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The thio-Mitsunobu reaction of D-glucitol, D-mannitol, galactitol and 1-seleno-D-xylitol☆

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Dedicated to Professor Ralf Miethchen on the occasion of his 60th birthday

Abstract

Unprotected D-glucitol is transformed into 5-*O*-acetyl-1,4-anhydro-6-thio-D-glucitol (**3**) in one step by use of the thio-Mitsunobu reaction. Rearrangement (acetyl group migration) to form 3-*O*-acetyl-1,4-anhydro-6-thio-D-glucitol occurs during column chromatography of **3** on silica gel. 2,5-Di-*O*-acetyl-1,6-dithio-D-mannitol and 1,6-di-*S*-acetyl-2,5-anhydro-1,6-dithio-D-glucitol (characterized as the corresponding *p*-nitrobenzoates) are formed from D-mannitol, whereas galactitol yields a mass of unidentified products. 1-Seleno-D-xylitol, produced by reduction of D-xylose with hydrogen selenide, does not undergo a Mitsunobu reaction.

Keywords: Alditols; Mitsunobu reaction; X-ray structural analysis; Thiosugars; Selenosugars

1. Introduction

The Mitsunobu reaction [1] is a well known versatile method to substitute hydroxy groups by a broad variety of nucleophiles — with inversion of configuration if secondary carbinols are used. We have applied thioacetic acid ('thio-Mitsunobu reaction' [2]) as the nucleophile for the synthesis of thiosugars and observed total chemoselectivity, i.e., primary hydroxy groups can be selectively replaced by acetylthio groups in the presence of secondary hydroxy groups [3]. This prompted us to try analogous reactions in the alditol series.

2. Results and discussion

First we performed the reaction of D-glucitol (**1**) with two equivalents each of diisopropyl azodicarboxylate (DIAD), triphenylphosphine and thioacetic acid, expecting the formation of 1,6-di-*S*-acetyl-1,6-dithio-D-glucitol (**2**). However, instead of **2**, 5-*O*-acetyl-1,4-anhydro-6-thio-D-glucitol (**3**) was formed in 64% yield according to the ^{1}H NMR spectrum (Scheme 1).

☆ Thiosugars, Part 6. For Part 5 see J. Wirsching, J. Voss, J. Balzarini, E. DeClerq, *Bioorg. Med. Chem. Lett.*, 10 (2000) 1339–1341.

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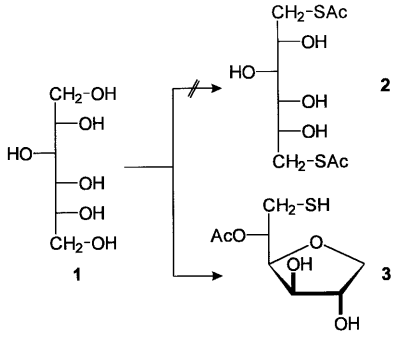


Scheme 1.

When we tried to remove traces of triphenylphosphine oxide from this product by means of column chromatography on silica gel, we observed an acetyl migration from O-5 to O-3 in the glucitol derivative **3** yielding 3-*O*-acetyl-1,4-anhydro-6-thio-D-glucitol (**4**). Although the mercapto sugars **3** and **4** were exposed to air over a weekend after chromatographic purification, they were not oxidized to the corresponding disulfides. Furthermore, we were able to isolate three diacetates **5**, **6** and **7** as byproducts from the original reaction mixture (Scheme 2).

The structure of the main product **3** was proved by X-ray measurement (Fig. 1) of the corresponding nitrobenzoate **8**, which could be separated from the congener **9** (Scheme 3).

We also prepared the tris-*p*-nitrobenzoate **10** from the rearranged product **4** (Scheme 3).

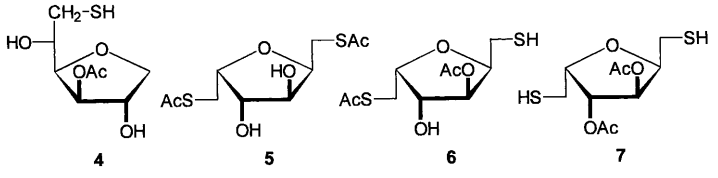
The connectivity of the atoms in **5**–**7** could be elucidated by means of ^{1}H^{1}H-COSY-, HMQC- and HMBC-spectra. The simplicity of the ^{1}H NMR spectra of **5** and **7** indicated C_s- or C_2-symmetry. A significant optical rotation of **5** indicated C_2 symmetry leaving only four possible isomers. Finally an X-ray diffraction study revealed that **5** exhibits the L-*ido*-configuration (Fig. 2).

These unexpected and complicated results prompted us to study the analogous reactions with D-mannitol (**11**) and galactitol, which exhibit C_2- and C_s-symmetry, respectively. First we performed the thio-Mitsunobu reaction with **11** exactly in the same way as described for **1**. Then — after a rapid silica gel filtration — we treated the crude product immediately with *p*-nitrobenzoyl chloride. After repeated chromatography with great losses the two main products were obtained, which turned out to be 2,5-di-*O*-acetyl-3,4-di-*O*-*p*-nitrobenzoyl-1,6-di-*S*-*p*-nitrobenzoyl-1,6-dithio-D-mannitol (**12**) and 1,6-di-*S*-acetyl-2,5-anhydro-3,4-di-*O*-*p*-nitrobenzoyl-1,6-dithio-D-glucitol (**13**) (Scheme 4).

The structure of **12** was elucidated by its ^{1}H^{1}H-COSY-, HMQC- and HMBC-spectra revealing C_2 symmetry. An X-ray diffraction study confirmed the *manno*-configuration of this product (Fig. 3). The NMR spectra of **13**, in particular the observed NOE spectrum, was only in agreement with the *gluco*-configurated structure (Fig. 4).

When we performed a Mitsunobu reaction with galactitol, we obtained a complex mixture of products, which was not purified chromatographically in order to avoid acetyl group migrations. Subsequent treatment with *p*-nitrobenzoyl chloride did, however, not yield any isolable and identifiable products even after repeated chromatography of the mixture in this case.

Our results raise two questions: What is the course of these reactions? Which structural peculiarity of **1** makes its thio-Mitsunobu reaction much more selective as compared with **11** or even galactitol? When we performed the reactions under exactly the same conditions but without thioacetic acid we obtained only complex mixtures of unidentified products.



Scheme 2.

