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Synthesis of 4-cyanophenyl 2-deoxy-1,5-dithio-β-D-*threo*-pentopyranoside [1,2,3]

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Abstract

2,3,4-Tri-*O*-acetyl-5-thio-α-D-xylopyranosyl bromide was converted with zinc in the presence of 4-picoline into 3,4-di-*O*-acetyl-1,5-anhydro-5-thio-D-*threo*-pent-1-enitol **5**. Treatment of **5** with *N*-iodosuccinimide–water in acetonitrile afforded a mixture which gave, after reduction with sodium borohydride–nickel chloride and subsequent acetylation, only 1,3,4-tri-*O*-acetyl-2,5-anhydro-5-thio-D-lyxitol. Deacetylation and subsequent benzoylation of **5** gave 3,4-di-*O*-benzoyl-1,5-anhydro-5-thio-D-*threo*-pent-1-enitol, the hydrogen bromide addition products of which were treated with sodium 4-cyanobenzenethiolate to give the anomeric mixture of the corresponding thioglycosides in low yield with an α,β-ratio of 3:7. When the mixture of the hydrogen bromide addition products was converted with silver acetate into their 1-*O*-acetates and condensation with 4-cyanobenzenethiol was performed in the presence of trimethylsilyl triflate, the thioglycosides were obtained in high yield with an α,β-ratio of 15:85. Deacetylation of this mixture afforded the title compound which showed high oral antithrombotic activity in rats. Conversion of methyl 2-deoxy-5-thio-D-*threo*-pentofuranoside into 2-deoxy-5-thio-D-*threo*-pentopyranose triacetate could be carried out in low yield only. Structures, including the conformation of the anomeric acetates and the thioglycosides, were determined by NMR spectroscopy. Because of the anomeric effect of the acetoxy group, the α-anomers are in the $^4C_1$ conformation and the β-anomers in the $^1C_4$. Both anomeric thioglycosides were present in their $^4C_1$ conformation.

Keywords: 2-Deoxy-5-thio-D-*threo*-pentose; 5-Thio-D-xylal derivatives; Glycosidation reactions; Thioglycosides; Transannular participation of the sulfur atom; Oral antithrombotic activity

1. Introduction

The oral antithrombotic activity of certain β-D-xylopyranosides, first reported by Bellamy et al. in 1993 [1], has triggered extensive research focusing on the structure–activity relationships by modification of the sugar as well as of the aglycon moiety. The

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[3] Dedicated to Prof. H. Paulsen on the occasion of his 75th birthday.

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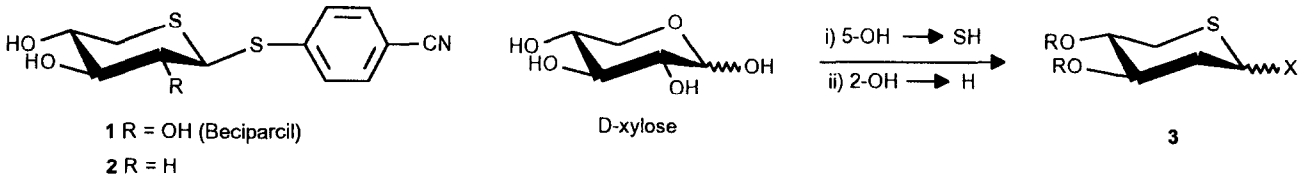


Scheme 1.

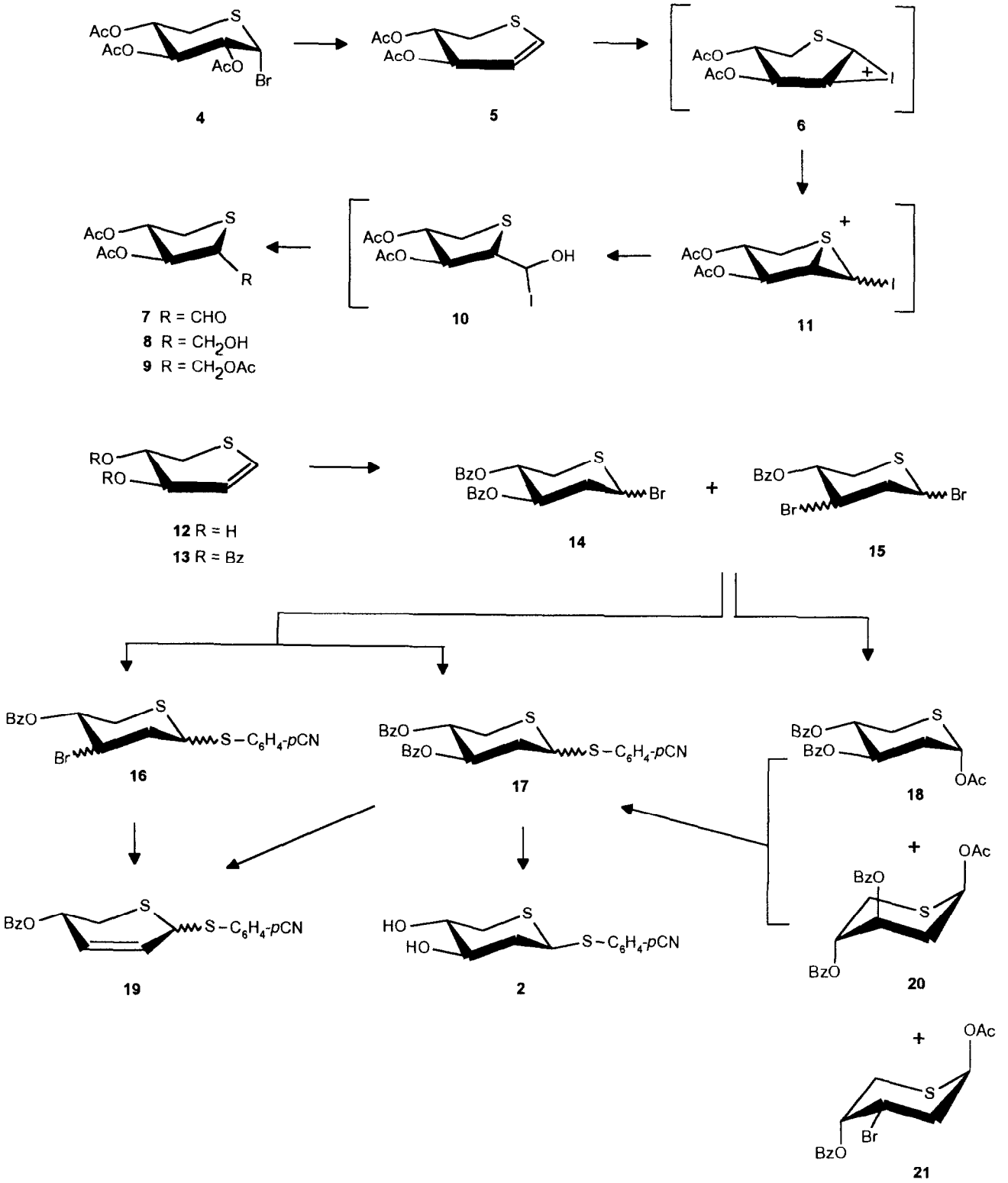
results of this study were published two years later [2] and pointed out that replacement of both the sugar-ring oxygen and the glycosidic oxygen atoms by sulfur resulted in a dramatic increase in the biological activity. Accordingly, one of the most active compounds was the 4-cyanophenyl glycoside of 1,5-dithio-β-D-xylopyranose (Beciparcil, **1**) which, however, failed in the clinical trials because of some unexpected side-effects [2]. With the purpose of investigating the role of the individual hydroxy groups on the biological activity, we decided to synthesise analogs and first of all the corresponding 2-deoxy analog (**2**) of Beciparcil. For this purpose, a properly substituted glycosyl donor **3** was needed, which can be obtained from D-xylose via two transformations: (i) the introduction of the thiol group at C-5, and (ii) the reductive removal of OH-2 (Scheme 1). The theoretically possible synthetic approaches may differ in the sequence of these transformations.

