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Synthesis of 4-substituted phenyl 2,5-anhydro-1,6-dithio-α-D-gluco- and -α-L-guloseptanosides possessing antithrombotic activity☆

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Abstract

Two independent approaches were investigated for the synthesis of 3,4-di-*O*-acetyl-1,6:2,5-dianhydro-1-thio-D-glucitol (**18**), a key intermediate in the synthesis of 1,3,4-tri-*O*-acetyl-2,5-anhydro-6-thio-α-D-glucoseptanose (**13**), needed as glycosyl donor. In the first approach 1,6-dibromo-1,6-dideoxy-D-mannitol was used as starting material and was converted via 2,5-anhydro-1,6-dibromo-1,6-dideoxy-4-*O*-methanesulfonyl-3-*O*-tetrahydropyranyl-D-glucitol into **18**. The second approach started from 1,2:5,6-di-*O*-isopropylidene-D-mannitol and the allyl, 4-methoxybenzyl as well as the methoxyethoxymethyl groups were used, respectively, for the protection of the 3,4-OH groups. The resulting intermediates were converted via their 1,2:5,6-dianhydro derivatives into the corresponding 3,4-O-protected 2,5-anhydro-6-bromo-6-deoxy-D-glucitol derivatives. The 1,6-thioanhydro bridge was introduced into these compounds by exchanging the bromine with thioacetate, activating OH-1 by mesylation and treating these esters with sodium methoxide. Among these approaches, the 4-methoxybenzyl protection proved to be the most suitable for a large scale preparation of **18**. Pummerer rearrangement of the sulfoxide, obtained via oxidation of **18** gave a 1:9 mixture of 1,3,4-tri-*O*-acetyl-2,5-anhydro-6-thio-α-L-gulo- (**12**) and -D-glucoseptanose **13**. When **12** or **13** were used as donors and trimethylsilyl triflate as promoter for the glycosylation of 4-cyanobenzenethiol, a mixture of 4-cyanophenyl 3,4-di-*O*-acetyl-2,5-anhydro-1,6-dithio-α-L-gulo- (**58**) and -α-D-glucoseptanoside (**61**) was formed suggesting an isomerisation of the heteroallylic system of the intermediate. A similar mixture of **58** and **61** resulted when **18** was treated with *N*-chloro succinimide and the mixture of chlorides was used in the presence of zinc oxide for the condensation with 4-cyanobenzenethiol. When 4-nitrobenzenethiol was applied as aglycon and boron trifluoride etherate as promoter, a mixture of 4-nitrophenyl 3,4-di-*O*-acetyl-2,5-anhydro-1,6-dithio-α-L-gulo- (**60**) and -α-D-glucoseptanoside (**62**) was obtained. Deacetylation of **58**, **61** and **62** according to Zemplén afforded 4-cyanophenyl 2,5-anhydro-1,6-dithio-α-L-guloseptanoside (**59**), 4-cyanophenyl 2,5-anhydro-1,6-dithio-α-D-glucoseptanoside (**63**) and 4-nitrophenyl 2,5-anhydro-1,6-dithio-α-D-glucoseptanoside (**66**), respectively. The 4-cyano group of **63** was transformed into the 4-aminothiocarbonyl, and the 4-(methylthio)(imino)methyl derivative and the 4-nitro group of **66** into the acetamido derivative. All of these thioglycosides displayed a stronger oral antithrombotic effect in rats compared with beciparcil, used as reference.

Keywords: 2,5-Anhydro-D-glucitol derivatives; 2,5-Anhydro-1,6-dithio-α-L-gulo- and -α-D-glucoseptanosides; Glycosidation reactions; Thioglycosides; Oral antithrombotic activity

☆ Orally active antithrombotic thioglycosides, Part X. For Part IX, see [1].

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1. Introduction

In a previous paper [2] we have shown that, in contrast to the statement of the literature [3], the oral antithrombotic effect of 4-cyanophenyl 1,5-dithio-pentopyranosides is not restricted to the β-D-*xylo* configuration as, e.g., the corresponding 1,5-dithio-β-D-glucopyranosides (**1**) and even the thioglycosides of overbridged, 2,6 - thioanhydro - hexopyranosides (**2**) [4], can exert significant biological activity. Based on these facts the synthesis of overbridged 2,5-anhydro-1,6-dithio-D-glucoseptanosides (**3**) was decided (Scheme 1).

