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# Synthesis of 4-cyanophenyl 1,5-dithio-β-D-glucopyranoside and its 6-deoxy, as well as 6-deoxy-5-ene derivatives as oral antithrombotic agents [1]

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**Abstract**

Condensation of 5-thio-D-glucopyranose pentaacetate with 4-cyanobenzenethiol, in the presence of trimethylsilyl triflate, gave 4-cyanophenyl 2,3,4,6-tetra-*O*-acetyl-1,5-dithio-α-D-glucopyranoside **7** and 3,4,6-tri-*O*-acetyl-2,5-anhydro-5-thio-D-mannose bis(4-cyanophenyl) dithioacetal **9** in a 2:3 ratio. The latter is probably formed from the 4-cyanophenyl 2,3,4,6-tetra-*O*-acetyl-1,5-dithio-β-D-glucopyranoside **6** via a transannular participation of the ring sulfur atom. When 2,3,4,6-tetra-*O*-acetyl-5-thio-α-D-glucopyranosyl bromide was used as donor and the reaction was carried out in the presence of potassium carbonate, **6**, **7**, 4-cyano-2-(2,3,4,6-tetra-*O*-acetyl-5-thio-α-D-glucopyranosyl)phenyl and 4-cyano-2-(2,3,4,6-tetra-*O*-acetyl-5-thio-β-D-glucopyranosyl)phenyl 1,5-dithio-β-D-glucopyranoside (**14** and **16**) were formed in a 23:4:2:1 ratio. The mechanism of formation of **14** and **16** is discussed. Condensation of 2,3,4-tri-*O*-acetyl-6-deoxy-5-thio-α-D-glucopyranosyl bromide with 4-cyanobenzenethiol in the presence of potassium carbonate gave 4-cyanophenyl 2,3,4-tri-*O*-acetyl-6-deoxy-1,5-dithio-α- and β-D-glucopyranoside (**29** and **30**) as well as 4-cyano-2-(2,3,4-tri-*O*-acetyl-6-deoxy-5-thio-α-D-glucopyranosyl)phenyl 2,3,4-tri-*O*-acetyl-6-deoxy-1,5-dithio-β-D-glucopyranoside in a ratio of ~1:8:1. Compound **30** could be obtained in a higher overall yield using **2** as starting material and converting it via its 4-cyanophenyl 2,3,4-tri-*O*-acetyl-6-*O*-methanesulfonyl-1,5-dithio-β-D-glucopyranoside derivative into the 4-cyanophenyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-1,5-dithio-β-D-glucopyranoside **33** which gave **30** on reduction with sodium borohydride–nickel(II) chloride. Treatment of **33** with silver acetate gave 4-cyanophenyl 2,3,4-tri-*O*-acetyl-6-deoxy-1,5-dithio-β-D-*xylo*-hex-5-enopyranoside **35**. The compounds obtained on deacetylation of **6**, **9**, **14**, **30**

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[1] Orally active antithrombotic thioglycosides, Part IV. For Part III, see Ref. [1].


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and **35** showed a stronger oral antithrombotic effect in rats as compared to beciparcil, used as reference. 

*Keywords:* Glycosidation reactions; Thioglycosides; Rearrangement reactions; Reaction mechanism; Oral antithrombotic activity

## 1. Introduction

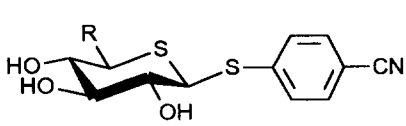
In previous parts of this series of papers [1,2], we have shown that the oral antithrombotic activity of 4-cyanophenyl 1,5-dithio-β-D-xylopyranoside (beciparcil, **1**) [3] could be significantly increased by exchanging the individual hydroxyl groups by azido groups. For further structure activity relationship studies, the synthesis of the corresponding 1,5-dithiohexose derivatives of beciparcil, i.e., 4-cyanophenyl 1,5-dithio-β-D-glucopyranoside **2**, its 6-deoxy analogue **3** as well as its 6-deoxy-5-ene derivative **4** differing from **1** only in the substitution at C-5 was decided.

## 2. Results and discussion

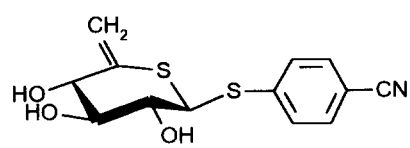
*Synthesis of the 4-cyanophenyl 1,5-dithio-β-D-glucopyranoside* (**2**).—In our first attempt, 5-thio-D-glucose pentaacetate (**5**, [4]) was used as donor in dichloromethane and trimethylsilyl triflate was used as promoter for the condensation with 4-cyanobenzenethiol. When the reaction was carried out at 20 °C, **5** was consumed in 6 h, and an inseparable mixture was formed containing two derivatives, the α-glycoside **7** and the 2,5-anhydro-5-thio-D-mannose mercaptal **9** in a 2:3 ratio (see Schemes 1 and 2). Both could be separated after deacetylation affording **8** and **10**, respectively. For structure elucidation, **8** and **10** were reacetylated yielding **7** and **9**, respectively. The structure of **9** was established by NMR spectroscopy. According to selective INEPT experiments, there was a three-bond $^{1}H-^{13}C$ connectivity between H-1 (5.05 ppm) and both aromatic C-1′ and C-1″ atoms (139.5 and 139.8 ppm). The NOE difference spectra proved the α-orientation of C-1. The ring contraction reaction leading to **9**, probably takes place via the overbridged episulfonium intermediate **11**. The latter can be formed from both glycosides **6** or **7** via activation of the 2-*O*-acetyl group by trimethylsilyl triflate and a subsequent transannular participation of the ring sulfur atom [1,5–7]. Rearrangement of **11** yields the carbonium ion **12** which can be attacked by the thiol to give **9**.

It is remarkable that the presence of the β-glycoside **6** could not be detected in the reaction mixture by NMR spectroscopy, despite the fact that participation of the 2-acetoxy group should give it as the kinetically favoured product. This was unprecedented as, e.g., the corresponding 4-azido-4-deoxy-5-thio-D-xylopyranose peracetate yielded under identical reaction conditions a 8:2:1 mixture of the α-anomer, the β-anomer and the corresponding rearranged product [1]. That means that, in the case of **5**, the primarily formed **6** must undergo an immediate isomerisation affording **7** and/or **9**. Formation of **6** could not be detected, even as an intermediate, by shortening the reaction time or lowering the temperature (see Table 1). This change in the conditions led only to a lower degree of conversion, but the ratio of **7** and **9** was not influenced essentially. In a separate experiment, the conversion of the isolated α-anomer **7** into **9** was investigated applying the same reaction conditions (TMSOTf, 6 h at 20 °C), but the conversion rate was only 25%. Accordingly, **9** was probably formed mainly via the **5** → **6** → **9** sequence, the second step of which must be faster than the first one.

