ^1H and ^{13}C NMR data, see Tables 1 and 2.

4-O-Acetyl-1,6-anhydro-3-S-(2,3,4,6-tetra-O-acetyl-3-thio-β-galactopyranosyl)-β-D-allo-hexo-pyranose (**12**, $C_{24}H_{33}O_{15}S$)

Yield: 170 mg (81.5%); $R_f = 0.33$ (hexane:EtOAc = 1:4); $[\alpha]^{30} = -30.4°$ ($c = 0.68$, $CHCl_3$); HRMS: $m/z = 592.17$ (calcd.: 592.57); for ^1H and ^{13}C NMR data, see Tables 1 and 2.

General method for the hydrolysis of (1→3)-S-thiodisaccharides **11** *and* **12**

a) 0.2 g Thiodisaccharide **11** or **12** (0.375 mmol) were dissolved in Ac_2O (8.5 cm^3) and CF_3COOH (6.2 cm^3), and the mixture was stirred at room temperature for 10 h. After the solvent was evaporated, the resulting brown syrup was chromatographed (hexane:Et_2OAc = 2:1) to afford an anomeric mixture of 160 mg (62%) heptaacetates **13** and **14** as colorless syrup (α:β-ratio: 1:5).
b) 0.4 g Thiodisaccharide **11** or **12** (0.75 mmol) were dissolved in Ac_2O (8.5 cm^3). Boron trifluoride etherate ($BF_3 \cdot Et_2O$, 0.1 cm^3) was added, and the mixture was stirred at room temperature for 10 h. After the solvent was evaporated, the resulting brown syrup was chromatographed (hexane:Et_2OAc = 2:1) to afford 0.30 g (68%) of an anomeric mixture of heptaacetates **13** and **14** as a colorless syrup (α:β-ratio = 1:5).
c) To a cooled solution (0°C) of 0.5 g of **11** or **12** (0.93 mmol) in acetic anhydride (10 cm^3) stirred under argon, two drops (3 mm^3) of trimethylsilyl trifluoromethanesulfonate were added. TLC

(EtOAc:hexane = 1:1) indicated the completion of the reaction after 12 h. A solution of saturated sodium bicarbonate was added, and the mixture was stirred for 30 min and was extracted with $3 \times 20\,cm^3$ ethyl acetate. The combined extracts were washed with $20\,cm^3$ saturated $NaHCO_3$ and $20\,cm^3$ brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure yielded 0.35 g (89%) of an inseparable anomeric mixture (α:β-ratio $\approx$ 1:6).

1,2,4,6-Tetra-O-acetyl-3-S-(2,3,4,6-tetra-O-acetyl-β-glucopyranosyl)-3-thio-α,β-D-allo-pyranose (**13**; $C_{28}H_{38}O_{18}S$)

Yield: 0.648 g (91%); colorless syrup; $R_f = 0.34$, 0.31 (hexane:EtOAc = 1:4); $[\alpha]^{30} = -12.4°$ (c = 0.82, $CHCI_3$); HRMS: $m/z = 636.17$ (calcd.: 636.62); for ^1H and ^{13}C NMR data (mainly the β-anomer), see Tables 1 and 2.

1,2,6-Tri-O-acetyl-3-S-(2,3,4,6-tetra-O-acetyl-β-galactopyranosyl)-3-thio-α,β-D-allopyranose (**14**; $C_{26}H_{38}O_{18}S$)

Yield: 0.641 g (86%); colorless syrup; $R_f = 0.42$, 0.41 (hexane:EtOAc = 1:4); $[\alpha]^{30} = -12.4°$ (c = 0.82, $CHCl_3$); HRMS: $m/z = 636.17$ (calcd.: 636.62); for ^1H and ^{13}C NMR data (mainly the β-anomer), see Tables 1 and 2.

General method for the deprotection of (1→3)-3-S-thiodisacharides **13** *and* **14**

0.250 mg of thiodisaccharides **13** or **14** (0.15 mmol) were dissolved in $15\,cm^3$ of a MeOH: Et_3N:H_2O = 4:1:5 mixture and stirred at room temperature. TLC indicated the completion of the reaction after 6 h. Evaporation of the solvent produced an inseparable anomeric mixture (α:β-ratio = 1:6).

3-S-(β-D-Glucopyranosyl)-3-thio-D-allopyranose (**15**; $C_{12}H_{22}O_{10}S$)

Yield: 119 mg (89%); colorless syrup; $[\alpha]^{30} = -10.2° \rightarrow -16.2°$ ($c = 0.82$, H_2O); HRMS: $m/z = 342.09$ (calcd.: 342.36); for ^1H and ^{13}C NMR data (mainly the β-anomer), see Tables 1 and 2.