2. Results and discussion

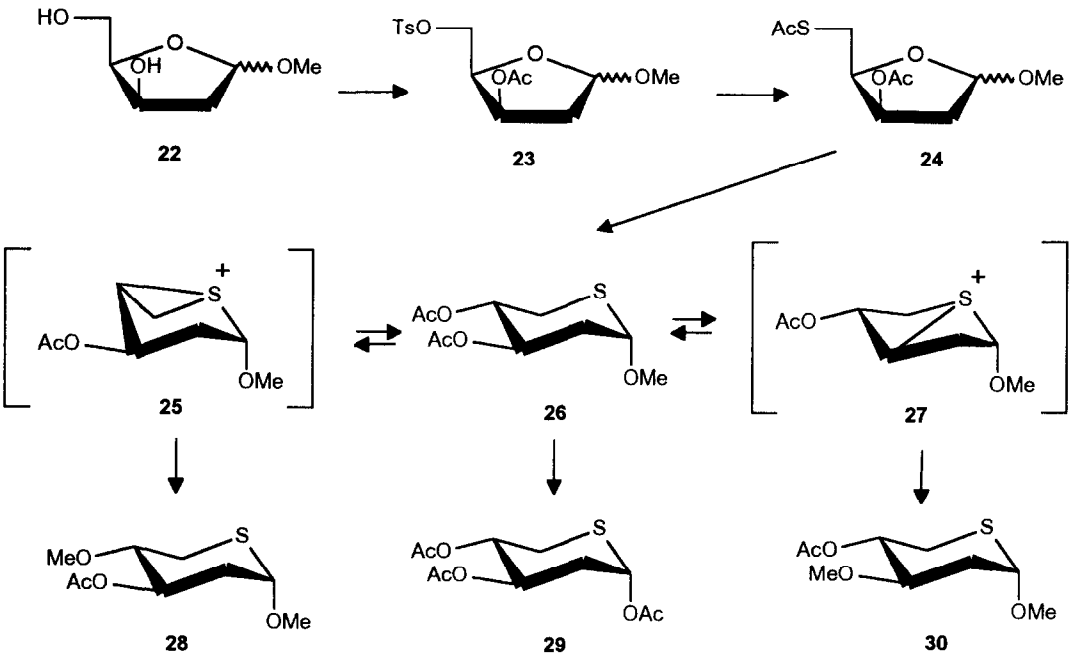
In our first attempt, route (i) → (ii) was investigated (Scheme 2). Introduction of the 5-thiol group into D-xylose was carried out along the original synthetic pathway of Whistler et al. [3] to yield 2,3,4-tri-*O*-acetyl-5-thio-α-D-xylopyranosyl bromide (**4**). For the reductive removal of the 2-OH group, we planned to use the *N*-iodosuccinimide–water addition reaction to 3,4-di-*O*-acetyl-1,5-anhydro-D-*threo*-pent-1-enitol (**5**) (5-thio-D-xylal), which was successfully applied by Thiem et al. [4] in the synthesis of the corresponding 2-deoxypyranosides. For this approach, **5** was obtained in 85% yield from **4** by using zinc in toluene in the presence of 4-picoline [5]. Treatment of **5** with *N*-iodosuccinimide–water in acetonitrile afforded a mixture, the reduction of which was carried out with sodium borohydride–nickel chloride to give, after subsequent acetylation, a multicomponent mixture. However, instead of the expected 2-deoxy-triacetate derivative, only the triacetate of 2,5-anhydro-5-thio-D-lyxitol **9** could be isolated in 24% yield as the main component by column chromatography. This was probably formed via the iodonium ion **6** which, as a consequence of the transannular participation of the ring sulfur atom [6,7], was rearranged into the sulfonium ion **11**. Hydrolysis of **11** gave **10** from which the 2,5-anhydro-sugar **7** was formed by elimination of hydrogen iodide. The latter was reduced by borohydride and the resulting alcohol **8** gave **9** on acetylation. The structure of **9** was proved by ^{13}C NMR as the two CH_2 groups appeared at 33.8 and 65.0 ppm, in agreement with a 5-CH_2-S and a 1-CH_2-O linkage only.