To avoid this unwanted rearrangement reaction,

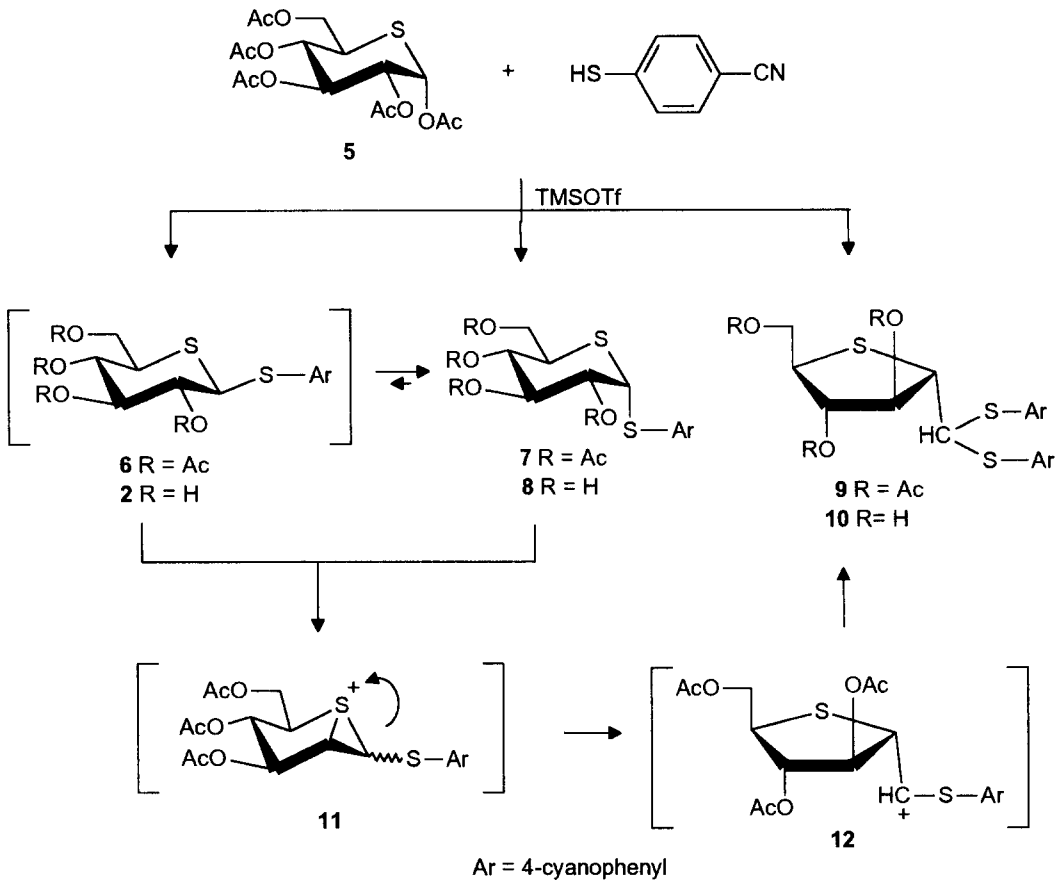



**1** R = H (beciparcil)
**2** R = $CH_2OH$
**3** R = $CH_3$




**4**

Scheme 1.




Scheme 2.

the pentaacetate **5** was converted according to the literature [8] into the acetobromo derivative **13** and this was reacted with 4-cyanobenzenethiol in acetone in the presence of potassium carbonate (see Scheme 3). Under these conditions, the following four components were formed in a 23:4:2:1 ratio, the expected $\beta$- and $\alpha$-glycosides (**6** and **7**), and two derivatives of the former containing a second 5-thio-D-gluco-pyranosyl unit attached via a *C*-glycosidic bond to C-2 of the aglycon. These two isomers **14** and **16** differed only in the stereochemistry of the C-glycosidic bond, which was $\alpha$ in **14** and $\beta$ in **16**. The structure of these two derivatives was proved by NMR spectroscopy. The shift of the $^{13}C$ signals of the sugar moiety, attached as *S*-glycoside were similar to those of **6** (e.g., C-1: 50.1 ppm (**6**), 51.9 ppm (**14**), and 52.0 ppm (**16**)), while those of the anomeric carbon atoms of the *C*-glycoside appeared at 38.5 ppm (**14**) and 44.3 ppm (**16**), respectively. At the same time, in the proton coupled $^{13}C$ NMR spectra, C-2 of the aglycon gave a singlet at 139.4 ppm (**14**), and 138.7 ppm (**16**). Location of the *C*-glycoside at C-2′ was proved further by INEPT long-range heterocouplings, as e.g., in the case of **14**, there was a $^{2}J$ coupling between H-1″ (5.16 ppm) and C-2′ (139.4 ppm) as well as a $^{3}J$ coupling between H-1″ and C-1′ (140.1 ppm), but none between this proton and C-4′. The value of $J_{1,2}$ 3.7 and 10.8 Hz for the anomeric proton of the *C*-glycosidic part in **14** and **16** were in full agreement with the proposed $\alpha$- and $\beta$-anomeric structure.

Table 1
Ratio[a] of **5**, **7** and **9** depending on the reaction conditions

| Temp. (°C) | Time (h) | 5 | 7 | 9 |
|---|---|---|---|---|
| 20 | 6 | – | 40% | 60% |
| 20 | 1.5 | 20% | 30% | 50% |
| 20 | 0.5 | 50% | 25% | 25% |
| −10 | 1.5 | 100% | – | – |

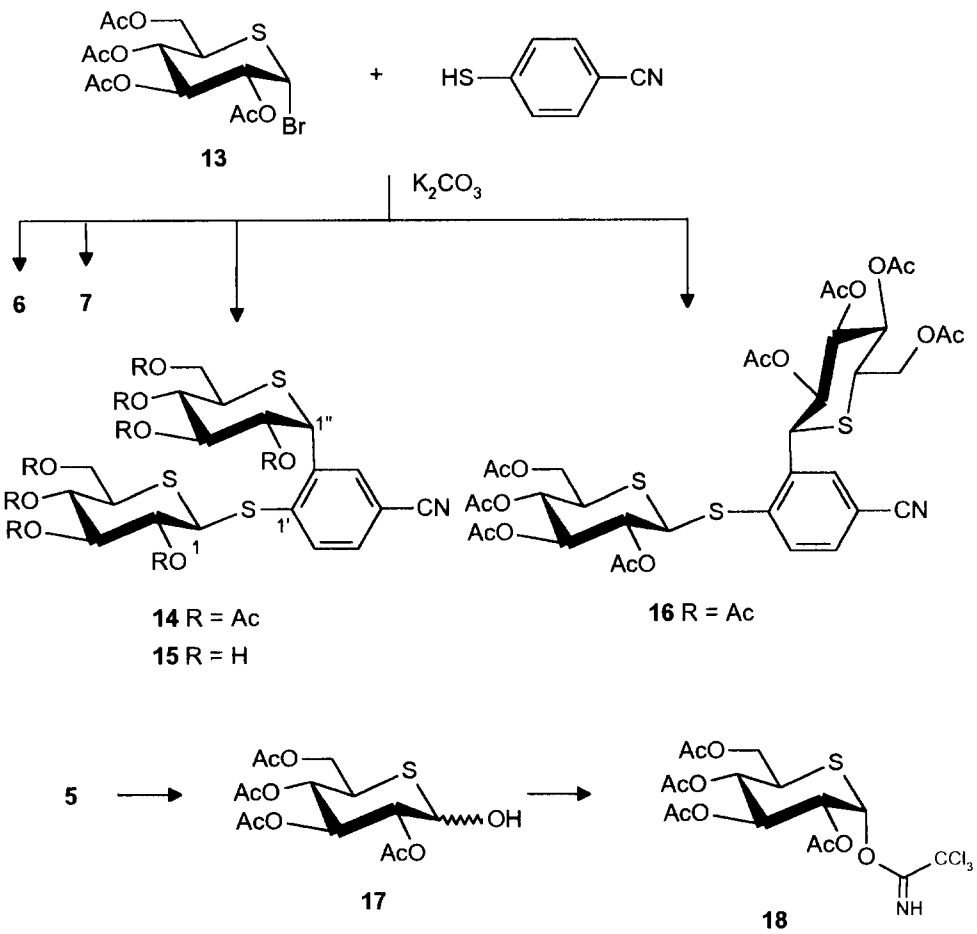
[a]Determined by $^{1}H$ NMR.