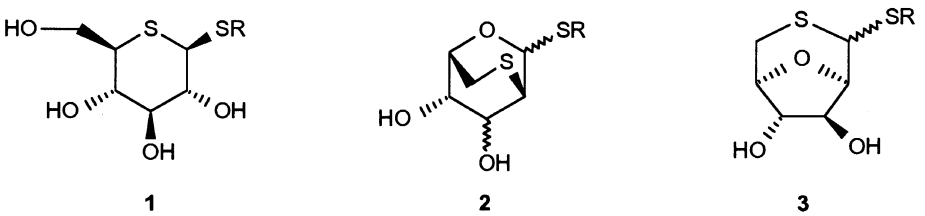
2. Results and discussion

Synthesis of the donor molecules.—For the synthesis of the aforementioned thioglycosides, the tri-*O*-acetate **13**, already described in 1976, was needed as donor [5]. This 11 step synthesis started from 1,6-dibromo-1,6-dideoxy-D-mannitol (**4**), but the overall yield of the applied sequence **4**→**5**→**6**→**9**→**15**→**18**→**14**→**13** [5–11] was ~2%, making this approach unsuitable for a larger scale preparation.

To avoid the lowest yielding step of this reaction sequence, i.e., the reductive splitting of the mesyloxy groups (**9**→**15**), an alternative approach was applied by tosylating the free 3-OH group of **5** and converting the obtained **7** via **10**→**16**→**17** into **15** [10]. Despite the fact that the individual reactions of this approach gave satisfactory yields, the overall yield was not increased substantially due to the increased number of steps.

