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The behavior of two thiosugar thioglycosides towards oxidation[†,‡]

Éva Bozó,[a] Ádám Demeter,[a] Attila Rill[a] and János Kuszmann[b,*]

[a]*Gedeon Richter Ltd., PO Box 27, H-1475 Budapest, Hungary*
[b]*Institute for Drug Research, PO Box 82, H-1325 Budapest, Hungary*

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Abstract—Oxidation of 4-cyanophenyl 2,5-anhydro-1,6-dithio-α-D-glucoseptanoside with magnesium monoperoxyphthalate (MMPP) resulted in a mixture containing two *endo*- and two *exo*-monosulfoxides as well as two *endo-exo* bis-sulfoxides differing in the chirality of the sulfoxide groups. Besides the aforementioned six products a further *endo–exo* bis-sulfoxide isomer as well as an *exo*-sulfone was obtained via oxidation with $NaIO_4$. Oxidation of 4-nitrophenyl 1,5-dithio-β-D-arabinopyranoside with MMPP yielded only two *endo*-sulfoxides, while oxidation with $NaIO_4$ in turn led to cleavage of the carbohydrate ring. The formed dialdehyde was stabilized by cyclisation to a hemiacetal, which on further treatment with MMPP afforded an *exo*-monosulfoxide. The position of oxidation as well as the chirality of the respective sulfoxide groups was established by NMR spectroscopy and X-ray crystallography.

1. Introduction

Some aromatic thioglycosides of thiosugars in which the ring oxygen is substituted by sulfur are known orally active anti-thrombotic agents.[2] Although the exact mechanism of their action is not yet fully understood,[3] the possibility that they may act via their metabolites cannot be ruled out. As thioethers can easily undergo in vivo oxidation to sulfoxides and sulfones, we investigated the behavior of the thiosugar thioglycosides **1** and **2** towards different oxidizing agents in order to establish any structure–activity relationship of the products obtained. Both model compounds, the 4-cyanophenyl 2,5-anhydro-1,6-dithio-α-D-glucoseptanoside **1** and the 4-nitrophenyl 1,5-dithio-β-D-arabinopyranoside **2**, exhibit significant oral antithrombotic activity[4] and they represent two distinct structures. They can undergo oxidation at the *endo* and/or at the *exo* sulfur atom[§] thus resulting theoretically in 16 derivatives for both **1** and **2**, that differ in the oxidation state and/or chirality of the respective sulfur atoms (Scheme 1, **A** and **C**). Furthermore, the sugar ring itself can also be oxidized due to the presence of two and three vicinal hydroxyl groups in **1** and **2**, respectively (Scheme 1, **B** and **D**). To date only the oxidation of one related compound, that of 4-cyanophenyl 1,5-dithio-β-D-xylopyranoside has been described in the literature[5] and only a single *endo*-sulfoxide was isolated after oxidation with 3-chloroperbenzoic acid (*m*CPBA). This was in agreement with the findings of Hashimoto's group, who oxidized the α- and β-anomers of phenyl 1,5-dithio-D-glucopyranoside peracetate and established a rule,[6,7] according to which the α- anomer is oxidized predominantly at the *exo*, and the β-anomer at the *endo* sulfur atom.

2. Results and discussion

2.1. Oxidation of 4-cyanophenyl 2,5-anhydro-1,6-dithio-α-D-glucoseptanoside 1

The oxidation of the glucoseptanoside **1** with one equivalent of magnesium monoperoxyphthalate (MMPP) (Scheme 2) resulted in a mixture of six compounds **3**, **4**, **5**, **7**, **8** and **9**, as shown by HPLC analysis. They could be separated by concerted use of column chromatography and preparative HPLC. Their structure was established by NMR spectroscopy (see Section 2.3).

As shown in Table 1 the *endo*-(*R*) and *exo*-(*R*) monosulfoxides **3** and **5** were formed as the main products in

* Corresponding author. E-mail: h13757kus@ella.hu

† Orally active antithrombotic thioglycosides, Part XIV. For Part XIII, see: Ref. 1.

‡ Dedicated to Professor Andras Messmer on the occasion of his 80th birthday.

§ *endo* refers to the sulfur atom incorporated into the carbohydrate ring and *exo* to the anomeric sulfur atom.

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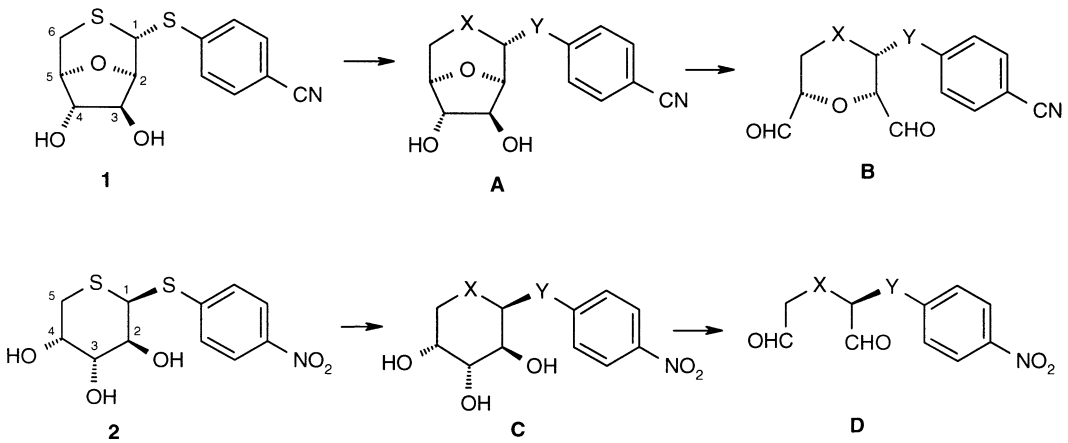


Scheme 1.

almost equal amounts (44 and 38%), while all other derivatives were only minor by-products in the oxidation reaction of **1** with MMPP. Besides the aforementioned six products, a further *endo–exo* bis-sulfoxide isomer **10** as well as a sulfone **11** could be isolated from the complex reaction mixture (Fig. 1) by using one equivalent of $NaIO_4$ for the oxidation of **1** (Scheme 2). In this case, however, the *exo*-(*R*)-sulfoxide **5** was the main product (51%) and all other derivatives were formed as by-products only (Table 1).

Scission of the sugar ring was not observed, which might be attributed to the fact that the two vicinal hydroxyl groups are in *trans*-arrangement and the ring-system is too rigid to allow complexation with the periodate anion.

While the configuration of the *endo*-sulfoxide group could be determined unambiguously [**3**, **8**, **9** *endo*-(*R*), **4**, **10** *endo*-(*S*)] by NMR spectroscopy, the configuration of the *exo*-sulfoxide group in **5** and **7** remained uncertain (see below). Therefore **5** was converted into its crystalline 3,4-di-*O*-4-nitrobenzoate derivative **6**, the X-ray analysis of which proved the *exo*-(*R*)-configuration of the sulfoxide group (Fig. 2 and Table 2). Accordingly, the parent compound **5** has *exo*-(*R*)-configuration and **7** has *exo*-(*S*)-configuration. Further oxidation of **5** resulted in **8** and **10**, respectively, while **7** was converted into **9**.