The formation of the *C*-glycosides **14** and **16** was unexpected, as electrophilic carbohydrate donors usually form aromatic *C*-glycosides only in the presence of Lewis-acids [9,10]. Nevertheless, the present reaction could be explained by an ionic, as well as by a radical mechanism (see Schemes 4 and 5). In the first case, the sulfonium ion **19** formed from **13** in the presence of potassium carbonate, should attack the aglycon of the already formed $\beta$-anomer **6**, and

elimination of a proton from the resulting carbonium ion should yield **14** and **16**, respectively. On the other hand, it was shown previously [1] that the thiolate anion can undergo a single-electron transfer reaction, by which **13** is transformed into the carbohydrate radical **20**. Attack of the latter at C-2 of the aglycon would give the radical **22** which, via elimination of a hydrogen radical should yield the same *C*-glycosides (**14** and **16**) mentioned above. In order to get a deeper insight into the mechanism, the reaction was repeated using 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO), or sulfur as radical scavenger. However, neither of them had influence on the outcome of the reaction; therefore, the radical mechanism is improbable. When the reaction was repeated, using **13** as donor and the isolated β-anomer **6** as acceptor, no reaction took place under the applied conditions. That means that the ionic mechanism, yielding **21** as intermediate, can also not be taken into consideration. Theoretically, a third possibility would be a pathway in which the *C*-glycosidic bond is formed first. It may be assumed that the thiolate ion **23** reacts in its mesomeric structure **24** with the sulfonium ion **19**, forming **25** as intermediate. The aromatic system of the latter can be restored by a 1,3-hydrogen shift, affording an anomeric mixture of the *C*-glycosides **26**. This react subsequently with the acetobromo derivative **13** via an $S_N2$ type mechanism, or via participation of the neighbouring acetoxy group, affording the β-thioglycosides **14** and **16**.

In order to compare the results of the different coupling methods, the imidate procedure [11] was also tried. For this purpose, **5** was converted according to the literature [12] via **17** into the 1-*O*-trichloroacetimidate **18** and this was coupled with 4-cyanobenzenethiol using boron trifluoride etherate as promoter. Despite the fact that only the two expected anomers **6** and **7** were formed, this reaction proved to be unsuitable for the preparation of the former because of the modest yield (53%) and the unfavourable α:β ratio (7:3).

For biological testing, the β-anomers **6** and **14** as



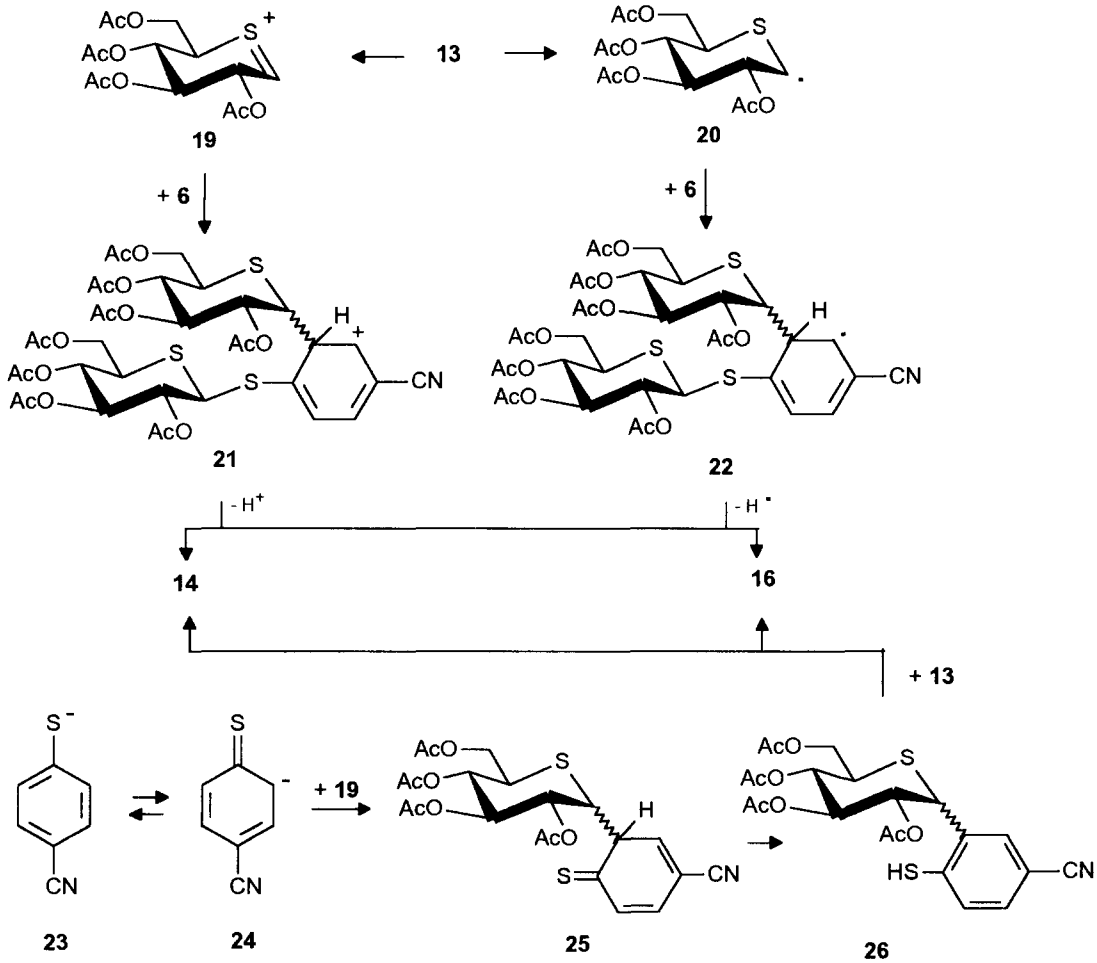

Scheme 3.

well as the 2,5-anhydro-5-thio derivative **9** were deacetylated by the Zemplén's method to give **2**, **15** and **10**, respectively. For biological data, see Table 2.