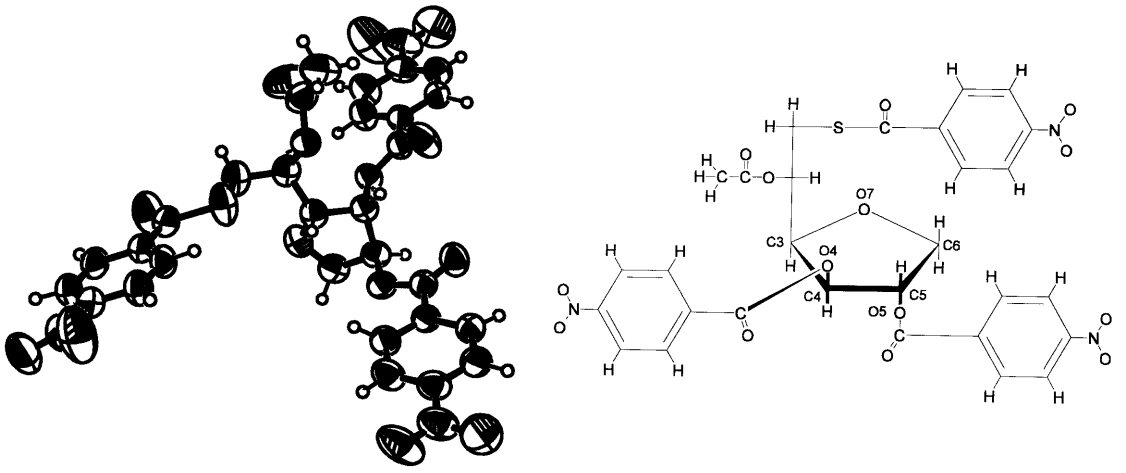
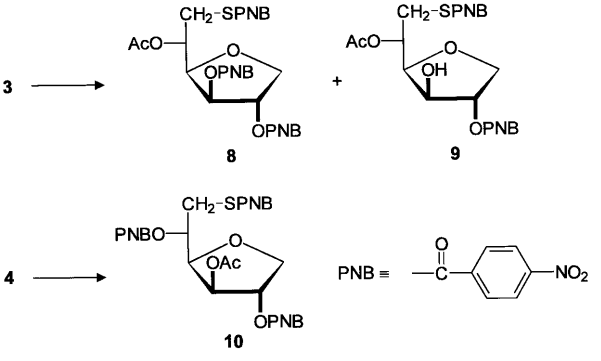


Fig. 1. ORTEP view of the X-ray diffraction structure of **8** with atom numbering. Thermal ellipsoids are drawn at the 50% probability level.

We conclude, therefore, that the first step of the reaction sequence is a thio-Mitsunobu reaction to form the two possible primary thioacetates. Subsequently intramolecular Mitsunobu reactions occur, which lead to two different reactive cyclic intermediates (oxirane [3] or 1,3,2-dioxa-λ^5-phospholane [4]). Finally, intramolecular nucleophilic $4 \rightarrow 1$ attack results in the main product **3**. Correspondingly, $2 \rightarrow 5$ attack in the second intermediate under inversion and acetyl migration leads to the byproducts **5**–**7**. In a similar way **11** is transformed via a cyclic intermediate, $5 \rightarrow 2$ ring opening and formation of the cyclic bisthioacetate, which finally yields **13** with D-*gluco*-configuration (Scheme 5).

It is known that D-glucitol possesses a unique hydrogen bonding feature in the solid state compared to other alditol structures [5]. We therefore were interested in the structure of an 'isolated' molecule with respect to intramolecular hydrogen bonds. A density functional theory (DFT) type MO calculation of **1** revealed that O-11 is a proton acceptor but not a proton donor whereas O-61 is a proton donor but not a proton acceptor (Table 1). Although the calculations do not account for intermolecular and solvent interactions, this might explain the different chemical behaviour of the two primary hydroxy groups in the thio-Mitsunobu reaction.

Sulfur can be introduced rather easily into carbohydrates since thioacetic acid is a stable compound which can be used in a thio-Mitsunobu reaction. The introduction of selenium requires a different strategy since selenoacetic acid is not a versatile reagent. We therefore treated D-xylose (**14**) with hydrogen selenide [6]



Scheme 3.

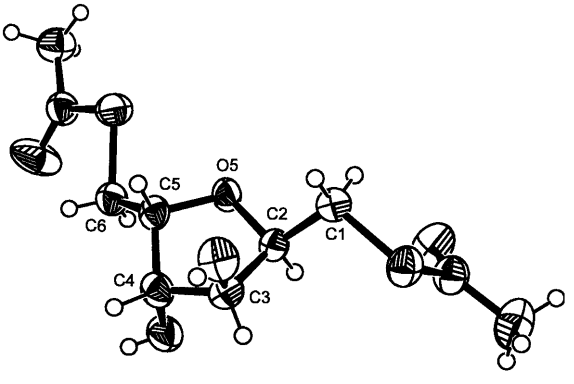
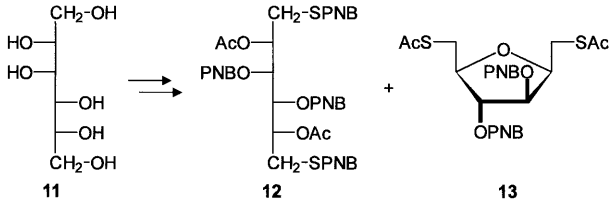


Fig. 2. ORTEP view of the X-ray diffraction structure of **5** with atom numbering. Thermal ellipsoids are drawn at the 50% probability level.



Scheme 4.

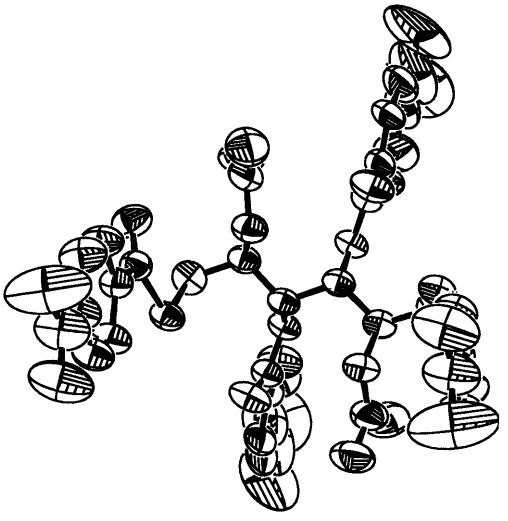


Fig. 3. ORTEP view of the X-ray diffraction structure of **12** with atom numbering. Thermal ellipsoids are drawn at the 50% probability level.