3-S-(β-D-Galactopyranosyl)-3-thio-D-allopyranose (**16**; $C_{12}H_{22}O_{10}S$)

Yield: 88 mg (66%); colorless syrup; $[\alpha]^{30} = -12.6° \rightarrow -14°$ ($c = 0.8$, H_2O); HRMS: $m/z = 342.12$ (calcd.: 342.36); for ^1H and ^{13}C NMR data (mainly the β-anomer), see Tables 1 and 2.

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References

[1] Witczak ZJ (1994) Pure Appl Chem **66**: 2189
[2] Witczak ZJ, Chhabra R, Chojnacki J (1997) Tetrahedron Lett **38**: 2215
[3] Witczak ZJ, Sun J, Mielguj R (1995) Bioorg Med Chem Lett **5**: 2169
[4] Witczak ZJ, Chhabra R, Chen H, Xie X-Q Carbohydr Res **301**: 167; Witczak ZJ, Chen H, Kaplon P (2000) Tetrahedron Asymm **11**: 519; Witczak ZJ, Chhabra R, Boryczewski D (2000) J Carbohydr Chem **19**: 543

[5] Witczak ZJ (1999) Curr Med Chem **6**: 165
[6] For reviews see a) Defaye J, Gelas J (1991) In: Atta-ur-Rahman (ed) Studies in Natural Products Chemistry, vol 8E. Elsevier, Amsterdam, p 315; b) Driguez H (1997) In: Driguez H, Thiem J (eds) Topics in Current Chemistry, vol 187. Springer Berlin Heidelberg New York, p 85
[7] Blanc-Muesser M, Defaye J, Driguez H (1982) J Chem Soc Perkin Trans 1, 15
[8] Defaye J, Guillot J-M (1994) Carbohydr Res **253**: 185
[9] Comber RN, Friedrich JD, Dunshee DA, Petty SL, Secrist III JA (1994) Carbohydr Res **262**: 245
[10] Hashimoto H, Shimada K, Horito S (1993) Tetrahedron Lett **34**: 4953
[11] Hashimoto H, Shimada K, Horito S (1994) Tetrahedron Asymm **12**: 2351
[12] Calvo-Asin JA, Calvo-Flores FG, Exposito-Lopez JM, Hernandez-Mateo F, Garcia-Lopez JJ, Isac-Garcia J, Santoyo-Gonzalez F, Vargas-Berenguel A (1997) J Chem Soc Perkin Trans 1, 1079
[13] Defaye J, Guillot J-M, Biely P (1992) Carbohydr Res **228**: 47
[14] Petrusova M, Lattova E, Matulova M, Petrus L, BeMiller JN (1996) Carbohydr Res **283**: 73
[15] Michael K, Kessler H (1996) Tetrahedron Lett **37**: 3453
[16] Becker B, Thimm J, Thiem J (1996) J Carbohydr Chem **15**: 1179
[17] Johnston BD, Pinto BM (2000) J Org Chem **65**: 4607
[18] Knapp S, Malolanarsimhan K (2000) Org Lett **1**: 611
[19] Ward DD, Shafizadeh F (1981) Carbohydr Res **95**: 155
[20] Shafizadeh F, Furneaux RH, Stevenson TT (1979) Carbohydr Res **71**: 161
[21] Witczak ZJ (1994) In: Witczak ZJ (ed) Levoglucosenone and Levoglucosans. Chemistry and Applications. ATL Press, Mount Prospect, p 7
[22] Matsumoto K, Ebata T, Koseki K, Okano K, Kawakami H, Matsushita H (1992) Heterocycles **34**: 1935
[23] Mori K, Chuman T, Kato K (1984) Carbohydr Res **129**: 73
[24] Bamba M, Nishikawa T, Isobe M (1996) Tetrahedron Lett **37**: 8199
[25] Forsyth AC, Gould RO, Paton RM, Sadler JH, Watt I (1993) J Chem Soc Perkin Trans 1, 2737
[26] Beakert A, Barberan O, Gervais M, Brion J-D (2000) Tetrahedron Lett **41**: 2903
[27] Horton D (1963) Methods Carbohydr Chem **2**: 433
[28] Černý M (1963) Monatshefte Chem **94**: 290
[29] Fragala J, Černý M, Stanek J (1975) Collect Czech Chem Commun **40**: 1411
[30] Joseph B, Rollin P (1993) J Carbohydr Chem **12**: 719
[31] Okano K, Ebata T, Koseki K, Kawakami H, Matsumoto K, Matsushita H (1993) Chem Pharm Bull **41**: 861
[32] Zotola M, Venkateswara B, Fraser-Reid B (1991) J Chem Soc Chem Commun 969
[33] Geyer A, Hummel G, Eisele T, Reinehardt S, Schmidt RR (1996) Chem Eur J **2**: 981
[34] Espinosa JF, Cañada FJ, Asensio JL, Dietrich H, Martin-Lomas M, Schmidt RR, Jiménez-Barbero J (1996) Angew Chem Int Ed Engl **35**: 303

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