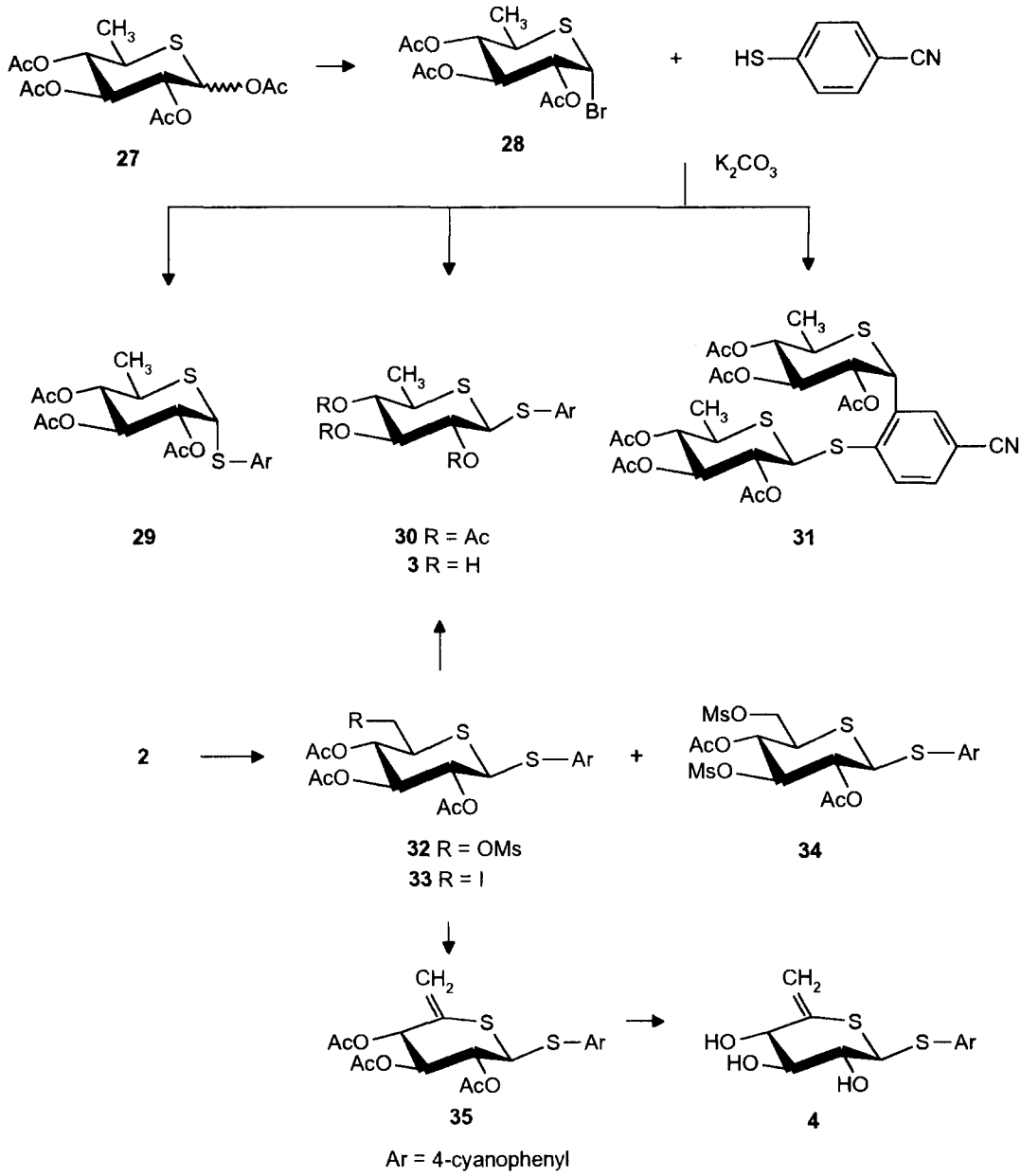
*Synthesis of the 4-cyanophenyl 6-deoxy-1,5-dithio-β-D-glucopyranoside* (**3**).—In our first attempt, the known 6-deoxy-5-thio-D-glucopyranose tetraacetate (**27**) [6] was converted into its acetobromo derivative **28** which was coupled with 4-cyanobenzenethiol in acetone in the presence of potassium carbonate. Under these conditions, a mixture of the α- and β-thioglycosides (**29** and **30**) as well as the corresponding *C*-glycosylated β-anomer **31** could be isolated in 7%, 56% and 8% yield, respectively. The β-anomer **30** was deacetylated to yield **3**. Nevertheless, this synthesis of **3** was not economic enough, as the tetraacetate donor **27** was obtained from D-glucose in a multistep process and a very modest yield. For this reason, the β-thioglucoside **2** was used in a second approach as starting material. It reacted in a one pot reaction with mesyl chloride in pyridine, and subsequently with acetic anhydride, to afford its 6-*O*-mesyl-peracetate **32**. The latter could be separated in 54% yield from the reaction mixture containing also the tetraacetate **6** (3%) and the 3,6-di-*O*-mesyl derivative **34** (4%). Treatment of **32** with sodium iodide in 3-pentanone at reflux afforded the 6-iodo derivative **33** in excellent yield. Reduction of the latter with sodium borohydride–nickel(II) chloride gave the expected 6-deoxy glycoside **30**, which, after Zemplén deacetylation, afforded **3** in an overall yield of 20% from **2**.

*Synthesis of the 4-cyanophenyl 6-deoxy-1,5-dithio-β-D-xylo-hex-5-enopyranoside* (**4**).—The 6-iodo-glycoside **33** proved to be a useful starting material for the introduction of the terminal double bond, as it gave **35** in 76% yield on treatment with silver fluoride in pyridine. Zemplén's deacetylation of **35** afforded **4** in an excellent yield (91%), and this was submitted to biological testing.

*Biological results.*—The oral antithrombotic activity of **2**, **3**, **4**, **10** and **15**, as well as that of beciparcil (**1**) as reference compound, was determined in rats, using Pescador's model [13]. All compounds were administered orally 3 h before ligation. From the data




Scheme 4.




Scheme 5.

listed in Table 2, it can be seen that all derivatives were more active than the reference compound. This was a quite unexpected result, as in the series of normal glycopyranosides (with an O in the sugar ring), the antithrombotic effect of the corresponding D-xylopyranosides, measured in a modified Wessler's model, superseded that of any other sugar residues, including D-glucose [14]. As far as the substitution at C-6 is concerned, the hydroxyl group is better than hydrogen or the double bond (**2** > **3** ≈ **4**). At the same time, the substitution of the aglycon moiety at C-2, even by such a bulky substituent as the 5-thio-glucopyranoside residue, has no influence of the activity (**2** ≈ **15**). The relative high activity of the 2,5-anhydro-5-thio derivative **10** is rather surprising as this structure is totally different from **1**. Consequently, the original proposal [3] according to which the thioxylopyranosides exhibit their antithrombotic effect by acting as primers for the biological synthesis of glycosaminoglycans has to be reconsidered.

Table 2
Oral antithrombotic activity of **1**, **2**, **3**, **4**, **10** and **15** in rats using Pescador's model [13]

| Compound | **1** | **2** | **3** | **4** | **10** | **15** |
|---|---|---|---|---|---|---|
| $ED_{50}$ (mg/kg) | 25 | 7 | 12 | 15 | 12 | 7 |

## 3. Experimental

*General methods.*—Organic solutions were dried over $MgSO_4$ and concentrated under diminished pressure at or below 40 °C. TLC: E. Merck precoated Silica Gel $60F_{254}$ plates, with hexane–EtOAc mixtures (A, 1:1; B, 2:1; C, 4:1), toluene–MeOH mixtures (D, 9:1; E, 4:1) and EtOAc–MeOH mixture (F, 2:1); detection by spraying the plates with a 0.02 M solution of iodine and a 0.30 M soln of potassium iodide in 10% aq $H_2SO_4$ soln followed by heating at ca. 200 °C. For column chromatography, Kieselgel 60 was used. Melting points are uncorrected. Optical rotations were determined on 0.5% solns in $CHCl_3$ at 20 °C unless otherwise stated. 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 ($^{13}C$) for solns in $CDCl_3$ (internal $Me_4Si$) unless otherwise stated (Tables 3 and 4). Multiplicities of the $^{13}C$ NMR spectra were obtained from DEPT experiments. The assignment of the protons were based on homonuclear decoupling and NOE experiments. Connectivities between identified protons and protonated carbons were observed by means of HETCOR and selective INEPT experiments. The ratio of $\alpha:\beta$ anomeric mixtures was determined by $^1H$ NMR.