In our next attempt, we tried to synthesise the appropriate glycosyl donor **3** by using the addition of hydrogen bromide to the double bond (Scheme 2). This reaction was extensively studied by Bock et al. [8] in the case of D-xylal derivatives. According to their results, the undesirable Ferrier rearrangement reaction [9], which after addition of hydrogen bromide to the double bond leads to the corresponding 3-bromo isomers as the main products in the case of 3,4-di-*O*-acetyl-D-xylal, can be avoided when the acetyl groups are replaced by benzoyl groups. Therefore, 5-thio-D-xylal diacetate **5** was deacetylated by the Zemplén procedure and the resulted diol **12** was converted with benzoyl chloride in pyridine into its dibenzoate **13**. Addition of hydrogen bromide to **13** was carried out in toluene, and the mixture of the resulting bromides **14** and **15** was allowed to react without isolation with sodium 4-cyanobenzenethiolate in *N,N*-dimethylformamide. However, under these conditions, the elimination of hydrogen bromide became the main reaction and the xylal derivative **13** was recovered in 43% yield. The corresponding thioxylosides could be isolated only as an anomeric mixture (**17**, 28%) containing the α,β-isomers in a 3:7 ratio. As a by-product (11%), an anomeric mixture (3:2) of the 2-ene derivative **19** was isolated which could be formed, either from the $^1C_4$ conformation of **17** via elimination of benzoic acid, or from **16** by elimination of hydrogen bromide. The structure of **19** was evident from the chemical shifts of the two vinylic protons H-2, H-3 in the ^1H

NMR spectrum (6.26 and 6.10, as well as 6.10 and 5.98, respectively) and their couplings $J_{2,3}$ 10.6 and 10.8 Hz, respectively. The major component shows two nearly equal $J_{4,5a}$ and $J_{4,5b}$ couplings (3.6 and 4.0 Hz), in agreement with a ^5T_S conformation. In the minor component, these couplings are 4.0 and 10.0 Hz, respectively, suggesting the presence of a $^ST_5$ conformation. In this latter isomer, a homoallylic $J_{1,4}$



Scheme 2.



Scheme 3.

coupling of 1.2 Hz was also observed. As the overall yield of **17** was too low for practical purposes, the basic conditions of the glycosidation reactions leading to the elimination products mentioned above had to be avoided. For this reason, the crude reaction mixture, containing bromides **14** and **15**, was treated in acetonitrile with silver acetate, whereby a mixture, containing the α-acetate **18**, the β-acetate **20**, the β-acetate of the 3-bromo derivative **21**, and the 5-thio-D-xylal derivative **13** in a ratio of 35:50:3:12 was formed. From this, only **13** could be separated by column chromatography, while the other three components had practically identical R_f values and crystallised together. Condensation of this crystalline mixture with 4-cyanobenzenethiol was carried out in dichloromethane, using trimethylsilyl triflate as the promoter. In this way, the thioglycosides **17** were formed in excellent yield (91%) and contained the α,β-isomers in the favourable ratio of 15:85. Zemplén deacylation of **17** afforded, after crystallisation, **2** in satisfactory yield (81%) (Scheme 2).

The only drawback of this reaction sequence was that tri-*O*-acetyl-5-thio-α-D-xylopyranosyl bromide (**4**), prepared from D-xylose in 8 steps [3], had to be used as starting material. For this reason, route (ii) → (i), which would lead to a proper glycosyl donor in less steps was taken into consideration (Scheme 3). The known [10] methyl 2-deoxy-D-*threo*-pentofuranoside **22**, which can be prepared from D-xylose in 5 steps, was converted in a one-pot reaction into the 3-*O*-acetyl-5-*O*-tosyl derivative **23** in 75% yield. Treatment of **23** with potassium thioacetate in *N,N*-dimethylformamide gave the 5-*S*-acetate **24**. For the deacetylation and subsequent transformation of the **24**α isomer into the corresponding methyl 2-deoxy-5-thio-D-*threo*-pentopyranoside, boiling with hydrogen chloride in methanol was used in the case of 2-deoxy-5-thio-D-*erythro*-pentofuranoside [11], resulting in the concomitant isomerisation under these conditions into its β-D-pyranoside. However, in the case of **24**, a multicomponent mixture was formed, which could be partially separated by column chromatography only after acetylation. As the main component (33%), the diacetate of the methyl α-D-pyranoside **26** was isolated, the structure of which was unambiguously proved by ^{1}H NMR. The $J_{1,2a}$ and $J_{1,2e}$ values (2.6 and 4.0 Hz, respectively) were in accordance with the *e,a* and *e,e* arrangements of the corresponding protons. The values of $J_{2a,3}$ 11.5, $J_{3,4}$ 9.9, and $J_{4,5a}$ 11.0 Hz proved both the diequatorial arrangement of the two acetoxy groups as well as the $^4C_1$ (D) conformation of the molecule. Among the different by-products, only one could be isolated in pure state (3%), which was the 3-methoxy derivative **30**. Substitution of the C-3 acetoxy group in **26** by a methoxy group in **30** with retention of configuration was proved by its ^{1}H NMR spectrum, which differed from that of the diacetate **26** by the presence of two methoxy and one acetoxy group and the shift of H-3 from 5.28 to 3.54 ppm (see Table 1). Forma-

Table 1
Selected ^{1}H NMR data for solutions in $CDCl_3$

Compound	Chemical shifts (δ)						
	H-1	H-2ax	H-2eq	H-3	H-4	H-5ax	H-5eq
2 [a]	4.68	1.78	2.45	3.30–3.50		2.55–2.85	
17α	4.69	2.59	2.71	5.72	5.40	3.34	3.14
17β	4.47	2.35	2.91	5.39	5.45	3.00	3.19
18	6.04	2.40	2.72	5.74	5.51	3.25	3.02
20	5.97	2.56	2.64	5.41	5.41	3.62	2.90
21	5.97	2.55	2.91	4.59	5.54	3.10	3.38
26	4.50	2.10	2.55	5.28	5.04	2.86	2.64
29	5.93	2.18	2.50	5.28	5.08	3.02	2.78
30	4.50	2.00	2.60	3.54	4.93	2.77	2.60