2.2. Oxidation of 4-nitrophenyl 1,5-dithio-β-D-arabinopyranoside 2

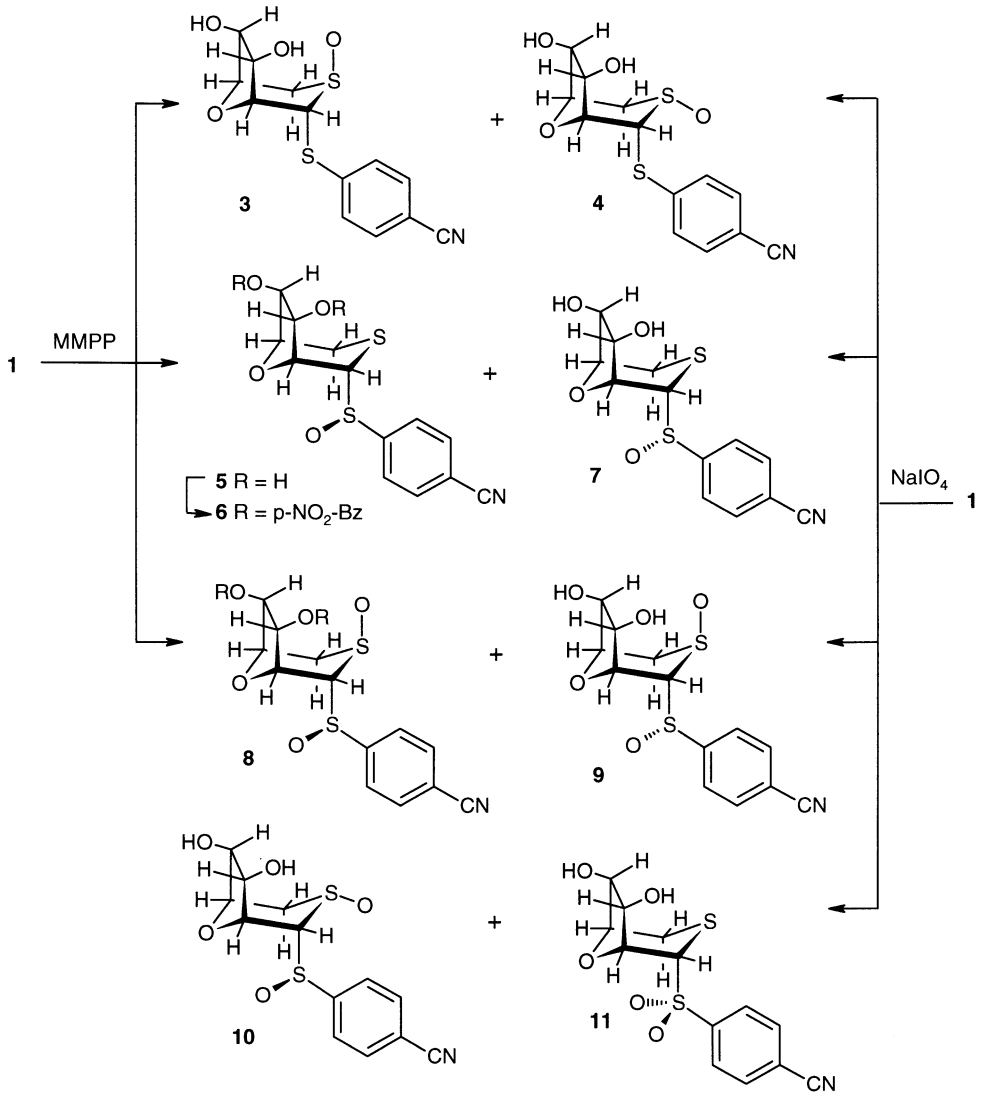
Under the same conditions the behavior of the arabinopyranoside **2** was quite different. On treatment with MMPP only the two sulfoxides, *endo*-(*R*)-**12** and the *endo*-(*S*)-isomer, **13** could be detected and isolated from the reaction mixture in yields of 30 and 33%, respectively (Scheme 3). On the other hand, when $NaIO_4$ was used as the oxidant, both sulfur atoms remained intact and only the carbohydrate moiety was oxidized affording, after workup, a single product **15**[¶] which could be isolated in high yield (84%). This means that, in accordance with the rule[8] established for the oxidation of methyl β-D-arabinopyranoside with $NaIO_4$, the thioarabinopyranoside **2** is also cleaved selectively between the *cis* related vicinal hydroxyl groups at C(3) and C(4). The first formed dialdehyde **14** rearranges via cyclisation to the isolated hemiacetal **15** which resisted further oxidation to the chain-shortened dialdehyde **D** (Scheme 1). When the bicyclic thioglycoside **15** was subjected to oxidation with MMPP, in contrast to **2** not the *endo*, but the *exo*-sulfur atom was oxidized, affording the sulfoxide **16** as the sole product.

2.3. Structure elucidation

The chemical structure of the present compounds was verified by standard high-resolution NMR methods as outlined in Section 3. The position of oxidation (*endo* and/or *exo*) as well as the chirality of the respective sulfoxide groups was established by NMR spectroscopy and X-ray crystallography. Complete ^1H and ^{13}C chemical shifts assignments as well as the measured ^1H–^1H coupling constants are given in Tables 3–5.

Comparison of the measured ^{13}C NMR chemical shifts of the starting compounds **1**, **2** and **15** and the products obtained on oxidation reveal clearly the position of oxidation (see Table 5). Oxidation of the *endo*-sulfur to sulfoxide leads to a ~13–24 ppm downfield shift of the C(1) and C(6) signals in **3** and **4** and the C(1) and C(5) signals in **12**, **13** and **16**, while a ~15–17 ppm downfield shift of the C(1) carbon as well as a ~6 ppm downfield shift of the C(1′) aromatic quaternary carbon was observed in the case of the *exo*-sulfoxides **5**, **6** and

[¶] The compound was numbered as a heterocyclic ring system.



Scheme 2.

Table 1. Yield of oxidation products obtained on treating 4-cyanophenyl 2,5-anhydro-1,6-dithio-α-D-glucoseptanoside **1** with MMPP and $NaIO_4$, respectively

Reagents	Oxidation products							
	3	**4**	**5**	**7**	**8**	**9**	**10**	**11**
endo/*exo*[a]	*R*/−	*S*/−	−/*R*	−/*S*	*R*/*R*	*R*/*S*	*S*/*R*	Sulfone
1+MMPP	44%	2%	38%	7%	1.4%	1.2%	−	−
1+$NaIO_4$	3%	1%	51%	9%	2%	1.6%	3%	1.6%

[a] Configuration of the sulfoxide group; *endo* refers to the sulfur atom incorporated into the ring and *exo* to the anomeric sulfur atom.

7. The *endo–exo* bis-sulfoxides **8**, **9** and **10** exert a combined downfield (~28–32 ppm) effect on the C(1) chemical shift, while the C(1) and C(1′) chemical shifts of the *exo*-sulfone **11** show an upfield shift as compared to the *exo*-sulfoxides **5**, **6** and **7**.