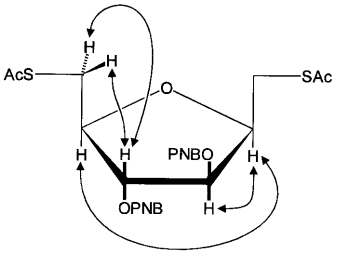


Fig. 4. Observed NOE-contacts in **13**.

hoping to obtain non racemic C_1 symmetric 1-seleno-D-xylitol (**15**) by nucleophilic attack of hydrogen selenide to the carbonyl group of the open chain form of **14** and subsequent reduction. We did not use xylitol itself because of its achiral C_s symmetry. We expected to obtain 1,5-anhydro-2,3,4-tri-*O*-acetyl-1-seleno-xylitol (**16**) from **15** by an intramolecular Mitsunobu reaction and subsequent acetylation (Scheme 6).

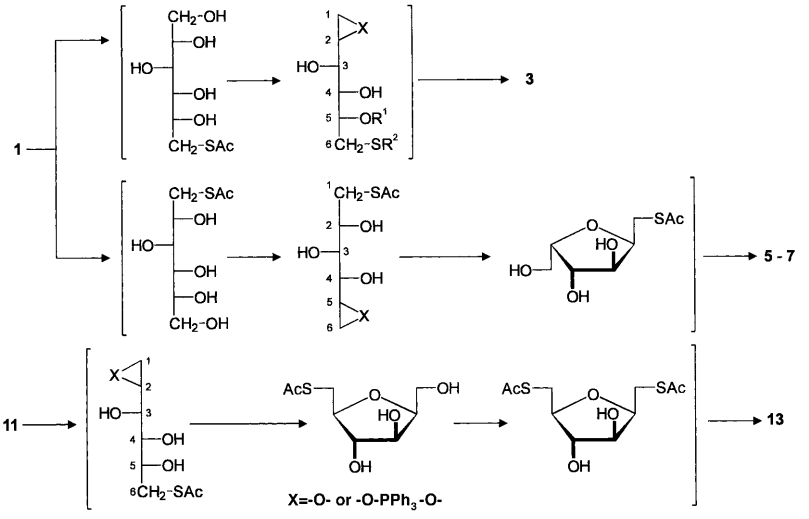
But instead of **16** we obtained 2,3,4,5-tetra-*O*-acetyl-1-*Se*-acetyl-1-seleno-D-xylitol (**17**) besides peracetylated D-xylofuranosides and D-xylopyranosides (Scheme 6). This proves that the intermediate **15** had been formed, but that an intramolecular seleno-Mitsunobu reaction obviously did not occur (Scheme 6).

3. Experimental

General procedures.—Melting points were determined by the use of an Electrothermal apparatus (values are corrected). IR spectra were measured with an ATI Mattson Genesis spectrometer. NMR spectra were recorded with Bruker AMX 400 and DRX 500 spectrometers. Chemical shifts (ppm) are related to Me_4Si (^1H and ^{13}C). Standard correlation techniques were used for assignments. Mass spectra were measured on Varian CH 7 (EI, 70 eV) and VG Analytical 70-250 S (HRMS) apparatus. Optical rotations were measured on a Perkin–Elmer Polarimeter 341. TLC was carried out on E. Merck PF_{254} foils (detection: UV light, EtOH–H_2SO_4 spray/200 °C), and column chromatography on E. Merck Kieselgel 60 (70–230 mesh). Solvents were purified and dried according to standard laboratory procedures [7]. The DFT calculation (B3LYP) was performed on a SNI SC900 calculator (R10000 processor, 194 MHz) using the GAUSSIAN 94 program [8] and the 6-31G* basis set. The calculation time was 2 days, 21 h, 48 min.

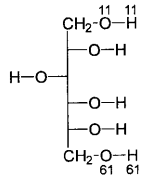
X-ray structure analysis.—The crystal data and a summary of experimental details for **8**, **5** and **12** are given in Table 2. Cell parameters were determined by least-squares refinement of the angular settings of 25 centred reflections with $\Theta = 25.6–36.2$ (**8**), 523 centred reflections with $\Theta = 1.0–25.03$ (**5**) and 125 centred reflections with $\Theta = 1.02–25.03$ (**12**). The structures were solved by direct methods using the SIR-97 [9] program, and refined by full-matrix-block least-squares on F^2 using all data and the SHELXL-97 [10] program. Hydrogen positions were obtained by difference Fourier synthesis and/or geometrical. Cremer–Pople puckering parameter calculations (Table 3) were performed with the PLATON [11] program.

Thio-Mitsunobu reaction of D-*glucitol* (**1**).— A solution of triphenylphosphine (3.45 g, 13.15 mmol) in dry pyridine (36 mL) was cooled to 0 °C. Then diisopropyl azodicarboxylate (2.5 mL, 12.86 mmol) and a cooled (0 °C) solution of **1** (1.00 g, 5.49 mmol) and purified (low temperature condensation) thioacetic acid (1.0 mL, 14.06 mmol) in dry pyridine (27 mL) were added. After the end of the reaction (30 min, TLC control) the solvent was evaporated at diminished pressure. After flash chromatography through silica gel (200 g, 8:1 EtOAc–



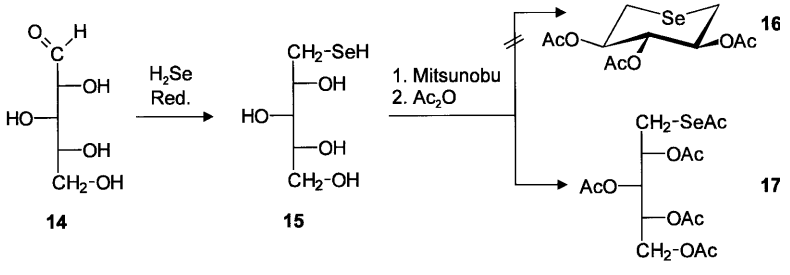
Scheme 5.

Table 1



Calculated intramolecular hydrogen bonds for **1**

Donor (D–H)	Acceptor (A)	Bond lengths (pm)			Bond angles (°)
		D–H	H···A	D···A	D–H···A
O-21–H-21	O-31	97.68	287.46	294.21	84.30
O-21–H-21	O-41	97.68	195.64	280.76	144.29
O-31–H-31	O-11	97.81	184.04	270.06	145.04
O-31–H-31	O-21	97.81	289.58	294.21	83.03
O-41–H-41	O-21	98.01	286.48	280.76	76.73
O-41–H-41	O-31	98.01	201.98	262.12	117.54
O-61–H-61	O-51	97.31	223.15	278.32	114.77



Scheme 6.