	Coupling constants (Hz)									
	$J_{1,2ax}$	$J_{1,2eq}$	$J_{2ax,2eq}$	$J_{2ax,3}$	$J_{2eq,3}$	$J_{3,4}$	$J_{4,5ax}$	$J_{4,5eq}$	$J_{5a,5b}$	$J_{1,5eq}$
2 [a]	11.7	3.6	13.1	11.6	3.5	nd	nd	nd	nd	–
17α	3.6	4.5	13.6	9.8	4.0	8.8	9.2	4.0	13.7	1.5
17β	10.8	3.0	13.0	9.5	4.2	9.0	9.5	4.0	13.8	–
18	3.0	4.0	13.0	11.5	4.5	9.8	11.0	4.5	13.5	1.4
20	3.2	3.4	14.8	nd	3.6	nd	2.1	nd	14.5	1.4
21	3.2	2.8	14.0	12.0	2.6	4.0	1.8	4.5	14.5	1.6
26	2.6	4.0	14.0	11.5	4.6	9.9	11.0	4.6	13.0	1.0
29	2.9	4.1	13.5	11.4	4.1	9.9	11.1	4.4	13.2	1.2
30	2.4	4.0	13.8	11.3	4.0	9.4	10.8	4.5	12.9	1.0

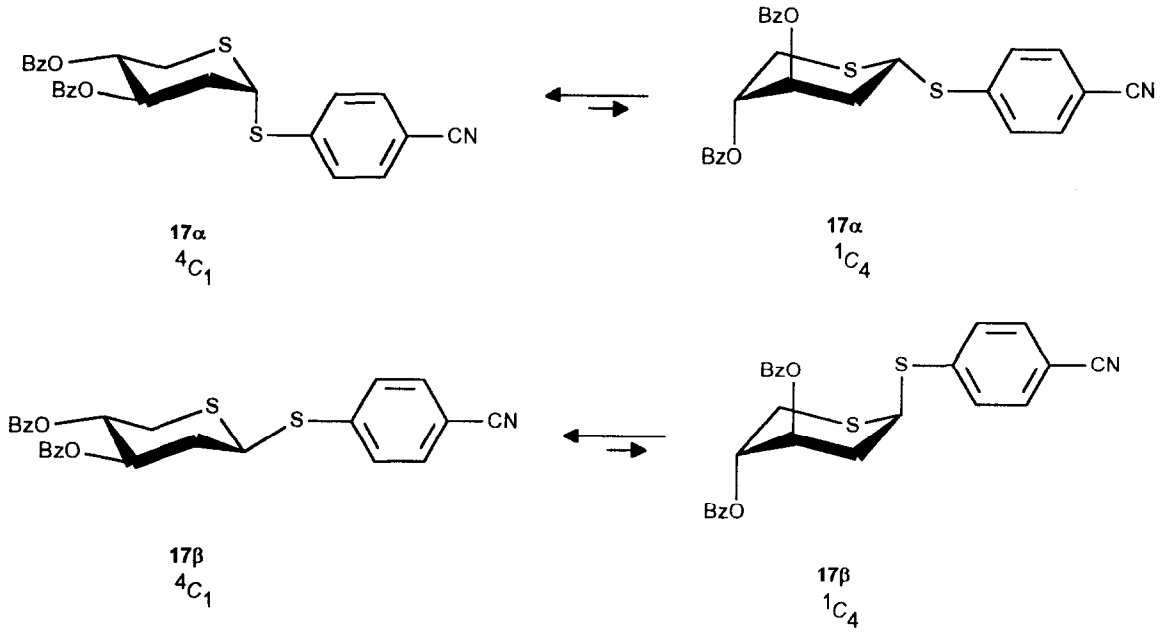
[a] Me_2SO-d_6.

tion of **30** can be explained via a bicyclic sulfonium intermediate **27**, formed by a transannular participation of the sulfur atom [6,7]. A similar reaction should lead, via the intermediate **25**, to the corresponding 4-methoxy derivative **28**, the presence of which was detected by NMR in one of the mixed fractions, but we failed to isolate it in the pure state. The relatively low yield of **26** is partly due to these side-reactions, but other decomposition products were formed also, as 2-deoxy-5-thiopentoses seems to be as sensitive towards strong acids as their oxygen containing analogs [12]. This acid-sensitivity might be why the acetolysis of **26**, which requires the presence of concentrated sulfuric acid, afforded triacetate **29** in a disappointingly low yield (14%) only, making this approach for the synthesis of a glycosyl donor less attractive than the aforementioned one.

Conformational analysis of the α- and β-isomers of 5-thioxylopyranose derivatives by NMR.—According to the investigations of Horton and Durette [13], the conformational equilibrium of tetrabenzoyl-α-D-xylopyranose is completely shifted towards the $^4C_1$ form, while in the β-anomer, due to the anomeric effect, the $^4C_1$ and the $^1C_4$ conformers are present in almost equal amounts. Exchange of the anomeric benzoyloxy group by the more polar bromo substituent increases the anomeric effect to such an extent that the equilibrium of the β-bromide is shifted completely towards the $^1C_4$ conformer [14,15].

Despite the less pronounced anomeric effect of the endocyclic sulfur atom [16], the conformational equilibrium of the 3,4-di-*O*-benzoyl α-acetate **18** was shifted completely towards the $^4C_1$ conformation, whereas that of the β-acetates **20** and **21** shifted towards the $^1C_4$ conformation. When the anomeric acetoxy group was replaced by the 4-cyanophenylthio substituent, the anomeric effect was further diminished, as a consequence of the exchange of the anomeric oxygen by sulfur [17]. Accordingly, both anomers adopt the $^4C_1$ conformation, i.e. the anomeric substituent occupies an axial position in the **17α** isomer only, while in the **17β** isomer all substituents are equatorially oriented, as the weak anomeric effect would not compensate the steric strain caused by the 1,3-diaxial arrangement of the 3-*O*-benzoyl and the 4-cyanophenylthio group in the $^1C_4$ conformation (Scheme 4).