The structure of the bicyclic glycoside **15** needs to be commented on here. From the ^{1}H and ^{13}C NMR spectra it was evident that the arabinopyranoside ring of the starting material **2** is not present (comparing the chemical shifts and the coupling constants with those of **2**, **12** and **13**). The C(5)H proton and the C(5) carbon resonate at 5.92 and 100.6 ppm, respectively. Furthermore, a singlet proton signal appears at 5.74 ppm and its corresponding carbon signal at 97.4 ppm and there is only one OH proton present. These carbon chemical

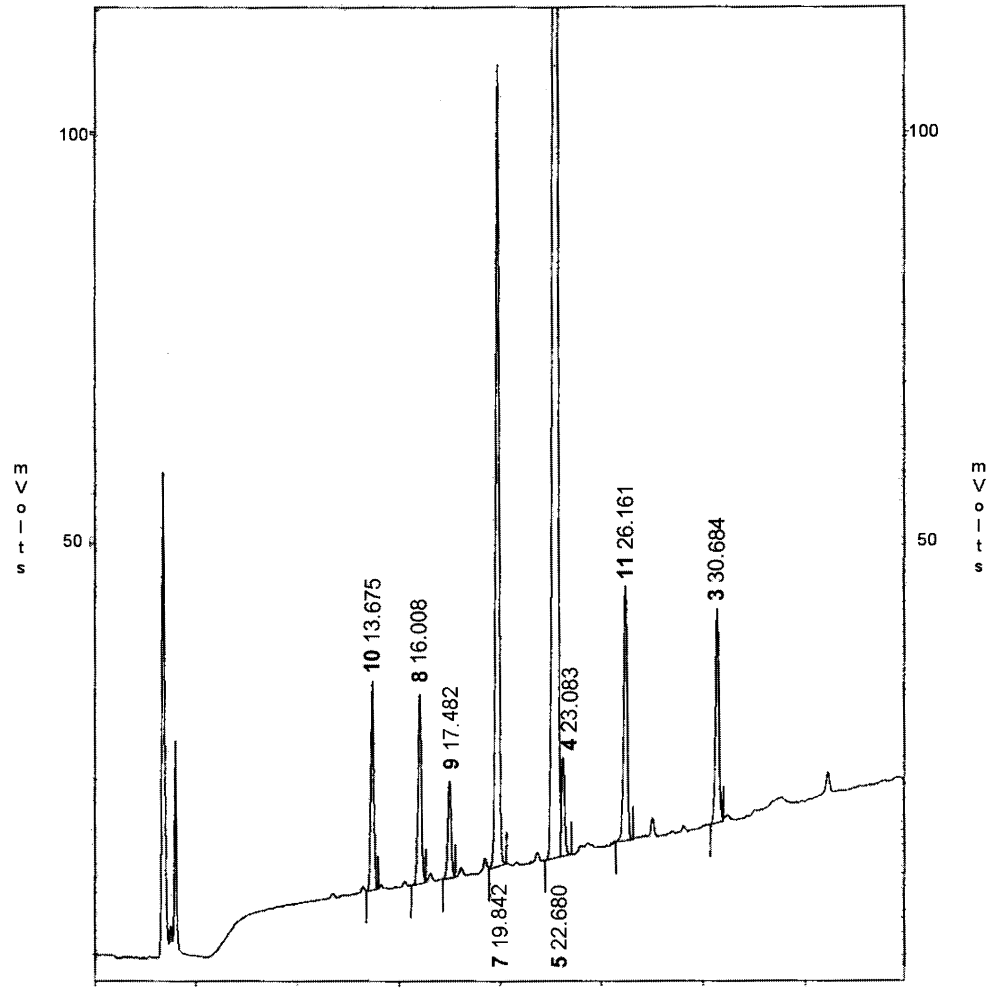


Figure 1. HPLC of the mixture obtained by oxidation of **1** with sodium periodate.

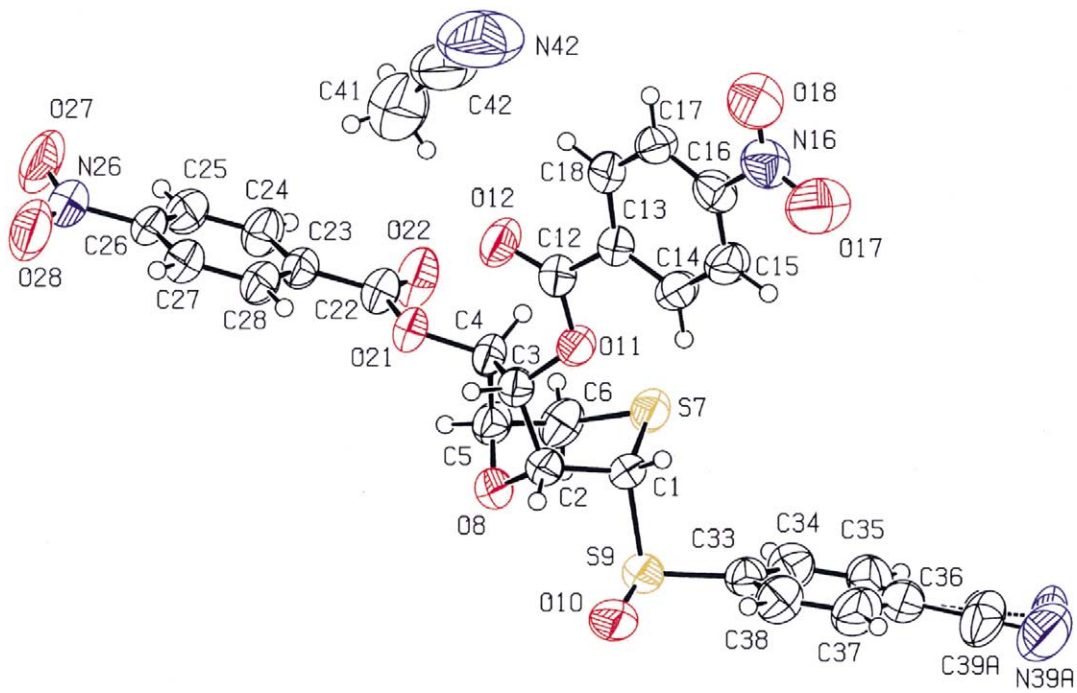


Figure 2. ORTEP plot (using the program PLATON) of **6**. Anisotropic displacement ellipsoids are represented at the 50% probability level.

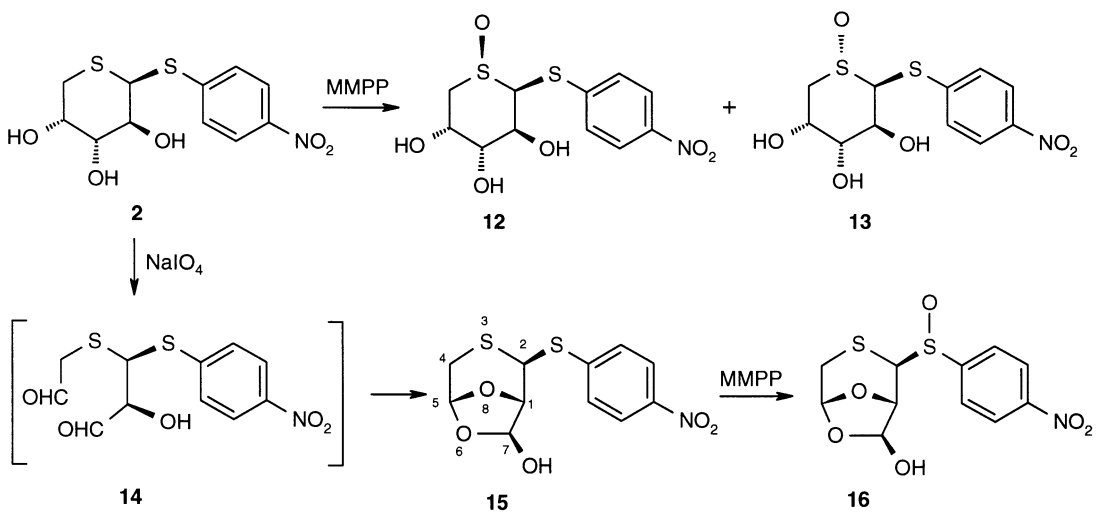
Table 2. Crystal data and structure refinement of **6**