*Glycosidation of 4-cyanobenzenethiol with* (**5**).—To a stirred soln of 4-cyanobenzenethiol (0.5 g, 3.7 mmol) and **5** [4] (0.75 g, 1.8 mmol) in $CH_2Cl_2$ (25 mL), under argon, TMSOTf (0.35 mL, 1.9 mmol) was added at 0 °C and the mixture was stirred at room temperature for 6 h. Then, the reaction was neutralised with $Et_3N$, washed with water, aq $NaHCO_3$, and water. The residue obtained on concentration was purified by column chromatography (solvent B) to yield **7** and **9** (0.6 g) in a ratio of 2:3; $R_f$ 0.7 (solvent A). This mixture of **7** and **9** was dissolved in MeOH (30 mL) and deacetylated under Zemplén's conditions (M NaOMe in MeOH, 0.1 mL). After 1 h at room temperature, the mixture was neutralised with carbon dioxide, concentrated and submitted to column chromatography (solvent E). Concentration of the first fraction gave 2,5-anhydro-5-thio-D-mannose bis(4-cyanophenyl) dithioacetal (**10**, 280 mg, 35%); mp 176–179 °C (ether); $[\alpha]_D$ −68° (*c* 0.5, MeOH); $R_f$ 0.5 (solvent E); $^1H$ NMR: ($Me_2SO$-$d_6$) δ 7.54–7.80 (m, 8 H, aromatic), 5.73 (d, 1 H, OH), 5.56 (d, 1 H, H-1), 5.40 (d, 1 H, OH), 4.80 (t, 1 H, OH), 3.97 (dd, 1 H, H-3), 3.80 (dd, 1 H, H-6a), 3.50 (dd, 1 H, H-4), 3.48 (dd, 1 H, H-2), 3.32 (dd, 1 H, H-6b), 3.13 (ddd, 1 H, H-5); $J_{1,2}$ 2.6, $J_{2,3}$ 8.4, $J_{3,4}$ 8.4, $J_{4,5}$ 8.3, $J_{5,6a}$ 3.3, $J_{5,6b}$ 8.3, $J_{6a,6b}$ 11.0 Hz; $^{13}C$ NMR: ($Me_2SO$-$d_6$) δ 141.9, 141.4, 133.0,

Table 4
Selected $^{13}C$ NMR data for solutions in $CDCl_3$

| Compound | Chemical shifts (δ) | | | | | |
|---|---|---|---|---|---|---|
| | C-1 | C-2 | C-3 | C-4 | C-5 | C-6 |
| **6** | 50.1 | 71.4[b] | 73.3[b] | 74.3[b] | 44.6 | 60.9 |
| **7** | 51.4 | 70.8[b] | 71.9[b] | 74.5[b] | 40.2 | 60.8 |
| **8**[a] | 53.4 | 73.8[b] | 74.9[b] | 75.1[b] | 46.5 | 60.4 |
| **29** | 51.4 | 70.6[b] | 74.8[b] | 76.4[b] | 35.5 | 15.0 |
| **30** | 50.0 | 73.6[b] | 74.3[b] | 75.7[b] | 40.1 | 15.3 |
| **32** | 50.2 | 71.2[b] | 73.1[b] | 74.0[b] | 44.4 | 64.9 |
| **33** | 50.0 | 73.3[b] | 73.9[b] | 74.2[b] | 46.6 | 0.2 |
| **34** | 50.3 | 72.8 | 80.6 | 70.6 | 44.4 | 64.7 |
| **35** | 50.8 | 73.6[b] | 73.2[b] | 73.1[b] | 134.0 | 118.3 |

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

Table 3
Selected $^1H$ NMR data for solutions in $CDCl_3$

| Compound | Chemical shifts (δ) | | | | | | | Coupling constants (Hz) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | H-1 | H-2 | H-3 | H-4 | H-5 | H-6a | H-6b | $J_{1,2}$ | $J_{2,3}$ | $J_{3,4}$ | $J_{4,5}$ | $J_{5,6a}$ | $J_{5,6b}$ | $J_{6a,6b}$ |
| **2**[a] | 4.46 | 3.32 | 3.15 | 3.34 | 2.95 | 3.76 | 3.50 | 10.2 | 8.6 | 8.6 | 8.9 | 3.3 | 6.6 | 11.4 |
| **3**[a] | 4.52 | 3.32 | 3.20–3.00 | | 2.85 | 1.12 | | 10.2 | 8.4 | nd[b] | nd | 6.9 | 6.9 | – |
| **4**[a] | 4.44 | 3.48 | 3.10 | 3.92 | – | 5.60 | 5.33 | 10.1 | 8.5 | 8.8 | – | – | – | ~ 1.0 |
| **6** | 4.27 | 5.24 | 5.10 | 5.28 | 3.32 | 4.26 | 4.10 | 10.6 | 9.4 | 9.4 | 10.6 | 5.3 | 3.3 | 12.0 |
| **7** | 4.94 | 5.30 | 5.49 | 5.27 | 3.72 | 4.38 | 4.06 | 4.1 | 9.8 | 9.8 | 9.8 | 4.8 | 2.0 | 12.0 |
| **8**[a] | 4.90 | 3.90 | 3.44–3.28 | 3.08 | 3.74 | 3.64 | | 4.3 | 8.8 | nd | ~ 10.0 | 3.3 | 6.3 | 11.4 |
| **29** | 4.86 | 5.30 | 5.46 | 5.06 | 3.43 | 1.17 | | 4.5 | 10.3 | 9.5 | 10.5 | 6.8 | 6.8 | – |
| **30** | 4.24 | 5.30–5.00 | | | 3.08 | 1.15 | | 10.7 | nd | nd | 9.9 | 6.6 | 6.6 | – |
| **32** | 4.28 | 5.23 | 5.12 | 5.27 | 3.38 | 4.30 | 4.24 | 10.3 | 9.5 | 9.5 | 10.3 | 5.2 | 3.7 | 10.9 |
| **33** | 4.32 | 5.30–5.05 | | | 3.36 | 3.20–3.04 | | 10.4 | nd | nd | nd | nd | nd | nd |
| **34** | 4.24 | 5.26 | 4.74 | 5.33 | 3.36 | 4.35 | 4.25 | 10.9 | 9.4 | 9.6 | 10.8 | 5.0 | 3.6 | 11.0 |
| **35** | 4.28 | 5.37 | 5.08 | 5.60 | – | 5.58 | 5.47 | 10.6 | 9.4 | 9.4 | – | – | – | ~ 1.0 |

[a] $Me_2SO$-$d_6$.
[b] nd Not determined.

132.9, 129.8, 129.3, 109.5, 109.0 (aromatic), 118.8, 118.7 (CN), 78.5 (C-3), 77.2 (C-4), 63.6 (C-6), 57.0 (C-1), 51.1, 50.5 (C-2, C-5). Anal. Calcd. for $C_{20}H_{18}N_2O_3S_3$: C, 55.79; H, 4.21; N, 6.51; S, 22.34. Found: C, 55.95; H, 3.98; N, 6.59; S, 22.53.

Concentration of the second fraction ($R_f$ 0.3, solvent E) gave 4-cyanophenyl 1,5-dithio-α-D-glucopyranoside (**8**, 130 mg, 23%); mp 174–176 °C (ether); $[\alpha]_D$ +493° (*c* 0.5, MeOH); $R_f$ 0.4 (solvent E); Anal. Calcd. for $C_{13}H_{15}NO_4S_2$: C, 49.82; H, 4.82; N, 4.47; S, 20.46. Found: C, 50.03; H, 4.77; N, 4.31; S, 20.53.