Table 2
Crystal data and structure refinement for **8**, **5** and **12**

	8	**5**	**12**
Diffractometer	CAD4 Nonius	Kappa CCD Nonius	Kappa CCD Nonius
Molecular formular	$C_{29}H_{23}N_3O_{14}S$	$C_{10}H_{16}O_5S_2$	$C_{38}H_{30}N_4O_{18}S_2$
Molecular weight (g Mol^{-1})	669.56	280.35	894.81
Temperature (K)	293(2)	293(2)	293(2)
Wavelength (Å)	1.54184, Cu K_α, graphite monochromated	0.71073, Mo K_α, graphite monochromated	0.71073, Mo K_α, graphite monochromated
Scan mode	$\theta-2\theta$ scan	rotation Φ	rotation Φ
Crystal system	orthorhombic	orthorhombic	monoclinic
Space group	$P2_12_12_1$	$P2_12_12_1$	$C2$
Unit cell dimensions			
a (Å)	10.625(1)	7.680(1)	20.488(1)
b (Å)	11.085(1)	10.918(1)	11.715(1)
c (Å)	26.066(1)	15.923(1)	10.688(1)
α (°)	90	90	90
β (°)	90	90	114.07 (10)
γ (°)	90	90	90
V (Å^3)	3070.0(4)	1335.1(2)	2342.2(3)
Z (molecules per cell)	4	4	2
D_{calcd} (g cm^{-3})	1.449	1.395	1.27
Absorption coefficient (mm^{-1})	1.611	0.405	0.191
F(000)	1384	592	988
Crystal size (mm)	$0.45\times0.42\times0.21$	$0.33\times0.21\times0.13$	$0.37\times0.28\times0.23$
θ Range for data collection (°)	3.39–69.84	2.26–25.21	2.05–25.04
Index ranges	$0\le h\le12$; $0\le k\le13$; $-31\le l\le12$	$0\le h\le9$; $0\le k\le12$; $-18\le l\le18$	$0\le h\le24$; $-12\le k\le13$; $-12\le l\le11$
Reflections collected	3773	7460	10997
Independent reflections	3545	2387	4039
Reflections with $I\ge2\sigma(I)$	3545	1905	3502
Refinement method	full-matrix-block least-squares on F^2	full-matrix-block least-squares on F^2	full-matrix-block least-squares on F^2
Function minimized	$\Sigma\, w(F_o^2-F_c^2)^2$ $w=1/[\sigma^2(F_o^2)+(0.1496P)^2+0.3413P]$ where $P=(F_o^2+2F_c^2)/3$	$\Sigma\, w(F_o^2-F_c^2)^2$ $w=1/[\sigma^2(F_o^2)+(0.0712P)^2+0.3136P]$ where $P=(F_o^2+2F_c^2)/3$	$\Sigma\, w(F_o^2-F_c^2)^2$ $w=1/[\sigma^2(F_o^2)+(0.2000P)^2+0.1000P]$ where $P=(F_o^2+2F_c^2)/3$
H-Atom refinement	difmap	geom and difmap	-
Data/restraints/parameters	3545/0/505	2387/0/195	4039/1/281
Goodness-of-fit on F^2	0.760	0.977	1.127
Final R indices [$I\ge2\sigma(I)$]	$R_1=0.0396$, $wR_2=0.1233$	$R_1=0.0477$, $wR_2=0.1117$	$R_1=0.0900$, $wR_2=0.2428$
R Indices (all data)	$R_1=0.0396$, $wR_2=0.1233$	$R_1=0.0682$, $wR_2=0.1230$	$R_1=0.0980$, $wR_2=0.2569$
Absolute structure parameter	0.01(3)	−0.12(13)	−0.04(15)
Largest difference peak and hole (e Å^{-3})	0.198 and −0.266	0.258 and −0.269	1.080 and −0.433

EtOH) a crude product (2.39 g, colourless syrup) was isolated, which still contained triphenylphosphine oxide. According to the ^{1}H NMR spectrum, the yield of 5-*O*-acetyl-1,4-anhydro-6-thio-D-glucitol (**3**) was 0.78 g (3.51 mmol, 64%). This product was immediately treated with *p*-nitrobenzoyl chloride. When the reaction was performed a second time repeated column chromatography (200 g silica gel, 3:1 EtOAc–EtOH first, then pure EtOAc) of the reaction product yielded 0.81 g of a mixture of **3** (1.39 mmol, 25%) and 3-*O*-acetyl-1,4-anhydro-6-thio-D-glucitol (**4**) (2.25 mmol, 41%) as a colourless syrup, 1,6-di-

S-acetyl-2,5-anhydro-1,6-dithio-L-iditol (**5**) (0.07 g, 0.25 mmol, 5%) as a colourless solid, and a mixture of 4-*O*-acetyl-1-*S*-acetyl-1,6-dithio-2,5-anhydro-L-iditol (**6**) and 3,4-di-*O*-acetyl-2,5-anhydro-1,6-dithio-L-iditol (**7**) (total 0.01 g, 0.04 mmol, 1%) as a colourless syrup. In $CDCl_3$ **6** gradually changes to **7**. Compound **5** was recrystallized from acetone.

5-O-*Acetyl-1,4-anhydro-6-thio*-D-*glucitol* (**3**). R_f 0.53 (EtOAc), 0.71 (8:1 EtOAc–EtOH), 0.68 (3:1 EtOAc–EtOH); IR (film): ν 3312, 2982, 2938, 2882, 1725, 1438, 1375, 1242, 1180, 1146, 1110, 1073, 1046, 969, 933, 753, 724, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.99 (ddd, 1H, H-5), 4.34 (ddd, 1H, H-2), 4.18 (dd, 1H, H-1b), 4.00 (dd, 1H, H-4), 3.95 (dd, 1H, H-3), 3.72 (dd, 1H, H-1a), 3.23 (s(b), 2H, OH-2, OH-3), 3.05 (ddd, 1H, H-6b), 2.86 (ddd, 1H, H-6a), 2.17 (s, 3H, OAc), 1.54 (dd, 1H, SH) ppm. $J_{1a,1b}$ 9.8, $J_{1a,2}$ 1.0, $J_{1b,2}$ 4.1, $J_{2,3}$ 1.1, $J_{3,4}$ 2.5, $J_{4,5}$ 8.9, $J_{5,6a}$ 7.5, $J_{5,6b}$ 2.9, $J_{6a,6b}$ 14.5, $J_{6a,SH}$ 8.5, $J_{6b,SH}$ 8.9 Hz; ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.45 (C=O), 80.35 (C-4), 76.88 (C-2), 76.06 (C-3), 73.96 (C-1), 72.48 (C-5), 26.79 (C-6), 21.02 (OAc) ppm.