Empirical formula	$C_{27}H_{19}N_3O_{10}S_2+C_2H_3N$
Formula weight	650.63
Temperature (K)	293(2)
Radiation and wavelength	Cu-Kα, $\lambda=1.54180$ Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	
a (Å)	12.000(3)
b (Å)	6.870(1)
c (Å)	17.915(4)
β (°)	91.07(2)
Volume (Å^3)	1476.7(5)
Z	2
Density (calculated) (Mg/m^3)	1.463
Absorption coefficient, μ (mm^{-1})	2.207
F(000)	672
Crystal colour	Colourless
Crystal description	Block
Crystal size (mm)	$0.40\times0.25\times0.04$
Absorption correction	psi-scans
Max. and min. transmission	0.9549 and 0.7939
Theta range for data collection	$4.40°\le\theta\le74.68°$
Index ranges	$-14\le h\le14$; $-8\le k\le8$; $-22\le l\le22$
Reflections collected	5976
Completeness to 2θ	0.987
Number of standard reflections	3
Decay (%)	3
Independent reflections	5976 [$R_{int}=0.0222$]
Reflections $I>2\sigma(I)$	4690
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5976/75/425
Goodness-of-fit on F^2	1.073
Final R indices [$I>2\sigma(I)$]	$R_1=0.0615$, $wR_2=0.1478$
R indices (all data)	$R_1=0.0777$, $wR_2=0.1572$
Absolute structure parameter	−0.02(2)
Max. and mean shift/esd	0.049, 0.003
Largest diff. peak and hole (e Å^{-3})	0.468 and −0.368

shifts together with the measured ^{1}H–^{13}C HMBC correlations (C(2)H–C(4), C(4)H$_\alpha$–C(2), C(4)H$_\alpha$–C(5), C(7)H–C(2), C(7)H–C(5), C(5)H–C(7) and C(1)H–C(5)) are in full agreement with the rigid bicyclic hemiacetal structure of **15**. The lack of coupling between the C(1)H and C(7)H protons (the calculated dihedral angle is close to 90° in **15**) and the observed strong NOE between the C(7)H and C(2)H protons proved the configuration at the C(7) stereogenic center.

2.3.1. Determination of the configuration of the *endo* sulfoxide group. According to literature data the sulfoxide configuration in relatively rigid six-membered rings, where the S=O bond is in either an axial or equatorial disposition, can be assigned on the basis of the following spectral features: an axial sulfoxide is associated with greater shielding of the carbon α to the sulfoxide,[9–11] and a larger geminal coupling constant of the α-methylene protons[9,11–13] as compared to an equatorial sulfoxide. Moreover, the significant deshielding of the protons that are in *syn*-axial arrangement to an axial sulfoxide can be used to assign the configuration of the S=O centre.[9,11,12,14]

Due to the overbridging oxygen between C(2) and C(5), the thioseptanoside ring of **1** adopts a considerably rigid $^{34}B^S$ boat conformation with the 4-cyano-thiophenyl group in the axial position (see Scheme 2). In this system the *endo*-sulfoxide oxygen can assume quasi-axial (β) or quasi-equatorial (α) orientation. The diagnostic greater shielding of the C(1) and C(6) carbons as well as the larger geminal $^2J_{6\alpha,6\beta}$ coupling could be safely used to distinguish between the axial isomers **3**, **8** and **9**, and the equatorial isomers **4** and **10** (see Tables 4 and 5). The observed ∼0.5–0.7 ppm upfield shift of the C(4)H proton in the equatorial sulfoxides **4** and **10** as compared to the axial isomers **3**, **8** and **9** might also be used to assign the sulfoxide configuration. This difference in shift might be attributed to the differences in shielding caused by the anisotropy of the



Scheme 3.

Table 3. ^{1}H NMR data for **1**–**16** as measured in DMSO-d_6 at 30°C at 500 MHz

Compound	Chemical shifts (ppm) relative to TMS (δ_{TMS}=0.00 ppm)												
	H-1	H-2	H-3	H-4	H-5	H-6α	H-6β	2-OH	3-OH	4-OH	H-2′	H-3′	Others
1	4.54	4.35	4.18	4.39	4.12	3.16	2.37		5.41	5.29	7.44	7.77	
2*	4.82	4.11	3.69	4.04	α 2.95 β 2.35			5.50	4.90	4.69	7.63	8.16	
3	4.84	4.90	4.29	4.60	4.14	3.41	3.09		4.95	5.52	7.70	7.85	
4	4.98	4.89	4.18	3.91	4.13	2.64	3.05		5.78	5.48	7.62	7.71	
5	3.39	4.87	4.28–4.34		4.16	3.10	2.39		5.49	5.38	8.00–8.07		
6	4.01	5.40	5.94–6.00		4.85	3.38	2.75				8.10	8.05	
7	3.70	4.78	4.12	4.24	3.93	2.73	2.22		5.51	5.27	7.92	8.01	
8	4.34	4.77	4.13	4.38	4.13	3.21	3.07		5.04	5.45	7.97	8.09	
9	4.20	5.25	4.26	4.47	4.19	3.08	3.19		4.83	5.52	8.03	8.12	
10	4.55–4.59		4.09	3.88	4.28	3.34	3.84		5.70	5.49	8.00	8.07	
11	3.97	4.91	4.19	4.24	3.97	2.50	2.26		5.65	5.33	8.13–8.17		
12*	4.83	4.27	3.79	4.40	α 3.29 β 3.10			5.39	5.20	5.05	7.73	8.14	
13*	4.46	4.22	3.76	4.04	α 3.12 β 3.37			6.00	5.37	5.06	7.81	8.14	
15	4.28	5.04		α 2.35 β 3.00	5.92						7.59	8.18	5.74 (H-7) 6.95 (7-OH)
16	4.69	4.13		α 2.37 β 3.00	6.01						8.14	8.42	5.71 (H-7) 7.08 (7-OH)

*Measured at 50°C.

Table 4. ^{1}H–^{1}H coupling constants (Hz) for **1**–**13**[a] as measured in DMSO-d_6 at 30°C at 500 MHz