*4-Cyanophenyl 2,3,4,6-tetra-O-acetyl-1,5-dithio-α-D-glucopyranoside* (**7**).—To a soln of **8** (100 mg, 0.3 mmol) in pyridine (5 mL), $Ac_2O$ (2.5 mL) was added. After 20 h at room temperature, the mixture was processed in the usual way to give, upon concn of the organic solution **7** (150 mg, 98%); mp 135–137 °C (MeOH); $[\alpha]_D$ +397°; $R_f$ 0.7 (solvent A); Anal. Calcd. for $C_{21}H_{23}NO_8S_2$: C, 52.38; H, 4.81; N, 2.91; S, 13.32. Found: C, 52.43; H, 4.74; N, 2.68; S, 13.51.

*3,4,6-Tri-O-acetyl-2,5-anhydro-5-thio-D-mannose bis(4-cyanophenyl) dithioacetal* (**9**).—To a soln of **10** (200 mg, 0.46 mmol) in pyridine (5 mL), $Ac_2O$ (2.5 mL) was added. After 20 h at room temperature, the mixture was processed in the usual way to give, upon concn of the organic solution, **9** (250 mg, 97%); $[\alpha]_D$ −68° (*c* 0.63, $CHCl_3$); $R_f$ 0.7 (solvent A); $^1H$ NMR: δ 7.38–7.70 (m, 8 H, aromatic), 5.69 (dd, 1 H, H-3), 5.40 (dd, 1 H, H-4), 5.05 (d, 1 H, H-1), 4.26 (dd, 1 H, H-6a), 4.11 (dd, 1 H, H-6b), 3.73 (ddd, 1 H, H-5), 3.72 (dd, 1 H, H-2), 2.06 (s, 3 H, OAc), 2.05 (s, 3 H, OAc), 2.04 (s, 3 H, OAc); $J_{1,2}$ 4.4, $J_{2,3}$ 6.6, $J_{3,4}$ 7.3, $J_{4,5}$ 7.3, $J_{5,6a}$ 5.8, $J_{5,6b}$ 6.8, $J_{6a,6b}$ 11.5 Hz; $^{13}C$ NMR: δ 171.3, 170.4, 169.5 (C=O), 139.8, 139.5, 132.6, 132.5, 132.0, 131.3, 111.6, 111.4 (aromatic), 118.0, 117.9 (CN), 78.7 (C-3), 77.1 (C-4), 63.9 (C-6), 61.0 (C-1), 51.7, 45.4 (C-2, C-5), 20.6, 20.6, 20.5 (OAc). Anal. Calcd. for $C_{26}H_{24}N_2O_6S_3$: C, 56.10; H, 4.35; N, 5.03; S, 17.28. Found: C, 56.25; H, 4.49; N, 5.17; S, 17.37.

*Glycosidation of 4-cyanobenzenethiol with* **13**.—To a stirred soln of 4-cyanobenzenethiol (0.98 g, 7.25 mmol) and **13** [8] (2.8 g, 6.55 mmol) in acetone (160 mL) under argon, potassium carbonate (1.65 g, 11.9 mmol) was added and the mixture was refluxed for 1 h. After cooling to room temperature, the precipitated salts were filtered off, washed with acetone, the filtrate was concentrated and submitted to column chromatography (solvent A). Concentration of the first fraction gave a mixture, containing **6** and **7** (2.15 g, 68%) in a ratio of 85:15; $R_f$ 0.7 (solvent A). Recrystallisation from ether yielded 4-cyanophenyl 2,3,4,6-tetra-*O*-acetyl-1,5-dithio-β-D-glucopyranoside (**6**, 1.55 g, 72%); $[\alpha]_D$ +38.5°; $R_f$ 0.7 (solvent A). Anal. Calcd. for $C_{21}H_{23}NO_8S_2$: C, 52.38; H, 4.81; N, 2.91; S, 13.32. Found: C, 52.21; H, 4.69; N, 2.73; S, 13.37.

Concentration of the second fraction gave 4-cyano-2-(2,3,4,6-tetra-*O*-acetyl-5-thio-α-D-glucopyranosyl)-phenyl 2,3,4,6 - tetra - *O* - acetyl - 1,5 - dithio - β - D-glucopyranoside (**14**, 280 mg, 10%); $[\alpha]_D$ +78°; $R_f$ 0.4 (solvent A); $^1H$ NMR: δ 7.90 (d, 1 H, H-3′), 7.78 (d, 1 H, H-6′), 7.63 (dd, 1 H, H-5′), 5.39 (t, 1 H, H-3″), 5.29 (m, 2 H, H-2, H-4), 5.26 (dd, 1 H, H-2″), 5.25 (m, 1 H, H-4″), 5.16 (d, 1 H, H-1″), 5.09 (t, 1 H, H-3), 4.46 (dd, 1 H, H-6a″), 4.26 (dd, 1 H, H-6a), 4.24 (dd, 1 H, H-6b″), 4.22 (d, 1 H, H-1), 4.08 (dd, 1 H, H-6b), 3.30 (m, 2 H, H-5, H-5″), 2.10–2.00 (m, 24 H, OAc); $J_{1,2}$ 10.7, $J_{3,4}$ 9.5, $J_{5,6a}$ 5.3, $J_{5,6b}$ 3.4, $J_{6a,6b}$ 12.2, $J_{1'',2''}$ 3.7, $J_{2'',3''}$ 6.0, $J_{3'',4''}$ 6.0, $J_{5'',6a''}$ 6.3, $J_{6a'',6b''}$ 11.7 Hz; $^{13}C$ NMR: δ 170.4, 170.4, 169.5, 169.4, 169.2, 169.2, 169.1, 168.9 (C=O), 140.1 (C-1′), 139.4 (C-2′), 133.0 (C-6′), 132.2 (C-3′), 131.9 (C-5′), 111.7 (C-4′), 117.8 (CN), 74.2, 73.4, 71.3 (C-2, C-3, C-4), 69.6, 69.5, 67.7 (C-2″, C-3″, C-4″), 62.5, 60.8 (C-6, C-6″), 51.9 (C-1), 44.6, 41.1 (C-5, C-5″), 38.5 (C-1″), 20.7, 20.6, 20.6, 20.6, 20.5, 20.5, 20.4, 20.3 (OAc). Anal. Calcd. for $C_{35}H_{41}NO_{16}S_3$: C, 50.78; H, 4.99; N, 1.69; S, 11.62. Found: C, 50.65; H, 4.77; N, 1.73; S, 11.48.