3-O-*Acetyl-1,4-anhydro-6-thio*-D-*glucitol* (**4**). R_f 0.43 (EtOAc); ^1H NMR (500 MHz, $CDCl_3$): δ 5.13 (dd, 1H, H-3), 4.30 (ddd, 1H, H-2), 4.12 (dd, 1H, H-1b), 4.02 (dd, 1H, H-4), 3.78 (ddd, 1H, H-5), 3.74 (dd, 1H, H-1a), 3.44 (s(b), 2H, OH-2, OH-5), 2.94 (ddd, 1H, H-6b), 2.74 (ddd, 1H, H-6a), 2.13 (s, 3H, OAc), 1.56 (dd, 1H, SH) ppm. $J_{1a,1b}$ 9.9, $J_{1a,2}$ 1.9, $J_{1b,2}$ 4.8, $J_{2,3}$ 1.1, $J_{3,4}$ 3.3, $J_{4,5}$ 9.0, $J_{5,6a}$ 6.9, $J_{5,6b}$ 3.0, $J_{6a,6b}$ 14.0, $J_{6a,SH}$ 8.2, $J_{6b,SH}$ 9.4 Hz; ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.56 (C=O), 80.47 (C-4), 79.38 (C-3), 75.58 (C-2), 73.75 (C-1), 68.80 (C-5), 29.56 (C-6), 21.02 (OAc) ppm.

1,6-Di-S-*acetyl-2,5-anhydro-1,6-dithio*-L-*iditol* (**5**). R_f 0.70 (EtOAc), 0.20 (1:1 EtOAc–petroleum ether); mp 105 °C; $[\alpha]_D^{20}$ −14.6° (*c* 1.0, $CHCl_3$); IR (KBr): ν 3508, 3400, 2972, 2941, 2977, 1694, 1673, 1417, 1374, 1354, 1310, 1274, 1247, 1229, 1136, 1121, 1107, 1084, 1061, 1022, 1010, 953, 906, 880, 849, 809, 791, 750, 720, 649, 627, 563, 536, 491, 448, 410 cm^{-1}; ^1H NMR (400 MHz, CD_3–CO–CD_3): δ 4.26 (2H, d, OH-3), 3.95 (ddd, 2H, H-2), 3.91 (dd, 2H, H-3), 2.93 (dd, 2H, H-1b), 2.88 (dd, 2H, H-1a), 2.14 (s, 6H, SAc-1) ppm. $J_{1a,1b}$ 13.3, $J_{1a,2}$ 7.3, $J_{1b,2}$ 6.7, $J_{2,3}$ 3.0, $J_{3,OH-3}$ 4.2 Hz; ^{13}C NMR (101 MHz, CD_3–CO–CD_3): δ 207.00 (acetone), 196.37 (C=O), 81.05 (C-2), 78.27 (C-3), 30.94 (SAc), 30.33 (acetone), 27.87 (C-1), ppm; FABHRMS (mNBA) $[M^+ + 1]$: calcd 281.0517, found: 281.0517. Anal. Calcd for $C_{10}H_{16}O_5S_2$: C, 42.84; H, 5.75; S, 22.87. Found: C, 42.75; H, 5.79; S, 21.03.

4-O-*Acetyl-1*-S-*acetyl-1,6-dithio-2,5-anhydro*-L-*iditol* (**6**). R_f 0.70 (EtOAc), 0.47 (1:1 EtOAc–petroleum ether); ^1H NMR (500 MHz, $CDCl_3$): δ 5.25 (d, 1H, H-4), 4.42 (ddd, 1H, H-5), 4.09–4.12 (m, 2H, H-2, H-3), 3.28 (dd, 1H, H-1b), 3.03 (dd, 1H, H-1a), 2.74 (ddd, 1H, H-6b), 2.60 (ddd, 1H, H-6a), 2.34 (s, 3H, SAc), 2.10 (s, 3H, OAc), 1.47 (dd, 1H, SH) ppm. $J_{1a,1b}$ 13.9, $J_{1a,2}$ 5.3, $J_{1b,2}$ 8.5, $J_{4,5}$ 3.7, $J_{5,6a}$ 7.7, $J_{5,6b}$ 6.7, $J_{6a,6b}$ 13.4, $J_{6a,SH}$ 9.3, $J_{6b,SH}$ 7.9 Hz; ^1H NMR (500 MHz, C_6D_6): δ 7.17 (benzene), 5.26 (dd, 1H, H-4), 4.39 (ddd, 1H, H-5), 4.15 (ddd, 1H, H-2), 3.99 (dd, 1H, H-3), 3.33 (dd, 1H, H-1b), 3.13 (dd, 1H, H-1a), 3.10 (s(b), 1H, OH-3), 2.62 (ddd, 1H, H-6b), 2.40 (ddd, 1H, H-6a), 1.78 (s, 3H, SAc), 1.52 (s, 3H, OAc), 1.33 (dd, 1H, SH) ppm. $J_{1a,1b}$ 13.8, $J_{1a,2}$ 6.0, $J_{1b,2}$ 8.2, $J_{2,3}$ 3.3, $J_{3,4}$ 1.3, $J_{4,5}$ 3.6, $J_{5,6a}$ 7.7, $J_{5,6b}$ 6.8, $J_{6a,6b}$ 13.3, $J_{6a,SH}$ 9.8, $J_{6b,SH}$ 7.5 Hz; ^{13}C NMR (101 MHz, $CDCl_3$): δ 197.57 (thioacetyl C=O), 170.13 (acetyl C=O), 81.00 (C-5), 80.69 (C-2), 78.41 (C-4), 74.69 (C-3), 30.53 (SAc), 27.13 (C-1), 23.04 (C-6), 20.85 (OAc) ppm.