	Compound												
	1	**2***	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12***	**13***
$^2J_{5\alpha,5\beta}$		12.7										13.4	11.0
$^2J_{6\alpha,6\beta}$	13.1		15.3	12.4	12.9	13.4	12.6	14.8	14.8	12.1	12.6		
$^3J_{1,2}$	2.1	2.4	2.1	2.7	1.8	2.2	1.6	1.6	1.8	N.d.	N.d.	2.7	2.0
$^3J_{2,3}$	6.9	5.6	7.2	7.2	6.5	6.9	7.0	7.6	7.2	6.9	7.3	6.0	4.5
$^3J_{3,4}$	3.0	2.5	2.0	2.1	N.d.	N.d.	3.2	2.7	2.2	2.3	3.3	N.r.	2.8
$^3J_{4,5}$	N.r.		N.r.	N.r.	N.r.	N.r.	N.r.	N.r.	N.r.	N.r.	N.r.		
$^3J_{4,5\alpha}$		10.2										9.5	12.4
$^3J_{4,5\beta}$		3.8										2.9	3.4
$^3J_{5,6\alpha}$	2.7		4.5	2.9	3.0	3.0	3.1	5.6	4.7	3.3	2.9		
$^3J_{5,6\beta}$	2.6		2.2	3.2	2.4	2.4	2.3	2.5	2.1	3.0	2.6		
$^3J_{2,2\text{-OH}}$		5.7										7.2	4.9
$^3J_{3,3\text{-OH}}$	4.9	4.3	11.8	3.9	4.6		4.9	N.r.	10.8	3.9	N.r.	4.6	N.r.
$^3J_{4,4\text{-OH}}$	4.8	5.8	4.3	4.5	4.8		4.9	N.r.	4.4	4.7	N.r.	5.4	N.r.
$^4J_{1,6\beta}$	1.1		2.2	1.9	0.7	N.r.	1.0	1.5	1.9	1.1	N.r.		
$^4J_{2,5}$	0.8		~0.5	0.8	N.r.	N.r.	0.8	N.d.	~0.6	0.8	N.d.		
$^4J_{3,5}$	0.8		1.2	0.8	0.9	0.8	0.8	N.d.	1.1	0.9	N.r.		
$^4J_{1,5\alpha}$		N.r.										1.3	N.r.
$^4J_{3,5\beta}$		N.r.										0.9	0.9
$^5J_{2,6\beta}$	0.9		1.1	0.8	1.1	0.9	N.r.	N.r.	1.1	1.1	1.1		

[a] For coupling constants of **15** and **16** see Section 3.
*Measured at 50°C.
N.r.—not resolved.
N.d.—not determined.

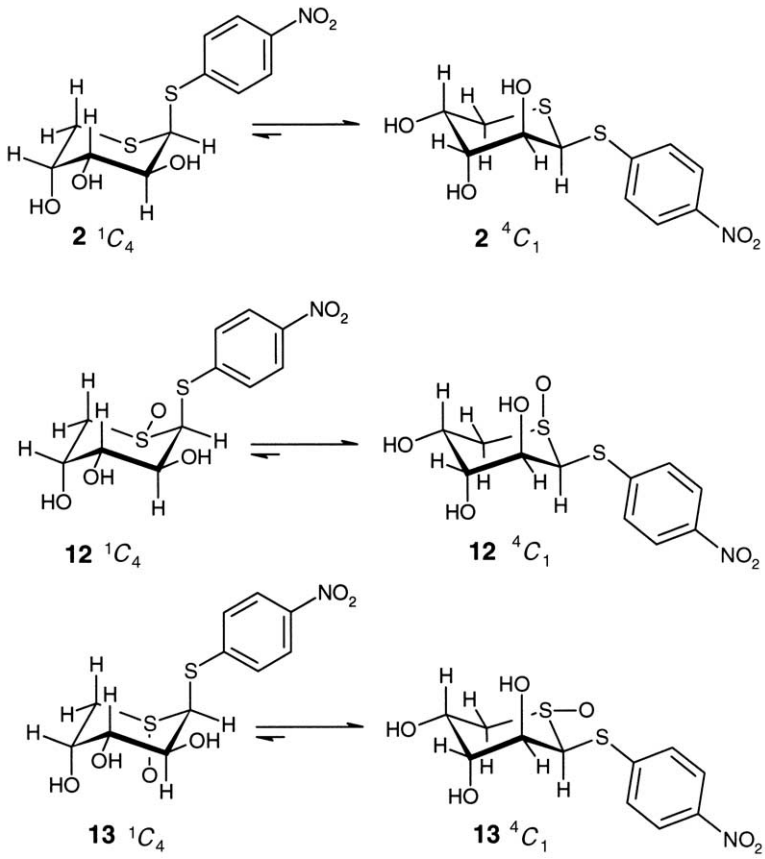
sulfoxide group. One conspicuous conformational feature of the axial isomers is the observed intramolecular H-bond between the *endo* sulfoxide oxygen and the C(3)-hydroxyl proton (3-OH···O=S). This is reflected in the large (~11 Hz) $^3J_{3,3OH}$ vicinal coupling constant, indicating a predominantly *trans*-arrangement of the C(3)OH and C(3)H protons as well as in the observed strong C(3)OH–C(1)H and C(3)OH–C(4)H NOE interactions.

The measured vicinal coupling constants (see Table 4) indicate that the arabinopyranosides **2**, **12** and **13** exist

Table 5. ^{13}C NMR data for **1**–**16** as measured in DMSO-d_6 at 30°C at 125 MHz

Compound	Chemical shifts (ppm) relative to TMS ($\delta_{TMS}=0.00$ ppm)											
	C-1	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	C-3′	C-4′	CN	Others
1	44.2	80.2	81.5	79.6	81.5	26.6	143.1	128.3	132.5	107.9	118.6	
2[a]	48.8	73.3	72.3	65.7	29.2		146.1	127.2	123.9	144.8		
3	57.7	78.6	82.4	78.2	79.0	43.2	139.8	128.9	132.9	109.4	118.3	
4	65.0	81.0	80.3	79.2	81.6	50.3	143.3	129.1	132.1	108.1	118.6	
5	60.0	74.1	80.3	80.5	80.9	26.7	149.4	127.0	132.4	114.0	118.0	
6	59.5	73.8	79.2	82.8	78.7	26.7	148.9	128.1	132.9	114.6	118.5	
7	60.8	76.0	80.7	80.5	81.4	27.3	149.1	126.7	132.9	114.0	118.6	
8	75.8	73.4	81.1	79.8	79.1	48.6	146.9	126.8	133.6	115.0	118.4	
9	72.9	78.0	82.0	79.3	79.1	48.8	148.2	126.2	133.6	114.6	118.4	
10	72.3	75.9	79.9	79.9	81.5	52.2	149.8	126.5	133.0	113.5	118.1	
11	58.0	75.3	80.0	79.5	80.8	26.2	141.5	130.4	132.9	116.4	117.5	
12[a]	62.5	73.8	71.8	60.5	47.9		144.5	128.8	123.6	145.6		
13[a]	70.7	74.6	71.3	62.5	51.0		145.4	129.1	123.6	145.7		
15	81.3	44.5		28.5	100.6		145.2	128.2	123.9	145.2		97.4 (C-7)
16	76.0	59.4		28.4	100.3		150.4	127.7	123.6	149.5		96.9 (C-7)

[a] Measured at 50°C.



Scheme 4.

predominantly in the $^4C_1$ conformation (see Scheme 4) with the bulky 4-nitro-thiophenyl group oriented equatorially. It should be noted that **12** exhibited relatively broad ^1H resonances at 30°C (the signals were beyond the coalescence point at this temperature) due to conformational exchange that is fast on the NMR chemical shift timescale, as discussed below. Therefore, the NMR analysis of **12** (as well as **2** and **13**) was accomplished at 50°C where the ^1H signals became sharper.

In agreement with literature data, the ^{13}C chemical shifts of C(1) and C(5) are smaller, and the geminal $^2J_{5\alpha,5\beta}$ coupling is larger (see Tables 4 and 5) for **12** (axial sulfoxide) as compared to **13** (equatorial sulfoxide). The

observed downfield shift of C(4)H in **12** relative to either **2** or **13** indicated the operation of the *syn*-axial effect. The measured 5.2 ppm **12** and 3.2 ppm **13** upfield shift of C(4) as compared to that of **2** can be attributed to the γ-*gauche* and γ-*anti* effect of the sulfoxide oxygen in the $^4C_1$ conformation. It is interesting to note that the presence of the sulfoxide tends to increase long-range couplings: W-coupling between C(3)H and C(5)H_β in **12** and **13** as well as a long-range coupling between C(1)H and C(5)H_α in **12** can be detected (see Table 4). These couplings are absent in the starting **2**.