Concentration of the third fraction gave 4-cyano-2-(2,3,4,6-tetra-*O*-acetyl-5-thio-β-D-glucopyranosyl)-phenyl 2,3,4,6 - tetra - *O* - acetyl - 1,5 - dithio - β - D - glucopyranoside (**16**, 140 mg, 5%), mp 224–228 °C; $[\alpha]_D$ +78° (*c* 0.2, $CHCl_3$); $R_f$ 0.3 (solvent A); $^1H$ NMR: δ 7.78 (d, 1 H, H-3′), 7.73 (d, 1 H, H-6′), 7.57 (dd, 1 H, H-5′), 5.52 (dd, 1 H, H-2″), 5.41 (dd, 1 H, H-4″), 5.32 (dd, 1 H, H-2), 5.30 (dd, 1 H, H-4), 5.18 (t, 1 H, H-3″), 5.07 (t, 1 H, H-3), 4.84 (d, 1 H, H-1″), 4.37 (dd, 1 H, H-6a″), 4.26 (dd, 1 H, H-6a), 4.25 (d, 1 H, H-1), 4.15 (dd, 1 H, H-6b″), 4.09 (dd, 1 H, H-6b), 3.52 (ddd, 1 H, H-5″), 3.30 (ddd, 1 H, H-5), 2.15–2.00 (m, 24 H, OAc); $J_{1,2}$ 10.5, $J_{2,3}$ 9.4, $J_{3,4}$ 10.0, $J_{4,5}$ 10.5, $J_{5,6a}$ 5.6, $J_{5,6b}$ 3.5, $J_{6a,6b}$ 12.2, $J_{1'',2''}$ 10.8, $J_{2'',3''}$ 9.5, $J_{3'',4''}$ 9.5, $J_{4'',5''}$ 10.5, $J_{5'',6a''}$ 5.6, $J_{5'',6b''}$ 3.1, $J_{6a'',6b''}$ 12.1 Hz; $^{13}C$ NMR: δ 170.5, 170.3, 169.6, 169.5, 169.3, 169.2, 168.8, 168.6 (C=O), 139.7 (C-1′), 138.7 (C-2′), 133.4 (C-6′), 132.1 (C-5′), 131.9 (C-3′), 113.1 (C-4′), 117.4 (CN), 74.8 (C-3″), 74.5 (C-2″), 74.2 (C-3), 73.8 (C-2), 71.8 (C-4″), 71.4 (C-4), 61.1, 61.0 (C-6, C-6″), 52.0 (C-1), 44.8, 44.7 (C-5, C-5″), 44.3 (C-1″), 20.8, 20.7, 20.6, 20.6, 20.5, 20.5, 20.4, 20.2 (OAc). Anal. Calcd. for

$C_{35}H_{41}NO_{16}S_3$: C, 50.78; H, 4.99; N, 1.69; S, 11.62. Found: C, 50.89; H, 4.85; N, 1.81; S, 11.70.

*4-Cyanophenyl 1,5-dithio-β-D-glucopyranoside* (**2**). —Deacetylation of **6** (1.50 g, 3.1 mmol) with M NaOMe (0.1 mL) in MeOH (60 mL) yielded, after deionisation with DOWEX 50 WX resin, concn and crystallisation with ether, **2** (1.0 g, 93%), mp 206–209 °C; $[\alpha]_D$ −14° (*c* 0.5, MeOH); $R_f$ 0.2 (solvent E). Anal. Calcd. for $C_{13}H_{15}NO_4S_2$: C, 49.82; H, 4.82; N, 4.47; S, 20.46. Found: C, 49.97; H, 4.71; N, 4.63; S, 20.37.

*4-Cyano-2-(5-thio-α-D-glucopyranosyl)phenyl 1,5-dithio-β-D-glucopyranoside* (**15**).—Deacetylation of **14** (280 mg, 0.34 mmol) with M NaOMe (0.1 mL) in MeOH (20 mL) yielded, after deionisation with DOWEX 50 WX resin and concn, **15** (160 mg, 96%); $[\alpha]_D$ +42° (*c* 0.8, MeOH); $R_f$ 0.5 (solvent F); $^1$H NMR: ($Me_2SO$-$d_6$) δ 7.89 (d, 1 H, H-3′), 7.82 (d, 1 H, H-6′), 7.65 (dd, 1 H, H-5′), 4.73 (d, 1 H, H-1″), 4.45 (d, 1 H, H-1), 3.80 (dd, 1 H, H-2″), 3.75 (dd, 1 H, H-6a), 3.55 (dd, 1 H, H-6b), 3.60–3.90 (m, 4 H, H-3″, H-4″, H-6a″, H-6b″), 3.36 (m, 2 H, H-2, H-4), 3.12 (dd, 1 H, H-3), 2.88 (ddd, 1 H, H-5), 2.75 (m, 1 H, H-5″); $J_{1,2}$ 10.0, $J_{2,3}$ 8.5, $J_{3,4}$ 8.5, $J_{4,5}$ 9.8, $J_{5,6a}$ 3.2, $J_{5,6b}$ 6.6, $J_{6a,6b}$ 11.5, $J_{1'',2''}$ 1.5 Hz; $^{13}$C NMR: ($Me_2SO$-$d_6$) δ 142.6, 140.6 (C-1′, C-2′), 132.4, 130.5, 129.8 (C-3′, C-5′, C-6′), 107.5 (C-4′), 119.2 (CN), 78.8, 75.9, 73.5, 72.8, 72.0, 70.5 (C-2, C-3, C-4, C-2″, C-3″, C-4″), 62.0, 60.6 (C-6, C-6″), 51.0 (C-1), 49.8, 48.7 (C-5, C-5″), 39.8 (C-1″). Anal. Calcd. for $C_{19}H_{25}NO_8S_3$: C, 46.42; H, 5.13; N, 2.85; S, 19.57. Found: C, 46.55; H, 5.21; N, 2.73; S, 19.68.

*Glycosidation of 4-cyanobenzenethiol with* **18**.—Under argon, to a stirred soln of 4-cyanobenzenethiol (0.17 g, 1.26 mmol) and **18** [10] (0.5 g, 0.98 mmol) in dry $CH_2Cl_2$ (20 mL), 0.1 M boron trifluoride etherate in $CH_2Cl_2$ (1.0 mL) was added at −20 °C and the mixture was stirred at −20 °C for 30 min. The reaction was quenched with $Et_3N$, concentrated and the residue was submitted to column chromatography (solvent B) to yield a mixture, containing **6** and **7** in a 3:7 ratio (0.25 g, 53%).

*Glycosidation of 4-cyanobenzenethiol with* **28**.—To a stirred soln of **27** [6] (1.3 g, 3.7 mmol) in dry $CH_2Cl_2$ (20 mL), 33% hydrogen bromide in $CH_3COOH$ (4 mL) was added. After 1 h at room temperature, the mixture was poured into ice-water, extracted with $CH_2Cl_2$, washed with 6% aqueous $NaHCO_3$, brine and concentrated to yield **28** (1.35 g, 98%), $R_f$ 0.5 (solvent B). The bromide **28** thus obtained was added to a stirred suspension of 4-cyanobenzenethiol (0.54 g, 4 mmol) and potassium carbonate (1.08 g, 7.8 mmol) in acetone (110 mL) and the mixture was refluxed for 3 h. After cooling to room temperature, the precipitated salts were filtered off, washed with acetone, the filtrate was concentrated and submitted to column chromatography (solvent B, then A). Concentration of the first fraction gave 4-cyanophenyl 2,3,4-tri-*O*-acetyl-6-deoxy-1,5-dithio-α-D-glucopyranoside (**29**, 110 mg, 7%), mp 184–186 °C (ether); $[\alpha]_D$ +446°; $R_f$ 0.45 (solvent B). Anal. Calcd. for $C_{19}H_{21}NO_6S_2$: C, 53.89; H, 5.00; N, 3.31; S, 15.14. Found: C, 53.95; H, 4.88; N, 3.47; S, 15.27.

Concentration of the second fraction yielded 4-cyanophenyl 2,3,4-tri-*O*-acetyl-6-deoxy-1,5-dithio-β-D-glucopyranoside (**30**, 0.87 g, 56%), mp 134–136 °C (ether); $[\alpha]_D$ +57°; $R_f$ 0.4 (solvent B). Anal. Calcd. for $C_{19}H_{21}NO_6S_2$: C, 53.89; H, 5.00; N, 3.31; S, 15.14. Found: C, 53.77; H, 5.13; N, 3.24; S, 15.09.