3,4-Di-O-*acetyl-2,5-anhydro-1,6-dithio*-L-*iditol* (**7**). R_f 0.70 (EtOAc), 0.47 (1:1 EtOAc–petroleum ether); ^1H NMR (500 MHz, $CDCl_3$): δ 5.35 (d, 2H, H-3), 4.32 (ddd, 2H, H-2), 2.72 (ddd, 2H, H-1b), 2.57 (ddd, 2H, H-1a), 2.14 (6H, OAc-3), 1.55 (dd, 2H, SH-1) ppm. $J_{1a,1b}$ 13.6, $J_{1a,SH-1}$ 9.3, $J_{1b,SH-1}$ 8.0, $J_{1a,2}$ 6.9, $J_{1b,2}$ 6.9, $J_{2,3}$ 3.4 Hz; ^1H NMR (500 MHz, C_6D_6): δ 7.17 (benzene), 5.35 (d, 2H, H-3),

Table 3
Cremer–Pople puckering parameters for **8** and **5**

	8	**5**
Atom sequence	O-7–C-3–C-4–C-5–C-6	O-5–C-2–C-3–C-4–C-5
Parameters (pm)	$Q(2) = 36.9(4)$	$Q(2) = 41.6(5)$
(°)	$\Phi(2) = 241.9(5)$	$\Phi(2) = 98.6(5)$
Closest pucker descriptor	twist C-6–C-4	twist C-3–C-4

4.11 (ddd, 2H, H-2), 2.52 (ddd, 2H, H-1b), 2.34 (ddd, 2H, H-1a), 1.53 (6H, OAc-3), 1.43 (dd, 2H, SH-1) ppm. $J_{1a,1b}$ 13.5, $J_{1a,SH-1}$ 9.6, $J_{1b,SH-1}$ 7.6, $J_{1a,2}$ 6.9, $J_{1b,2}$ 7.3, $J_{2,3}$ 3.4 Hz; ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.43 (C=O-3), 81.32 (C-2), 76.04 (C-3), 23.10 (C-1), 20.70 (OAc-3) ppm.

Reaction of **3** *with* p-*nitrobenzoyl chloride*.—At −18 °C, a concd solution of *p*-nitrobenzoyl chloride (1.42 g, 7.65 mmol) in CH_2Cl_2 was added to a solution of **3** (0.78 g, 3.51 mmol) and triethylamine (1.2 mL, 8.66 mmol) in CH_2Cl_2 (20 mL). After 1 h, the reaction mixture was diluted with ethyl acetate and filtered. After evaporation of the solvent, the residue was filtered through silica gel (EtOAc). Purification by repeated chromatography ($CHCl_3$) yielded **8** (1.63 g, 69%) as yellow needles and **9** (0.12 g, 7%) as a yellow solid. Compound **8** was recrystallized from acetone.

Treatment of a mixture of **3** and **4** (0.81 g, 3.64 mmol, ratio 5:8 according to a ^{1}H NMR spectrum) in pyridine (50 mL) with a concd solution of *p*-nitrobenzoyl chloride (3.47 g, 18.7 mmol) in pyridine at −18 °C gave **10** (1.02 g, 68% from **4**) as a yellow solid and **8** (0.90 g, 96.4% from **3**) as a yellow solid after aq workup, filtration over silica gel and fractionated crystallization from acetone.

5-O-*Acetyl-1,4-anhydro-2,3-di*-O-p-*nitrobenzoyl-6*-S-p-*nitrobenzoyl-6-thio*-D-*glucitol* (**8**). R_f 0.29 ($CHCl_3$), 0.37 (2:1 EtOAc–petroleum ether), 0.46 (EtOAc); mp 224 °C; $[\alpha]_D^{20}$ +55.7° (*c* 1.0, $CHCl_3$); IR (KBr): *v* 3111, 3079, 3047, 2998, 2959, 2883, 1737, 1660, 1607, 1529, 1490, 1469, 1409, 1395, 1351, 1324, 1262, 1218, 1203, 1103, 1050, 1013, 980, 959, 927, 871, 851, 783, 759, 721, 696, 657, 636, 614, 507, 475 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11–8.36 (m, 12H, ArH), 5.85 (dd, 1H, H-3), 5.56 (ddd, 1H, H-2), 5.48 (ddd, 1H, H-5), 4.59 (dd, 1H, H-1b), 4.44 (dd, 1H, H-4), 4.10 (dd, 1H, H-1a), 3.90 (dd, 1H, H-6b), 3.40 (dd, 1H, H-6a), 1.93 (s, 3H, OAc) ppm. $J_{1a,1b}$ 11.1, $J_{1a,2}$ 2.2, $J_{1b,2}$ 5.0, $J_{2,3}$ 0.9, $J_{3,4}$ 3.5, $J_{4,5}$ 9.2, $J_{5,6a}$ 6.2, $J_{5,6b}$ 3.4, $J_{6a,6b}$ 14.5 Hz; ^{13}C NMR (101 MHz, $CDCl_3$): δ 189.33 (C=O-6), 169.49 (C=O-5), 163.52, 163.33 (C=O-2, C=O-3), 151.01, 150.97, 150.71, 141.10, 134.22, 134.14 (C_q), 131.06, 128.36, 123.98, 123.76 ($C_{Ar}H$), 79.87 (C-4), 78.61 (C-2), 76.27 (C-3), 72.31 (C-1), 67.76 (C-5), 31.35 (C-6), 20.67 (OAc) ppm; FABMS (mNBA); *m/z* 670 [$M^+ + 1$]. Anal. Calcd for $C_{29}H_{23}N_3O_{14}S$: C, 52.02; H, 3.46; N, 6.28; S, 4.79. Found: C, 51.86; H, 3.32; N, 6.15; S, 4.86.

5-O-*Acetyl-1,4-anhydro-2*-O-p-*nitrobenzoyl-6*-S-p-*nitrobenzoyl-6-thio*-D-*glucitol* (**9**). R_f 0.23 (2:1 EtOAc–petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14–8.34 (m, 8H, ArH), 5.46 (dd, 1H, H-2), 5.29 (ddd, 1H, H-5), 4.48 (dd, 1H, H-1b), 4.33 (d, 1H, H-3), 4.06 (dd, 1H, H-4), 4.02 (dd, 1H, H-1a), 3.91 (dd, 1H, H-6b), 3.79 (s(b), 1H, OH), 3.44 (dd, 1H, H-6a), 2.11 (s, 3H, OAc) ppm. $J_{1a,1b}$ 10.7, $J_{1a,2}$ 1.1, $J_{1b,2}$ 4.3, $J_{2,3}$, $J_{3,4}$ 2.5, $J_{4,5}$ 8.4, $J_{5,6a}$ 7.8, $J_{5,6b}$ 3.0, $J_{6a,6b}$ 14.4 Hz; ^{13}C NMR (101 MHz, $CDCl_3$): δ 189.53 (C=O-6), 171.64 (C=O-5), 163.78 (C=O-2), 150.82, 150.64, 141.20, 134.74 (C_q), 130.90, 128.38, 123.96, 123.66 ($C_{Ar}H$), 81.58 (C-4), 80.50 (C-2), 74.02 (C-3), 71.60 (C-1), 70.01 (C-5), 31.31 (C-6), 20.95 (OAc) ppm.