The observed conformational exchange in **12** might be attributed to a $_4C^1 \leftrightarrow {}^4C_1$ equilibrium that is moderately fast on the NMR chemical shift timescale. In the $^1C_4$ conformation the bulkiest 4-nitro-thiophenyl group (as well as the C(4)OH group) assumes the unfavorable axial orientation, while the equatorial position of the 4-nitro-thiophenyl group in the $^4C_1$ conformation comes at the cost of three axial substituents (S=O, C(2)OH, C(3)OH). Although in the $^4C_1$ conformation there is an unfavorable 1,3-diaxial steric interaction between the oxygen of the *S*-oxide and the C(2)OH group, this conformation could be stabilized by C(2)OH···O=S hydrogen bonding. In a fully H-bonded structure a value of ~11 Hz would be expected with vicinal $^3J_{2,2\text{-OH}}$ coupling (see below). The observed intermediate value (7.2 Hz) in **12** as compared to the equatorial sulfoxide **13** (4.9 Hz) can be rationalized in terms of the proposed H-bonded $^4C_1$ conformation and the $^1C_4 \leftrightarrow {}^4C_1$ equilibrium that is fast on the NMR chemical shift timescale. In the case of **2** and **13** we did not observe spectral effects (minor resonances, conspicuous line-broadening or NOE effects), consequently the $^1C_4 \leftrightarrow {}^4C_1$ equilibrium is shifted toward the $^4C_1$ form.

From **13** a single crystal suitable for X-ray crystallographic analysis could be grown. The X-ray data showed that in the solid phase **13** exists in the $^4C_1$ conformation (Fig. 3 and Table 6) and the sulfoxide oxygen is equatorial in agreement with the NMR data.

2.3.2. Determination of the *exo*-sulfoxide configuration. In contrast to the *endo*-sulfoxide, the configuration of the *exo*-sulfoxide could not be established by NMR. Therefore X-ray crystallographic analysis of **6** was completed (Fig. 2) revealing the (*R*)-configuration of the sulfoxide group. Accordingly the same configuration holds for the parent compound **5**, consequently the other *endo* sulfoxide must have (*S*)-configuration. The ~2 and 5 ppm upfield shift of the C(2) carbon observed for the *exo*-(*R*)-sulfoxides **5** and **8** as compared with the *exo*-(*S*)-sulfoxides **7** and **9** (see Table 5) seems to be diagnostic of the sulfoxide configuration.

2.4. Conclusion

The rules postulated in the literature[6,7] for the site of the oxidation of thiosugar thioglycosides are certainly not generally valid. Contrary to their predictions the α-glycoside **1** gave predominantly the *endo*-sulfoxides, irrespective of the oxidising agent (MMPP or $NaIO_4$), whereas the β-glycoside **2** afforded exclusively *exo*-sulfoxides in the case of MMPP and the ring scission product in the presence of $NaIO_4$.

2.5. Biological results

The oral antithrombotic activity of **1**, **2**, **3**, **5**, **12**, **13**, **15** and **16** was determined on rats using Pescador's model.[15] All compounds were administered orally 3 h before ligation.

From the data listed in Table 2 it can be seen that the biological activity of the oxidation products depend on both the location (*endo*/*exo*) as well as the chirality (*R* or *S*) of the sulfoxide groups but no generally valid structure–activity relationship could be established. Oxidative cleavage of the sugar ring is accompanied by a decrease in activity (compare **15** and **16** to the parent compound **2**) (Table 7).

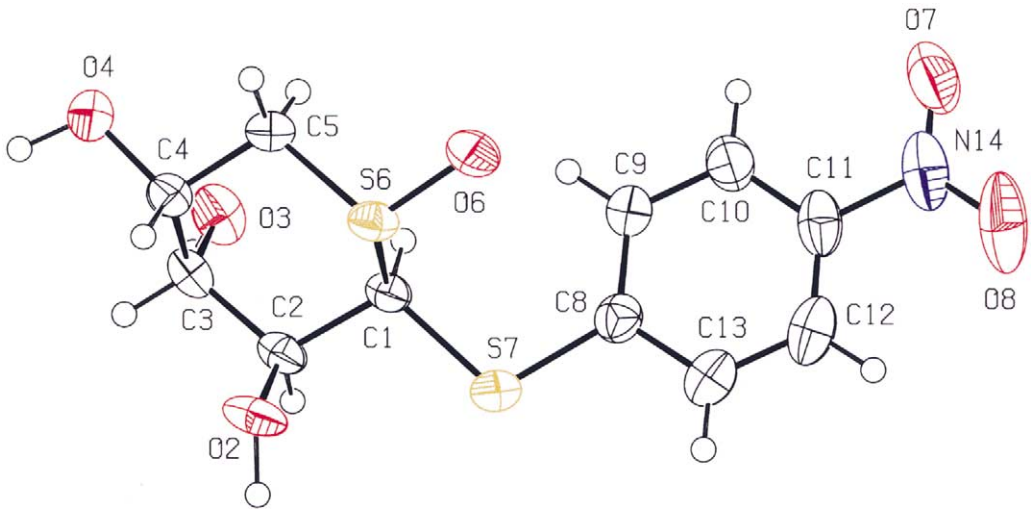


Figure 3. ORTEP plot (using the program PLATON) of **13**. Anisotropic displacement ellipsoids are represented at the 50% probability level.

Table 6. Crystal data and structure refinement of **13**

Empirical formula	$C_{11}H_{13}NO_6S_2$
Formula weight	319.34
Temperature (K)	293(2)
Radiation and wavelength	Mo-Kα, $\lambda = 0.71073$ Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	
a (Å)	8.932(1)
b (Å)	6.621(1)
c (Å)	11.556(1)
β (°)	101.87(1)
Volume (Å^3)	668.79(14)
Z	2
Density (calculated) (Mg/m^3)	1.586
Absorption coefficient, μ (mm^{-1})	0.423
F(000)	332
Crystal colour	Yellow
Crystal description	Prism
Crystal size (mm)	$0.40 \times 0.20 \times 0.20$
Absorption correction	psi-scan
Max. and min. transmission	0.9826 and 0.9593
Theta range for data collection	$2.33° \leq \theta \leq 34.97°$
Index ranges	$-14 \leq h \leq 14$; $-10 \leq k \leq 10$; $-18 \leq l \leq 18$
Reflections collected	5884
Completeness to 2θ	1
Number of standard reflections	3
Decay (%)	10.00
Independent reflections	5884 [$R_{int} = 0.0133$]
Reflections $I > 2\sigma(I)$	4500
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5884/1/181
Goodness-of-fit on F^2	1.04
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0341$, $wR_2 = 0.0815$
R indices (all data)	$R_1 = 0.0540$, $wR_2 = 0.0864$
Absolute structure parameter	0.02(4)
Max. and mean shift/esd	0.001, 0.000
Largest diff. peak and hole (e Å^{-3})	0.281 and −0.185