The conformations mentioned above were determined by ^{1}H NMR measurements of the corresponding mixtures, which gave well-resolved spectra at 400 MHz, enabling the structural elucidation of the individual compounds without previous separation. In **18**, the value of $J_{3,4}$ 9.8 Hz is in agreement with the *trans* diaxial relationship of the C-3-4 protons, while



Scheme 4.

the equatorial orientation of H-1 is in good agreement with the $J_{1,2a}$ and $J_{1,2e}$ values of 3 and 4 Hz, respectively. Furthermore, the existence of a long-range $J_{1,5e}$ 1.4 Hz coupling is indicative of the diequatorial arrangement of H-1 and H-5*e*. In the β-isomer **20**, the same coupling pattern prevails for H-1, i.e. the value of $J_{1,2a}$ and $J_{1,2e}$ were 3.2 and 3.4 Hz and that of $J_{1,5e}$ 1.4 Hz. Because of signal overlapping, the value of $J_{3,4}$ could not be determined, but H-5*a* gave a well-resolved signal with two couplings $J_{5a,5e}$ 14.5 and $J_{4,5a}$ 2.1 Hz. This means that H-4 must occupy an equatorial position, otherwise it would show a large $J_{4,5a}$ coupling.

The $^1C_4$ conformation of the 3-bromo derivative **21** was supported by the coupling constant of H-4 ($J_{4,5a}$ 1.8 and $J_{4,5e}$ 4.5 Hz), proving its equatorial arrangement. The long-range coupling $J_{1,5e}$ 1.6 Hz was in agreement with the equatorial position of H-1, in agreement with the β-anomeric configuration. The equatorial position of the bromo atom at C-3 was proved by the large $J_{2a,3}$ 12.0 Hz coupling of its geminal proton. Comparison of the ^{13}C NMR spectra of **21** with that of the corresponding dibenzoate **20** provided further evidence for the structure, since no diaxial interaction exists in **21** where the bromo substituent at C-3 is equatorially oriented, and as a result, C-5 appears at 29.08 ppm and C-1 at 69.58 ppm. Due to the γ-gauche effect of the axially oriented C-3 *O*-benzoyl substituent in **20**, C-5 appears at 24.78 ppm and C-1 at 72.46 ppm, due to the δ-syn diaxial effect of the axially oriented acetoxy group.

The $^4C_1$ conformation of **17α**, which was formed as a minor component, was proved by the large $J_{2a,3}$ and $J_{3,4}$ couplings of 9.8 and 8.8 Hz indicating the diaxial orientation of the corresponding protons. At the same time, the equatorial position of H-1 is in full agreement with the $J_{1,2a}$, $J_{1,2e}$, and the long-range $J_{1,5e}$ coupling of 3.6, 4.5, and 1.5 Hz, respectively. In the ^1H NMR spectrum of the major component **17β**, the large $J_{1,2a}$ 10.8 Hz value as well as the absence of any long-range $J_{1,5}$ coupling proves the axial arrangement of H-1. As the $^4C_1$ conformation is evident from the large $J_{2a,3}$, $J_{3,4}$, and $J_{4,5a}$ couplings of 9.5, 9.0, and 9.5 Hz, the axial position of H-1 confirms the β-anomeric configuration.

Biological results.—The oral antithrombotic activity of **2** was established in rats, using Pescador's model [18]. Beciparcil (**1**) was used as reference. Both compounds were administered orally 3 h before ligation. The ED_{50} dose of **2** was 7 mg/kg, while that of **1** was 25 mg/kg. Consequently, **2** is a significantly more potent antithrombotic agent than **1**, i.e. replacement of the 2-OH group by H has a beneficial effect on the biological activity.

3. Experimental

General methods.—Organic solutions were dried over $MgSO_4$ and concd under diminished pressure at or below 40 °C. TLC: precoated Silica Gel 60 F_{254} (E. Merck) plates, with hexane–EtOAc mixtures (*A*,

2:1; *B*, 4:1; *C*, 9:1) and toluene–MeOH mixtures (*D*, 4:1); detection by spraying the plates with a 0.02 M soln of I_2 and a 0.30 M soln of KI in 10% aq H_2SO_4 soln followed by heating at ca. 200 °C. For column chromatography, Kieselgel 60 was used. Mp are uncorrected. Optical rotations were determined on 0.5% solns in $CHCl_3$ at 20 °C unless stated otherwise. NMR spectra were recorded with a Bruker AC 250 spectrometer at 250 MHz (^1H) and 62.9 MHz (^{13}C) and a Varian XL-400 spectrometer at 400 MHz (^1H) and 100 MHz (^{13}C) on solns in $CDCl_3$ (internal Me_4Si) unless stated otherwise. Multiplicities of the ^{13}C NMR spectra were obtained from DEPT experiments. The assignment of the protons were based on homonuclear decoupling. Connectivities between identified protons and protonated carbons were observed by means of HETCOR experiments. The ratio of α,β-anomers was determined by ^1H NMR spectroscopy.

3,4-Di-O-*acetyl-1,5-anhydro-5-thio*-D-threo-*pent-1-enitol* (**5**).—To a stirred soln of **4** [3] (11.2 g, 31.5 mmol) in dry toluene (110 mL) were added 4-picoline (3.2 mL, 32.9 mmol) and Zn powder (13 g, 0.2 mmol) and the mixture was kept at 80 °C for 1 h. The reaction was cooled to room temperature and the solid was filtered off. The filtrate was concd and the residue was purified by column chromatography (solvent *A*) to yield **5** (5.8 g, 85%), $[\alpha]_D$ −324°; R_f 0.7 (solvent *A*); ^1H NMR: δ 6.36 (d, 1 H, H-1), 5.75 (dd, 1 H, H-2), 5.28 (dd, 1 H, H-3), 5.16 (m, 1 H, H-4), 3.00–3.10 (m, 2 H, H-5*a*, H-5*b*), 2.08 (s, 3 H, OAc), 2.04 (s, 3 H, OAc); $J_{1,2}$ 10.0, $J_{2,3}$ 4.4, $J_{3,4}$ 4.6 Hz; ^{13}C NMR: δ 169.9, 169.8 (C=O), 125.8 (C-1), 117.2 (C-2), 66.7, 66.4 (C-3, C-4), 26.3 (C-5), 21.0, 20.9 (OAc). Anal. Calcd for $C_9H_{12}O_4S$: C, 49.99; H, 5.59; S, 14.83. Found: C, 50.12; H, 5.71; S, 14.89.