3-O-*Acetyl-1,4-anhydro-2,5-di*-O-p-*nitrobenzoyl-6*-S-p-*nitrobenzoyl-6-thio*-D-*glucitol* (**10**). R_f 0.30 (2:1 EtOAc–petroleum ether); mp 80 °C; $[\alpha]_D^{20}$ +93.4 (*c* 1.0, $CHCl_3$); IR (KBr): *v* 3112, 3080, 3055, 2999, 2947, 2888, 2876, 1731, 1671, 1606, 1528, 1409, 1351, 1321, 1270, 1222, 1174, 1102, 1043, 1014, 988, 966, 921, 864, 849, 783, 759, 719, 695 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03–8.31 (m, 12H, ArH), 5.66 (ddd, 1H, H-5), 5.64 (dd, 1H, H-3), 5.43 (ddd, 1H, H-2), 4.51 (dd, 1H, H-1b), 4.49 (dd, 1H, H-4), 4.07 (dd, 1H, H-1a), 3.99 (dd, 1H, H-6b), 3.56 (dd, 1H, H-6a), 2.12 (s, 3H, OAc) ppm. $J_{1a,1b}$ 11.1, $J_{1a,2}$ 1.9, $J_{1b,2}$ 4.7, $J_{2,3}$ 1.1, $J_{3,4}$ 3.8, $J_{4,5}$ 8.6, $J_{5,6a}$ 6.8, $J_{5,6b}$ 3.3, $J_{6a,6b}$ 14.6 Hz; ^{13}C NMR (101 MHz, $CDCl_3$): δ 189.22 (C=O-6), 169.27 (C=O-3), 163.61, 163.48, (C=O-2, C=O-5), 150.95, 150.76, 150.71, 140.94, 134.67, 134.30 (C_q), 131.01, 130.80, 128.31, 123.97, 123.71, 123.62, ($C_{Ar}H$), 79.81 (C-4), 78.80 (C-2), 74.66 (C-3), 72.27 (C-1), 69.61 (C-5), 31.21 (C-6), 20.72 (OAc) ppm; FABHRMS (mNBA) [$M^+ + 1$]: calcd 670.0979, found: 670.0696. Anal. Calcd for $C_{29}H_{23}N_3O_{14}S$: C, 52.02; H, 3.46; N, 6.28; S, 4.79. Found: C, 52.37; H, 3.46; N, 6.11; S, 4.91.

Thio-Mitsunobu reaction of D-*mannitol* (**11**).—The Mitsunobu reaction of **11** (1.00 g, 5.49 mmol) was performed exactly in the same

way as described for **1**. **11** yielded a mixture of several products which were not isolated and not identified. After evaporation of the solvent and a rapid filtration over silica gel (EtOAc) the crude product (1.05 g as a yellow syrup) was dissolved in pyridine (50 mL) and treated with a concd solution of *p*-nitrobenzoyl chloride (4.5 g, 24.25 mmol) in pyridine at −18 °C. After 5 h the reaction mixture was poured on ice and extracted with $CHCl_3$. After evaporation of the solvent the residue was filtered through silica gel (EtOAc). Repeated chromatography (1:2 EtOAc–petroleum ether) yielded pure fractions of the main products **12** and **13** as yellow solids and further fractions containing **12**, **13** and at least four byproducts. Compound **12** was recrystallized from acetone.

2,5-Di-O-*acetyl-3,4-di*-O-p-*nitrobenzoyl-1,6-di*-S-p-*nitrobenzoyl-1,6-dithio*-D-*mannitol* (**12**). R_f 0.46 (2:1 EtOAc–petroleum ether); mp 128 °C; $[\alpha]_D^{20}$ + 73.4 (*c* 1.0, $CHCl_3$); IR (KBr): *v* 3112, 3079, 2923, 2853, 1748, 1735, 1674, 1606, 1528, 1491, 1406, 1370,1350, 1321, 1256, 1219, 1179, 1117, 1089, 1040, 1013, 920, 870, 849, 782, 757, 719, 696, 641 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.05–8.35 (m, 16H, ArH), 5.91–5.94 (m, 2H, H-3), 5.45–5.50 (m, 2H, H-2), 3.75 (dd, 2H, H-1b), 3.26 (dd, 2H, H-1a), 2.03 (6H, s, OAc-2) ppm. $J_{1a,1b}$ 14.6, $J_{1a,2}$ 7.3, $J_{1b,2}$ 3.4 Hz; ^{13}C NMR (101 MHz, $CDCl_3$): δ 189.21 (C=O-1), 169.75 (C=O-2), 163.82 (C=O-3), 151.04, 150.74, 140.80, 134.07 (C_q), 130.99, 128.37, 123.97, 123.92 ($C_{Ar}H$), 71.14 (C-3), 68.99 (C-2), 29.66 (C-1), 20.75 (OAc-2) ppm; FABMS (mNBA); *m/z* 895 [$M^+ + 1$]. Anal. Calcd for $C_{38}H_{30}N_4O_{18}S_2$: C, 51.01; H, 3.38; N, 6.26; S, 7.17. Found: C, 52.39; H, 3.82; N, 5.29; S, 6.57.