3. Experimental

3.1. General methods

Organic solutions were dried over $MgSO_4$ and concentrated under diminished pressure at or below 40°C. TLC: Merck precoated silica gel 60 F_{254} plates, with EtOAc (A), EtOAc–EtOH (B, 9:1), $CHCl_3$–MeOH (C, 9:1) and toluene–acetone (D, 2:1) mixtures; detection by spraying the plates with a 0.02 M solution of I_2 and a 0.30 M solution of KI in 10% aq. H_2SO_4 solution followed by heating at ca. 200°C. For column chromatography Kieselgel 60 was used. Melting points are uncorrected. Analytical HPLC was carried out on a SHIMADZU instrument, using WATERS Symmetry-Shield RP-18 250×4.6 mm S-5 μm column, and the following eluents: eluent A: 0.1% TFA in water and B: 0.1% TFA in 80% aq. acetonitrile over 35 min with a gradient of 5–40% B in A. Preparative HPLC was carried out on a SHIMADZU instrument, using a WHATMAN Partisil M20 10/50 ODS-3; 22 mm I.D., 10 μm, 100 Å column, eluent 0.1% TFA in water and 0.1% TFA in 80% aq acetonitrile. Optical rotations were determined at 20°C. The NMR spectra were recorded on a Varian *INOVA*™ spectrometer operating at 500 MHz (^{1}H) and 125 MHz (^{13}C) by using a Varian 5-mm ^{1}H{^{13}C/^{15}N} PFG Indirect NMR™ probe. ^{1}H and ^{13}C NMR chemical shifts are given relative to TMS ($\delta_{TMS} = 0.00$ ppm), as measured in DMSO-d_6 at 30°C. Long range ^{1}H–^{1}H coupling constants were determined from the resolution enhanced (sinebell apodization) ^{1}H NMR spectrum. ^{1}H and ^{13}C NMR assignments were straightforward by a concerted use of standard high-field one- and two-dimensional (2D) NMR methods: 1D DPFGSE-NOE (selective excitation by I-Burp2 shaped pulses) and 2D ^{1}H–^{1}H as well as ^{13}C–^{1}H shift correlations (PFG-DQFCOSY, PFG-HSQC, PFG-HMBC). The obtained scalar and NOE connectivities provided abundant information to ensure unambiguous spectral assignments.

3.2. Reaction of 1 with magnesium monoperoxyphthalate (MMPP)

To a solution of **1**[16] (1.7 g, 5.75 mmol) in ethanol (170 mL) was added a solution of MMPP (1.9 g, 3.8 mmol) in water (20 mL) and the mixture was stirred at room temperature for 1 h. Then the reaction mixture was concentrated and the residue was submitted to column chromatography (solvent A, then B). Concentration of the first fraction gave 4-cyanophenyl 2,5-anhydro-1,6-dithio-α-D-glucoseptanoside (6*R*)-*S*-oxide (**3**, 0.79 g, 44%): mp 212–215°C (EtOAc); $[\alpha]_D$ +143 (*c* 0.5, MeOH); R_f 0.6 (solvent B); anal. calcd for $C_{13}H_{13}NO_4S_2$: C, 50.15; H, 4.21; N, 4.50; S, 20.59. Found: C, 50.22; H, 4.18; N, 4.63; S, 20.67%.

Concentration of the second fraction and subsequent recrystallization of the residue from acetone gave 4-cyanophenyl 2,5-anhydro-1,6-dithio-α-D-glucoseptanoside (1*R*)-*S*-oxide (**5**, 0.68 g, 38%): mp 172–174°C (acetone); $[\alpha]_D$ +141 (*c* 0.5, MeOH); R_f 0.45 (solvent B); anal. calcd for $C_{13}H_{13}NO_4S_2$: C, 50.15; H, 4.21; N, 4.50; S, 20.59. Found: C, 50.06; H, 4.28; N, 4.61; S, 20.55%.

Table 7. Oral antithrombotic activity of **1**, **2**, **3**, **5**, **12**, and **13** in rats using Pescador's model[15]

Compound	**1**	**2**	**3**	**5**	**12**	**13**	**15**	**16**
S-Oxide[a]	–	–	*endo* (*R*)	*exo* (*R*)	*endo* (*R*)	*endo* (*S*)	–	*exo* (?)
Inhibition[b] (%)	37	43	25	47	43	27	34	20

[a] Location and chirality of the sulfoxide group.
[b] Inhibition % at an oral dose of 2 mg/kg.

The mother liquor was concentrated and separated by HPLC (WHATMAN Partisil M20 10/50 ODS-3; 22 mm I.D., 10 μm, 100 Å, eluent 0.1% TFA in water and 0.1% TFA in 80% aq. acetonitrile). Concentration of the first fraction gave 4-cyanophenyl 2,5-anhydro-1,6-dithio-α-D-glucoseptanoside (1*R*)-*S*-oxide (6*R*)-*S*-oxide (**8**, 26 mg, 1.4%): mp 183–186°C (ether); $[\alpha]_D$ −114 (*c* 0.39, pyridine); R_f 0.4 (solvent B); anal. calcd for $C_{13}H_{13}NO_5S_2$: C, 47.70; H, 4.00; N, 4.28; S, 19.59. Found: C, 47.82; H, 4.08; N, 4.33; S, 19.67%.

Concentration of the second fraction gave 4-cyanophenyl 2,5-anhydro-1,6-dithio-α-D-glucoseptanoside (1*S*)-*S*-oxide (6*R*)-*S*-oxide (**9**, 23 mg, 1.2%): mp 158–161°C (ether); $[\alpha]_D$ +125 (*c* 0.26, pyridine); R_f 0.45 (solvent B); anal. calcd for $C_{13}H_{13}NO_5S_2$: C, 47.70; H, 4.00; N, 4.28; S, 19.59. Found: C, 47.65; H, 4.13; N, 4.22; S, 19.50%.

Concentration of the third fraction gave 4-cyanophenyl 2,5-anhydro-1,6-dithio-α-D-glucoseptanoside (1*S*)-*S*-oxide (**7**, 125 mg, 7%): mp 87–91°C (ether); $[\alpha]_D$ +311 (*c* 0.35, MeOH); R_f 0.4 (solvent B); anal. calcd for $C_{13}H_{13}NO_4S_2$: C, 50.15; H, 4.21; N, 4.50; S, 20.59. Found: C, 50.11; H, 4.13; N, 4.58; S, 20.63%.

Concentration of the fourth fraction gave 4-cyanophenyl 2,5-anhydro-1,6-dithio-α-D-glucoseptanoside (6*S*)-*S*-oxide (**4**, 35 mg, 2%): mp 189–193°C (ether); $[\alpha]_D$ +468 (*c* 0.3, pyridine); R_f 0.3 (solvent B); anal. calcd for $C_{13}H_{13}NO_4S_2$: C, 50.15; H, 4.21; N, 4.50; S, 20.59. Found: C, 50.19; H, 4.17; N, 4.55; S, 20.54%.

3.3. Reaction of 5 with magnesium monoperoxyphthalate (MMPP)

To a solution of **5** (0.31 g, 1 mmol) in ethanol (30 mL) was added a solution of MMPP (0.5 g, 1 mmol) in water (6 mL) and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated and the residue was submitted to column chromatography (solvent B). Concentration of the first fraction gave **8** (170 mg, 52%): identical to that obtained above.

Concentration of the second fraction gave **10** (110 mg, 34%): identical to that obtained above.