1,3,4-Tri-O-*acetyl-2,5-anhydro-5-thio*-D-*lyxitol* (**9**).—To a stirred soln of **5** (2.1 g, 9.7 mmol) in MeCN (50 mL) were added NIS (3.4 g, 15.1 mmol) and water (0.5 g, 28 mmol) and the mixture was stirred at room temperature with exclusion of light for 4 h when according to TLC, all starting material was consumed (R_f 0.8 → 0.5, solvent *D*). The mixture was concd, the residue was dissolved in $CHCl_3$, washed with 5% $Na_2S_2O_3$ and water, dried, and concd. The residue was dissolved in EtOH (150 mL), $NaBH_4$ (1.1 g, 29 mmol) was added and the mixture was stirred in the presence of $NiCl_2 \cdot 6H_2O$ (110 mg, 0.46 mmol) at room temperature for 1 h. The reaction was neutralised with 4% HCl, concd, then coevaporated with toluene. The residue was treated with Ac_2O in pyridine to give, after usual processing, a syrup which was submitted to column chromatography (solvent *A*) to yield **9** (0.65 g, 24%). $[\alpha]_D$ −36°; R_f 0.5 (solvent *A*); ^1H NMR: δ 5.25–5.40 (m, 2 H, H-3, H-4), 4.28 (dd, 1 H, H-1*a*), 4.16 (dd, 1 H, H-1*b*), 3.56 (ddd, 1 H, H-2), 3.26 (ddd, 1 H, H-5*a*), 2.98 (ddd, 1 H, H-5*b*), 2.0–2.1 (m, 9 H, OAc); $J_{1a,1b}$ 11.2, $J_{1a,2}$ 8.6, $J_{1b,2}$ 6.7, $J_{2,3}$ 2.5, $J_{4,5a}$ 4.8, $J_{4,5b}$ 3.5, $J_{5a,5b}$ 12.0 Hz; ^{13}C NMR: δ 170.6, 169.6, 169.4 (C=O), 78.5, 78.1 (C-3, C-4), 65.0 (C-1), 48.8 (C-2), 33.8 (C-5), 20.8, 20.8, 20.7 (OAc). Anal. Calcd for $C_{11}H_{16}O_6S$: C, 47.82; H, 5.84; S, 11.60. Found: C, 47.72; H, 5.89; S, 11.64.

1,5-Anhydro-3,4-di-O-*benzoyl-5-thio*-D-threo-*pent-1-enitol* (**13**).—To a stirred soln of **5** (4.2 g, 19.4 mmol) in MeOH (50 mL) was added M NaOMe (0.1 mL) and the mixture was left at room temperature for 1 h. The reaction was neutralised with solid CO_2 and concd. The residue was dissolved in a mixture of pyridine (15 mL) and CH_2Cl_2 (60 mL) and a soln of benzoyl chloride (7.0 mL, 60.3 mmol) in CH_2Cl_2 (35 mL) was added dropwise during 10 min at room temperature. The reaction was stirred at room temperature overnight, then poured into water and processed in the usual way to yield, after recrystallisation from EtOH, **13** (4.95 g, 75%), mp 119–122 °C; $[\alpha]_D$ −468°; R_f 0.6 (solvent *C*); ^1H NMR: δ 7.40–8.02 (m, 10 H, Ar), 6.46 (d, 1 H, H-1), 5.95 (dd, 1 H, H-2), 5.75 (dd, 1 H, H-3), 5.58 (m, 1 H, H-4), 3.25–3.35 (m, 2 H, H-5*a*, H-5*b*); $J_{1,2}$ 10.2, $J_{2,3}$ 4.2, $J_{3,4}$ 4.2 Hz; ^{13}C NMR: δ 165.5, 165.4 (C=O), 133.3, 133.2, 129.8, 129.7, 128.4, 128.4 (Ar), 126.1 (C-1), 117.4 (C-2), 67.3, 67.0 (C-3, C-4), 26.8 (C-5). Anal. Calcd for $C_{19}H_{16}O_4S$: C, 67.04; H, 4.74; S, 9.42. Found: C, 67.19; H, 4.83; S, 9.59.

1-O-*Acetyl-3,4-di*-O-*benzoyl-2-deoxy-5-thio-α*-D-threo-*pentopyranose* (**18**), *1*-O-*acetyl-3,4-di*-O-*benzoyl-2-deoxy-5-thio-β*-D-threo-*pentopyranose* (**20**) *and 1*-O-*acetyl-4*-O-*benzoyl-3-bromo-2,3-dideoxy-5-thio-β*-D-erythro-*pentopyranose* (**21**).—A stirred soln of **13** (1.7 g, 5 mmol) in dry toluene (20 mL) was satd with HBr at 10 °C during 20 min, then argon was bubbled through the mixture to remove the excess of HBr. The resulting soln of bromides **14** and **15** was added to a stirred mixture of AgOAc (4.0 g, 24 mmol) in dry MeCN (35 mL) at room temperature and stirring was continued for 2 h. Silver salts were filtered off, the filtrate was concd and the residue was purified by column chromatography (solvent *C*, then *B*). Concentration of the first fraction yielded **13** (160 mg, 9%).

Concentration of the second fraction gave a crystalline mixture of **18**, **20**, and **21** (1.5 g) in a ratio of

Table 2
Selected ^{13}C NMR data for solutions in $CDCl_3$

Compound	Chemical shifts (δ)				
	C-1	C-2	C-3	C-4	C-5
2 [a]	44.2	42.7	72.7 [b]	73.2 [b]	33.8
17α	47.1	37.7	69.4	71.5	28.1
17β	45.9	39.5	71.9	71.7	31.0
18	71.6	38.9	69.6	73.2	27.3
20	72.5	31.9	66.5 [b]	67.3 [b]	24.8
21	69.6	38.0	45.5	68.5	29.1
26	80.9	40.2	69.2	73.0	25.6
29	68.8 [b]	38.6	71.4 [b]	72.4 [b]	26.9
30	81.4	39.9	74.9 [b]	76.7 [b]	25.8

[a] Me_2SO-d_6.
[b] Arbitrary assignment.