1,6-Di-S-*acetyl-2,5-anhydro-3,4-di*-O-p-*nitrobenzoyl-1,6-dithio*-D-*glucitol* (**13**). R_f 0.57 (2:1 EtOAc–petroleum ether); mp 57 °C; $[\alpha]_D^{20}$ − 61.4 (*c* 1.0, $CHCl_3$); IR (KBr): *v* 3112, 3080, 3055, 2995, 2928, 2869, 1730, 1693, 1607, 1528, 1411, 1349, 1320, 1264, 1172, 1102, 1014, 960, 911, 873, 847, 782, 755, 719, 627, 508 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.25–8.37 (m, 8H, ArH), 5.70 (dd, 1H, H-3), 5.39 (dd, 1H, H-4), 4.44 (ddd, 1H, H-2), 4.24 (ddd, 1H, H-5), 3.45 (dd, 1H, H-6b), 3.34 (dd, 1H, H-6a), 3.33 (dd, 1H, H-1b), 3.25 (dd, 1H, H-1a), 2.35 (s, 3H, SAc), 2.34 (s, 3H, SAc) ppm. $J_{1a,1b}$ 13.8, $J_{1a,2}$ 7.1, $J_{1b,2}$ 6.5, $J_{2,3}$ 3.8, $J_{3,4}$ 1.2, $J_{4,5}$ 3.4, $J_{5,6a}$ 6.5, $J_{5,6b}$ 6.2, $J_{6a,6b}$ 14.0 Hz; ^{13}C NMR (101 MHz, $CDCl_3$): δ 194.60, 194.50 (C=O-1, C=O-6), 163.41, 163.30, (C=O-3, C=O-4), 150.93, 150.91, 134.42, 134.26, (C_q), 131.13, 131.07, 123.82, 123.71 ($C_{Ar}H$), 82.45 (C-5), 80.96 (C-4), 79.56 (C-2), 78.04 (C-3), 31.09 (C6), 30.48 (SAc), 30.46 (SAc), 27.40 (C-1) ppm; FABHRMS (mNBA) [$M^+ + 1$]: calcd 579.0743, found: 579.0744. Anal. Calcd for $C_{24}H_{22}N_2O_{11}S_2$: C, 49.82; H, 3.83; N, 4.84; S, 11.08. Found: C, 49.58; H, 3.73; N, 4.77; S, 10.88.

2,3,4,5-Tetra-O-*acetyl-1*-Se-*acetyl-1-seleno*-D-*xylitol* (**17**).—EtOH was added dropwise to a mixture of black selenium (1.58 g, 20.01 mmol) and $NaBH_4$ (0.80 g, 21.15 mmol) under an atmosphere of nitrogen. When the reaction slowed down additional EtOH and $NaBH_4$ were added until the reaction mixture was nearly colourless. Deoxygenated HCl (20%) was added to the H_2Se solution. With a stream of nitrogen the resulting H_2Se was transferred into a flask containing a solution of D-xylose (1.00 g, 6.66 mmol) in pyridine (120 mL). This flask was connected with another flask containing an aq solution of lead acetate (10%) in order to absorb excessive H_2Se, which is extremely obnoxious and toxic! After 10 min the reaction mixture was slowly warmed. When the temperature reached 90 °C the addition of H_2Se was stopped. After cooling to rt, triphenylphosphine (1.80 g, 6.86 mmol) and diisopropyl azodicarboxylate (1.5 mL, 7.71 mmol) were added and the mixture was stirred at rt overnight. Acetic anhydride (30 ml, 317.37 mmol) was added. After 6 h of reflux the reaction mixture was poured on ice and extracted with $CHCl_3$. The resulting residue was filtered through silica gel (EtOAc) and then purified by repeated column chromatography (1:1 petroleum ether–EtOAc then 1:1 benzene–EtOAc) yielding **17** (0.49 g, 17%) as a yellow syrup.

2,3,4,5-Tetra-O-*acetyl-1*-Se-*acetyl-1-seleno*-D-*xylitol* (**17**). R_f 0.81 (EtOAc), 0.73 (1:1 EtOAc–benzene), 0.48 (1:1 EtOAc–petroleum ether); $[\alpha]_D^{20}$ − 28.4° (*c* 1.0, $CHCl_3$); IR (film): *v* 2984, 2961, 1748, 1719, 1430, 1372, 1219, 1106, 1045, 951, 859, 758 cm^{-1}; ^1H

NMR (500 MHz, $CDCl_3$): δ 5.36 (dd, 1H, H-3), 5.30 (ddd, 1H, H-4), 5.20 (ddd, 1H, H-2), 4.33 (dd, 1H, H-5b), 4.00 (dd, 1H, H-5a), 3.18 (dd, 1H, H-1b), 2.97 (dd, 1H, H-1a), 2.41 (s, 3H, SeAc), 2.12 (s, 3H, OAc), 2.11 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.06 (s, 3H, OAc) ppm. $J_{1a,1b}$ 13.1, $J_{1a,2}$ 7.6, $J_{1b,2}$ 5.3, $J_{2,3} \approx 5.3$, $J_{3,4} \approx 5.7$, $J_{4,5a}$ 6.0, $J_{4,5b}$ 4.3, $J_{5a,5b}$ 12.0 Hz; ^{1}H NMR (400 MHz, benzene-d_6): δ 5.59 (ddd, 1H, H-4), 5.57 (dd, 1H, H-3), 5.51 (ddd, 1H, H-2), 4.48 (dd, 1H, H-5b), 4.06 (dd, 1H, H-5a), 3.26 (dd, 1H, H-1b), 2.89 (dd, 1H, H-1a), 1.825 (s, 3H, Ac), 1.821 (s, 3H, Ac), 1.77 (s, 3H, Ac), 1.75 (s, 3H, Ac), 1.73 (s, 3H, Ac) ppm. $J_{1a,1b}$ 13.0, $J_{1a,2}$ 8.0, $J_{1b,2}$ 5.0, $J_{2,3} \approx 5.1$, $J_{3,4} \approx 5.1$, $J_{4,5a}$ 6.1, $J_{4,5b}$ 4.1, $J_{5a,5b}$ 11.9 Hz; ^{13}C NMR (126 MHz, $CDCl_3$): δ 195.87 (Se–C=O), 170.35, 170.04, 169.88, 169.84 (O–C=O), 70.99 (C-3), 70.42 (C-2), 69.33 (C-4), 61.88 (C-5), 34.35 (SeAc), 25.30 (C-1), 20.78 (2 OAc), 20.63 (OAc), 20.57 (OAc) ppm; ^{13}C NMR (101 MHz, benzene-d_6): δ 195.45 (Se–C=O), 169.92, 169.82, 169.59, 169.56, (O–C=O), 71.54 (C-3 or C-4), 70.73 (C-3 or C-4), 69.81 (C-2), 62.20 (C-5), 33.67 (SeAc), 25.70 (C-1), 20.41, 20.37, 20.23, 20.16 (OAc) ppm. $J_{Se,C\text{-}1}$ 66.4, $J_{Se,Me}$ 45.5 Hz.

4. Supplementary material

Full crystallographic details, excluding structure features, have been deposited with the Cambridge Crystallographic Data Centre. These data may be obtained, on request, from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Tel.: +44-1223-336408; fax +44-1223-336033; e-mail deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk). Deposition numbers CCDC 142693 (**8**), 142694 (**5**) and 142695 (**12**)).

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