Concentration of the third fraction gave 4-cyano-2-(2,3,4,6-tetra-*O*-acetyl-6-deoxy-5-thio-α-D-glucopyranosyl)phenyl 2,3,4,6-tetra-*O*-acetyl-6-deoxy-1,5-dithio-β-D-glucopyranoside (**31**, 105 mg, 8%), mp 188–190 °C (ether); $[\alpha]_D$ +181° (*c* 0.4, $CHCl_3$); $R_f$ 0.2 (solvent B). $^1$H NMR: δ 7.92 (d, 1 H, H-3′), 7.84 (d, 1 H, H-6′), 7.62 (dd, 1 H, H-5′), 5.50–4.95 (m, 7 H, H-2, H-3, H-4, H-1″, H-2″, H-3″, H-4″), 4.20 (d, 1 H, H-1), 3.08 (m, 1 H, H-5), 2.96 (m, 1 H, H-5″), 1.22 (d, 1 H, H-6″), 1.12 (d, 1 H, H-6), 1.92–2.10 (m, 18 H, OAc); $J_{1,2}$ 10.8, $J_{4,5}$ 9.7, $J_{5,6}$ 6.8, $J_{4'',5''}$ ~ 10, $J_{5'',6''}$ 6.8 Hz; $^{13}$C NMR: δ 170.4, 169.5, 169.4, 169.2, 169.1, 168.9 (C=O), 139.9, 139.4 (C-1′, C-2″), 133.5 (C-6′), 131.5 (C-3′), 131.5 (C-5′), 111.9 (C-4′), 117.6 (CN), 75.6, 75.6, 74.2, 73.6, 71.8, 71.2 (C-2, C-3, C-4, C-2″, C-3″, C-4″), 52.0 (C-1), 40.8, 40.2 (C-5, C-5″), 36.1 (C-1″), 16.3, 15.2 (C-6, C-6″), 20.6, 20.6, 20.5, 20.5, 20.4, 20.3 (OAc). Anal. Calcd. for $C_{31}H_{37}NO_{12}S_3$: C, 52.31; H, 5.24; N, 1.97; S, 13.51. Found: C, 52.47; H, 5.14; N, 2.06; S, 13.70.

The ratio of products did not change when the reaction was carried out in the presence of TEMPO (0.2 equiv.), or sulfur (0.1 equiv.).

*4-Cyanophenyl 6-deoxy-1,5-dithio-β-D-glucopyranoside* (**3**).—Deacetylation of **30** (0.8 g, 1.9 mmol) with M NaOMe (0.1 mL) in MeOH (40 mL) yielded, after deionisation with DOWEX 50 WX resin and concn, **3** (0.52 g, 93%), mp 207–212 °C (ether); $[\alpha]_D$ −28° (*c* 0.5, MeOH); $R_f$ 0.3 (solvent D). Anal. Calcd. for $C_{13}H_{15}NO_3S_2$: C, 52.50; H, 5.08; N, 4.71; S, 21.56. Found: C, 52.63; H, 5.13; N, 4.89; S, 21.47.

*4-Cyanophenyl 2,3,4-tri-O-acetyl-6-O-methanesulfonyl-1,5-dithio-β-D-glucopyranoside* (**32**)

and *4-cyanophenyl 2,4-di-O-acetyl-3,6-di-O-methanesulfonyl-1,5-dithio-β-D-glucopyranoside* (**34**). —To a stirred soln of **2** (1.3 g, 4.15 mmol) in pyridine (18 mL) mesyl chloride (0.4 mL, 5.2 mmol) in $CHCl_3$ (5 mL) was added at 0 °C. The mixture was stirred at room temperature for 3 h, then acetic anhydride (8 mL) was added and the reaction was kept overnight at room temperature. The mixture was poured into ice-water, extracted with $CH_2Cl_2$ and the organic layer was processed in the usual way. The residue obtained upon concn was submitted to column chromatography (solvent A). Concentration of the first fraction gave **6** (60 mg, 3%).

Concentration of the second fraction yielded **32** (1.15 g, 54%), mp 119–122 °C (ether); $[\alpha]_D$ +28°; $R_f$ 0.3 (solvent A). Anal. Calcd. for $C_{20}H_{23}NO_9S_3$: C, 46.41; H, 4.48; N, 2.71; S, 18.58. Found: C, 46.54; H, 4.31; N, 2.85; S, 18.63.

Concentration of the third fraction gave **34** as an unstable syrup (90 mg, 4%), $R_f$ 0.25 (solvent A). Anal. Calcd. for $C_{19}H_{23}NO_{10}S_4$: C, 41.22; H, 4.19; N, 2.53; S, 23.16. Found: C, 41.43; H, 4.13; N, 2.71; S, 23.27.

*4-Cyanophenyl 2,3,4-tri-O-acetyl-6-deoxy-6-iodo-1,5-dithio-β-D-glucopyranoside* (**33**).—To a stirred soln of **32** (1.15 g, 2.2 mmol) in 3-pentanone (55 mL), sodium iodide (0.6 g, 4.0 mmol) was added and the mixture was refluxed for 4 h. After cooling to room temperature, the precipitated salts were filtered off, washed with $CH_2Cl_2$, the filtrate was concentrated and the residue was submitted to column chromatography (solvent B) to yield **33** (1.2 g, 98%), $[\alpha]_D$ 0°; $R_f$ 0.4 (solvent B). Anal. Calcd. for $C_{19}H_{20}INO_6S_2$: C, 41.54; H, 3.67; I, 23.10; N, 2.55; S, 11.67. Found: C, 41.42; H, 3.75; I, 23.21; N, 2.67; S, 11.72.

*Reduction of* **33**.—To a stirred mixture of **33** (1.2 g, 2.18 mmol) and sodium borohydride (0.22 g, 5.8 mmol) in EtOH (45 mL) nickel(II) chloride hexahydrate (20 mg) was added and stirring was continued at room temperature for 30 min. The reaction mixture was neutralised with 4% aq HCl, filtered, the filtrate was concentrated and submitted to column chromatography (solvent B) to yield **31** (0.4 g, 43%) identical with the compound described above.

*4-Cyanophenyl 2,3,4-tri-O-acetyl-6-deoxy-1,5-dithio-β-D-xylo-hex-5-enopyranoside* (**35**).—To a stirred soln of **33** (0.5 g, 0.91 mmol) in pyridine (12 mL), silver fluoride (0.4 g, 3.15 mmol) was added and stirring was continued at room temperature for 2 h. The mixture was diluted with $CHCl_3$, filtered, concentrated and submitted to column chromatography (solvent B) to yield **35** (0.29 g, 76%), mp 150–153 °C (ether); $[\alpha]_D$ −36°; $R_f$ 0.4 (solvent B). Anal. Calcd. for $C_{19}H_{19}NO_6S_2$: C, 54.14; H, 4.54; N, 3.32; S, 15.21. Found: C, 54.05; H, 4.69; N, 3.26; S, 15.33.

*4-Cyanophenyl 6-deoxy-1,5-dithio-β-D-xylo-hex-5-enopyranoside* (**4**).—Deacetylation of **35** (200 mg, 0.47 mmol) with M NaOMe (0.1 mL) in MeOH (60 mL) yielded, after deionisation with DOWEX 50 WX resin, concn and crystallisation with ether, **4** (130 mg, 93%), mp 152–156 °C (ether); $[\alpha]_D$ −99° (*c* 0.3, MeOH); $R_f$ 0.4 (solvent E). Anal. Calcd. for $C_{13}H_{13}NO_3S_2$: C, 52.86; H, 4.44; N, 4.74; S, 21.71. Found: C, 52.69; H, 4.31; N, 4.83; S, 21.57.

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