40:55:5. R_f 0.4 (solvent *B*). For NMR data see Tables 1 and 2.

Glycosidation of 4-cyanobenzenethiol with a mixture of bromides **14** and **15**.—To a stirred soln of 4-cyanobenzenethiol (0.6 g, 4.4 mmol) in dry DMF (10 mL) was added 50% NaH dispersion in oil (0.2 g, 4.2 mmol) and the mixture was stirred at room temperature for 30 min. The soln of **14** + **15** obtained as described above was added and stirring was continued for 24 h. The mixture was poured into ice–water, extracted with toluene, washed with aq $NaHCO_3$ and water. After evaporation, the residue was purified by column chromatography (solvent *C* then *B*). Concentration of the first fraction yielded **13** (0.73 g, 43%).

Concentration of the second fraction gave *4-cyanophenyl 4-O-benzoyl-1,5-dithio*-D-glycero-*pent-2-enopyranoside* (**19**) (190 mg, 11%) as an anomeric mixture (3:2). R_f 0.5 (solvent *C*); ^1H NMR: δ major anomer, 6.26 (dd, 1 H, H-2), 6.10 (dd, 1 H, H-3), 5.54 (ddd, 1 H, H-4), 4.93 (d, 1 H, H-1), 3.44 (dd, 1 H, H-5*a*), 3.00 (dd, 1 H, H-5*b*); $J_{1,2}$ 4.9, $J_{2,3}$ 10.6, $J_{3,4}$ 4.6; $J_{4,5a}$ 3.6, $J_{4,5b}$ 4.0, $J_{5a,5b}$ 14.5 Hz; δ minor anomer, 6.10 (dd, 1 H, H-2), 5.98 (dd, 1 H, H-3), 4.82 (dd, 1 H, H-1), 4.80 (m, 1 H, H-4), 3.14 (dd, 1 H, H-5*a*), 2.98 (dd, 1 H, H-5*b*); $J_{1,2}$ 3.3, $J_{1,4}$ 1.2, $J_{2,3}$ 10.8, $J_{3,4}$ 1.4; $J_{4,5a}$ 10.0, $J_{4,5b}$ 4.0, $J_{5a,5b}$ 13.0 Hz; ^{13}C NMR: δ 165.7 (C=O), 142.0, 141.4, 127–134, 110.4 (Ar, C-2, C-3), 118.4, 117.2 (CN), 67.7, 62.7 (C-4), 46.3, 46.1 (C-1), 28.0, 25.0 (C-5). Anal. Calcd for $C_{19}H_{15}NO_2S_2$: C, 64.57; H, 4.28; N, 3.96; S, 18.14. Found: C, 64.32; H, 4.15; N, 4.09; S, 18.29.

Concentration of the third fraction yielded *4-cyanophenyl 3,4-di-O-benzoyl-2-deoxy-1,5-dithio*-D-threo-*pentopyranoside* (**17**) (0.59 g, 28%) as an anomeric mixture (α:β 3:7). R_f 0.3 (solvent *B*); ^1H NMR: δ 7.3–8.0 (m, Ar), for further data see Table 1; ^{13}C NMR: δ 165.5 (C=O), 148.0, 128–134, 110.7 (Ar), 118.3 (CN), for further data see Table 2. Anal. Calcd for $C_{26}H_{21}NO_4S_2$: C, 65.66; H, 4.45; N, 2.95; S, 13.48. Found: C, 65.73; H, 4.67; N, 3.08; S, 13.57.

4-Cyanophenyl 1,5-dithio-2-deoxy-β-D-threo-*pentopyranoside* (**2**).—Debenzoylation of the α:β 15:85 mixture of **17** (1.1 g, 2.3 mmol) with M NaOMe (0.1 mL) in MeOH (70 mL) yielded, after deionisation with DOWEX 50 WX resin, concn and crystallisation with ether, **2** (0.50 g, 81%), mp 169–172 °C; $[\alpha]_D$ −15° (*c* 0.5, MeOH); R_f 0.4 (solvent *D*); ^1H NMR: δ 7.60–7.80 (m, 4 H, Ar), for further data see Table 1; ^{13}C NMR: δ 142.0, 132.7, 128.6, 108.5 (Ar), 119.0 (CN), for further data see Table 2. Anal. Calcd for $C_{12}H_{13}NO_2S_2$: C, 53.91; H, 4.90; N, 5.24, S, 23.98. Found: C, 53.72; H, 4.89; N, 5.11, S, 23.84.

Glycosidation of 4-cyanobenzenethiol with a mixture of acetates **18**, **20** and **21**.—Under argon atmosphere, to a soln of the mixture of **18**, **20**, and **21** obtained as described above (1.15 g, 2.87 mmol) and 4-cyanobenzenethiol (0.75 g, 5.5 mmol) in CH_2Cl_2 (30 mL), was added TMSOTf (0.6 mL, 3.3 mmol) at −10 °C and the mixture was stirred for 1 h at room temperature. Then, the reaction was neutralised with Et_3N, washed with water, aq $NaHCO_3$, and water. The residue obtained on concn was purified by column chromatography (solvent *A*) to yield **17** (1.24 g, 91%) as an anomeric mixture (α:β 15:85).