3.4. Reaction of 7 with magnesium monoperoxyphthalate (MMPP)

To a solution of **7** (50 mg, 0.16 mmol) in ethanol (10 mL) was added a solution of MMPP (80 mg, 0.16 mmol) in water (1 mL) and the mixture was stirred at room temperature overnight. Then the reaction mixture was concentrated and the residue was submitted to column chromatography (solvent B) to give **9** (33 mg, 63%): identical to that obtained above.

3.5. Reaction of 1 with sodium periodate

To a solution of $NaIO_4$ (1.15 g, 5.4 mmol) in water (35 mL) was added a solution of **1** (1.45 g, 4.9 mmol) in acetone (30 mL) and the mixture was stirred at room temperature for 1 h. The reaction mixture was filtered, the filtrate was concentrated and the residue was separated by HPLC. Concentration of the first fraction gave 4-cyanophenyl 2,5-anhydro-1,6-dithio-α-D-glucoseptanoside (1*R*)-*S*-oxide (6*S*)-*S*-oxide (**10**, 50 mg, 3%): mp 200–202°C (ether); $[\alpha]_D$ −7 (*c* 0.5, pyridine); R_f 0.25 (solvent B); anal. calcd for $C_{13}H_{13}NO_5S_2$: C, 47.70; H, 4.00; N, 4.28; S, 19.59. Found: C, 47.78; H, 4.12; N, 4.35; S, 19.63%.

Concentration of the subsequent fractions gave **8** (39 mg, 2%), **9** (26 mg, 1.6%), **7** (138 mg, 9%), **5** (780 mg, 51%) and **4** (17 mg, 1%): all of them identical to those mentioned above.

Concentration of the seventh fraction gave 4-cyanophenyl 2,5-anhydro-1,6-dithio-α-D-glucoseptanoside 1-*S*-dioxide (**11**, 26 mg, 1.6%) as an oil: $[\alpha]_D$ +98.5 (*c* 0.26, MeOH); R_f 0.6 (solvent B); anal. calcd for $C_{13}H_{13}NO_5S_2$: C, 47.70; H, 4.00; N, 4.28; S, 19.59. Found: C, 47.82; H, 4.07; N, 4.35; S, 19.54%.

Concentration of the eighth fraction gave **3** (46 mg, 3%): identical with the one prepared above.

3.6. 4-Cyanophenyl 2,5-anhydro-3,4-di-*O*-(4-nitrobenzoyl)-1,6-dithio-α-D-glucoseptanoside (1*R*)-*S*-oxide 6

A mixture of **5** (0.36 g, 1.16 mmol), pyridine (60 mL) and 4-nitrobenzoyl chloride (3.65 g, 20 mmol) was stirred at 80°C for 8 h, then cooled to room temperature and poured into ice-water. The precipitated crystals were filtered off, washed with water and recrystallized from acetonitrile to give **6** (0.58 g, 82%); mp 172–175°C (acetonitrile); $[\alpha]_D$ −45 (*c* 1, $CHCl_3$); R_f 0.7 (solvent C); anal. calcd for $C_{27}H_{19}N_3O_{10}S_2$: C, 53.20; H, 3.14; N, 6.89; S, 10.52. Found: C, 53.27; H, 3.12; N, 6.80; S, 10.61%.

3.7. Reaction of 2 with magnesium monoperoxyphthalate (MMPP)

To a solution of **2**[17] (1.3 g, 4.3 mmol) in ethanol (210 mL) was added a solution of MMPP (1.44 g, 2.9 mmol) in water (15 mL) and the mixture was stirred at room temperature for 1 h. Then it was concentrated and water (30 mL) was added to the residue. The precipitated crystals were filtered off and washed with water to give 4-nitrophenyl 1,5-dithio-β-D-arabinopyranoside (5*R*)-*S*-oxide (**12**, 410 mg, 30%): mp 221–223°C (water); $[\alpha]_D$ −339 (*c* 0.5, pyridine); R_f 0.4 (solvent C); anal. calcd for $C_{11}H_{13}NO_6S_2$: C, 41.37; H, 4.10; N, 4.39; S, 20.08. Found: C, 41.29; H, 4.17; N, 4.33; S, 20.17%.

The filtrate was concentrated and the residue was submitted to column chromatography (solvent C) to give 4-nitrophenyl 1,5-dithio-β-D-arabinopyranoside (5*S*)-*S*-oxide (**13**, 450 mg, 33%): mp 176–178°C (MeOH); $[\alpha]_D$ +131 (*c* 0.5, MeOH); R_f 0.3 (solvent C); anal. calcd for $C_{11}H_{13}NO_6S_2$: C, 41.37; H, 4.10; N, 4.39; S, 20.08. Found: C, 41.43; H, 4.18; N, 4.45; S, 20.01%.

3.8. Reaction of 2 with sodium periodate

To a solution of $NaIO_4$ (1.15 g, 5.4 mmol) in water (35 mL) a solution of **2** (1.5 g, 5 mmol) in acetone (30 mL) was added and the mixture was stirred at room temperature for 1 h. Then the reaction mixture was filtered, the filtrate was concentrated and water (30 mL) was added to the residue. The precipitated crystals were filtered off and washed with water to give (1*S*,2*S*,5*R*,7*S*)-7-hydroxy-2-(4-nitrophenylthio)-6,8-dioxa-3-thia-bicyclo[3,2,1]octane (**15**, 1.25 g, 84%): mp 127–130°C (water); $[\alpha]_D$ −312 (*c* 1, MeOH); R_f 0.7 (solvent C); NMR coupling constants: $^2J_{4\alpha,4\beta}$ 13.4, $^3J_{1,2}$ 2.4, $^3J_{4\alpha,5}$ 2.5, $^3J_{4\beta,5}$ 1.1, $^4J_{2,4\alpha}$ 1.0, $^5J_{2,5}$ 1.2, $^5J_{1,4\alpha}$ 0.9 Hz. Anal. calcd for $C_{11}H_{11}NO_5S_2$: C, 43.84; H, 3.68; N, 4.65; S, 21.28. Found: C, 43.90; H, 3.73; N, 4.55; S, 21.32%.

3.9. Reaction of 15 with magnesium monoperoxyphthalate

To a solution of **15** (0.90 g, 3 mmol) in EtOH (180 mL) a solution of MMPP (1.0 g, 2 mmol) in water (10 mL) was added and the mixture was stirred at room temperature for 1 h. Then the reaction mixture was concentrated and the residue was submitted to column chromatography (solvent D) to give (1*S*,2*S*,5*R*,7*S*)-7-hydroxy-2-(4-nitrophenylsulfinyl)-6,8-dioxa-3-thia-bicyclo[3,2,1]octane (**16**, 0.5 g, 53%): mp 141–143°C (ether); $[\alpha]_D$ −78 (*c* 0.5, MeOH); R_f 0.4 (solvent D); NMR coupling constants: $^2J_{4\alpha,4\beta}$ 13.3, $^3J_{1,2}$ 2.3, $^3J_{4\alpha,5}$ 2.3, $^3J_{4\beta,5}$ 1.2, $^3J_{7,7\text{-OH}}$ 4.7, $^4J_{2,4\alpha}$ 0.8, $^5J_{2,5}$ 1.3, $^5J_{1,4\alpha}$ 0.8 Hz. Anal. calcd for $C_{11}H_{11}NO_6S_2$: C, 41.64; H, 3.49; N, 4.41; S, 20.21. Found: C, 41.43; H, 3.48; N, 4.20; S, 20.25%.

Crystallographic data (excluding structure factors) for the structures **6** and **13** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 175687 and CCDC 175688, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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