Methyl 3-O-acetyl-2-deoxy-5-O-tosyl-D-threo-*pentofuranoside* (**23**).—To an α:β 4:1 mixture of **22** [10] (1.9 g, 12.8 mmol) in pyridine (10 mL) was added a soln of TsCl (2.7 g, 14 mmol) in $CHCl_3$ (10 mL) at 0 °C and the mixture was stirred at room temperature for 2 h. Then Ac_2O (3 mL) was added, and the reaction was left overnight at room temperature, then poured into water and processed in the usual way to yield **23** (3.3 g, 75%) as an anomeric mixture (α:β 4:1), R_f 0.4 (solvent *A*); ^1H NMR: δ 7.35–7.80 (m, Ar), α-anomer, 5.35 (ddd, 1 H, H-3), 5.08 (dd, 1 H, H-1), 4.10–4.30 (m, 3 H, H-4, H-5*a*, H-5*b*), 3.30 (s, 3 H, OMe), 2.45 (s, 3 H, OTs), 2.24 (ddd, 1 H, H-2*a*), 2.12 (ddd, 1 H, H-2*b*), 1.98 (s, 3 H, OAc); $J_{1,2a}$ 2.6, $J_{1,2b}$ 5.5, $J_{2a,2b}$ 14.6; $J_{2a,3}$ 6.6, $J_{2b,3}$ 4.5, $J_{3,4}$ 4.3 Hz; β-anomer, 5.42 (m, 1 H, H-3), 5.16 (dd, 1 H, H-1); $J_{1,2a}$ 2.7, $J_{1,2b}$ 5.6 Hz; ^{13}C NMR: δ 170.0 (C=O), 144.9, 132.7, 129.8, 127.8, (Ar), 104.0 (C-1), 75.7, 73.0 (C-3, C-4), 67.1 (C-5), 55.2 (OMe), 40.1 (C-2), 21.5 (OTs), 20.6 (OAc). Anal. Calcd for $C_{15}H_{20}O_7S$: C, 52.32; H, 5.85; S, 9.31. Found: C, 52.19; H, 5.93; S, 9.59.

Methyl 3-O-acetyl-5-S-acetyl-2-deoxy-α-D-threo-pentofuranoside (**24**).—To a soln of **23** (3.3 g, 9.6 mmol) in DMF (20 mL) was added KSAc (3.3 g, 28.9 mmol) and the mixture was stirred at 110 °C for 1 h. The reaction was concd, the residue was dissolved in $CHCl_3$ and washed with water and brine to yield after column chromatography (solvent *B*) **24** (1.52 g, 63%), $[\alpha]_D$ +89.5° (*c* 0.63, $CHCl_3$); R_f 0.4 (solvent *B*); ^{1}H NMR: δ 5.32 (ddd, 1 H, H-3), 5.12 (dd, 1 H, H-1), 4.14 (ddd, 1 H, H-4), 3.35 (s, 3 H, OMe), 3.15 (m, 2 H, H-5*a*, H-5*b*), 2.35 (s, 3 H, SAc), 2.28 (ddd, 1 H, H-2*a*), 2.18 (ddd, 1 H, H-2*b*), 2.04 (s, 3 H, OAc); $J_{1,2a}$ 2.9, $J_{1,2b}$ 5.5, $J_{2a,2b}$ 14.9; $J_{2a,3}$ 6.3, $J_{2b,3}$ 2.6, $J_{3,4}$ 4.1, $J_{4,5a}$ 6.9, $J_{4,5b}$ 6.9 Hz; ^{13}C NMR: δ 194.6, 170.1 (C=O), 103.8 (C-1), 77.4, 73.6 (C-3, C-4), 55.2 (OMe), 40.7 (C-2), 30.3 (SAc), 27.4 (C-5), 20.8 (OAc). Anal. Calcd for $C_{10}H_{16}O_5S$: C, 48.37; H, 6.50; S, 12.91. Found: C, 48.51; H, 6.64; S, 12.83.

Methyl 3,4-di-O-acetyl-2-deoxy-5-thio-α-D-threo-pentopyranoside (**26**) *and methyl 4-O-acetyl-2-deoxy-3-O-methyl-5-thio-α-D-threo-pentopyranoside* (**30**).—A soln of **24** (1.2 g, 4.8 mmol) in MeOH (15 mL) containing 1% HCl was refluxed for 2 h, neutralised with Et_3N and concd. The residue was acetylated in pyridine to give, after usual processing, a syrup which was separated by column chromatography (solvent *B*). Concentration of the first fraction yielded **30** (30 mg, 3%), $[\alpha]_D$ +193° (*c* 0.15, $CHCl_3$); R_f 0.4 (solvent *B*); ^{1}H NMR: δ 3.40 (s, 3 H, OMe), 3.36 (s, 3 H, OMe), 2.08 (s, 3 H, OAc), for further data see Table 1; ^{13}C NMR: δ 170.3 (C=O), 56.2, 57.9 (OMe), 21.2 (OAc), for further data see Table 2. Anal. Calcd for $C_9H_{16}O_4S$: C, 49.07; H, 7.32; S, 14.55. Found: C, 49.19; H, 7.47; S, 14.49.

Concentration of the second fraction gave **26** (0.39 g, 33%), $[\alpha]_D$ +214°; R_f 0.35 (solvent *B*); ^{1}H NMR: δ 3.38 (s, 3 H, OMe), 2.06 (s, 3 H, OAc), 2.02 (s, 3 H, OAc), for further data see Table 1; ^{13}C NMR: δ 170.1,. 169.8 (C=O), 56.1 (OMe), 21.0, 20.9 (OAc), for further data see Table 2. Anal. Calcd for $C_{10}H_{16}O_5S$: C, 48.37; H, 6.50; S, 12.91. Found: C, 48.51; H, 6.43; S, 12.82.

1,3,4-Tri-O-acetyl-2-deoxy-5-thio-α-D-threo-pentopyranose (**29**).—To a soln of **26** (0.32 g, 1.3 mmol) in Ac_2O (4 mL) was added concd H_2SO_4 (0.05 mL) at 0 °C and the reaction was stirred at 0 °C for 15 min. Then NaOAc (0.5 g) and aq $NaHCO_3$ (10 mL) were added, the mixture was stirred at room temperature for 2 h, extracted with $CHCl_3$, washed with water, and the residue obtained on concn was purified by column chromatography (solvent *A*) to yield **29** (50 mg, 14%), $[\alpha]_D$ +184°; R_f 0.3 (solvent *A*); ^{1}H NMR: δ 2.12 (s, 3 H, OAc), 2.04 (s, 3 H, OAc), 2.00 (s, 3 H, OAc), for further data see Table 1; ^{13}C NMR: δ 169.9, 169.8, 169.0 (C=O), 21.0, 20.8, 20.8 (OAc), for further data see Table 2. Anal. Calcd for $C_{11}H_{16}O_6S$: C, 47.82; H, 5.84; S, 11.60. Found: C, 47.71; H, 5.93; S, 11.49.

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