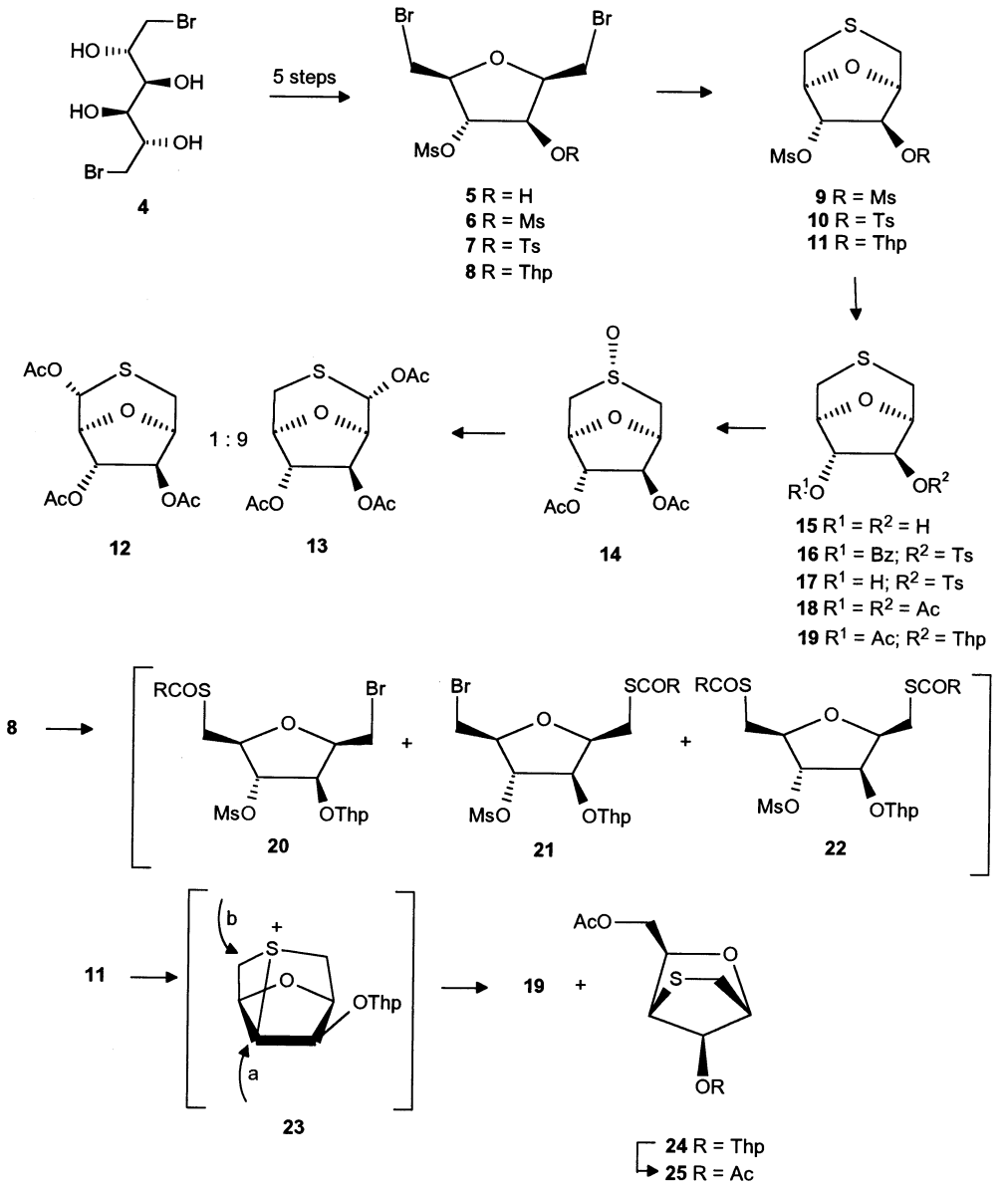
To circumvent the reductive cleavage of the 3-*O*-sulfonic esters, the tetrahydropyranyl blocking group was applied in the next approach for the protection of the 3-OH group of **5**. According to NMR spectroscopy the ether **8**, which was obtained in quantitative yield, proved to be a mixture containing the two tetrahydropyranyl diastereomers in a 1:1 ratio. Reaction of **8** with sodium sulfide afforded the 1,6-thioanhydro derivative **11** in modest yield, which could be substantially increased by applying a two step process. Accordingly **8** was treated with a slight excess (1.2 equivalents) of the potassium salt of a thioacid and the formed mixture was converted without separation into **11** with an excess of sodium methoxide in the presence of methanol. When potassium thiobenzoate was applied as reagent the yield of **11** was 50%, while potassium thioacetate gave somewhat lower yields. The 4-mesyloxy group of **11** could be exchanged with retention of configuration with the acetoxy group on treatment with sodium acetate in *N*,*N*-dimethylformamide. In this reaction a large excess of sodium acetate had to be applied, otherwise the reaction was sluggish, and besides **19** (route a) a relatively large amount (> 10%) of the rearranged 1,4-thioanhydro derivative **24** was formed, which could be isolated after hydrolysis and acetylation as its diacetate **25**. Formation of **24** can be explained via the attack of the acetoxy anion at C-6 of the sulfonium intermediate **23** (route b). The tetrahydropyranyl group of the formed monoester **19** could be removed in methanol in the presence of an ion exchange resin (H^+) and gave diacetate **18** after subsequent acetylation in crystalline state. In spite of the fact that the overall yield of the conversion of **4** into **18** by this approach was essentially the same as that of the original reaction sequence [10], the applied reactions were much simpler and could be easily scaled up (Scheme 2).

A further drawback of all these approaches was that dibromide **4** was needed as starting material, which is no longer available



1 2 3

Scheme 1.



Scheme 2.

commercially[2] and the conversion of D-mannitol into **4** in a laboratory is quite cumbersome [12,13], especially on a large scale. To overcome these difficulties, another synthetic strategy was considered by using a properly substituted 2,5-anhydro-6-bromo-6-deoxy-D-glucitol derivative as the key intermediate, which can be prepared from D-mannitol via its easily obtainable 1,2:5,6-di-*O*-isopropylidene derivative **26** [14]. For the protection of the two hydroxyl groups of **26**, the allyl group was chosen and subsequent hydrolysis of the *O*-isopropylidene groups of the formed ether **27** led to **30** [15], which was converted via **33** into diepoxide **42** [16]. Treatment of the latter with hydrogen bromide in acetone afforded the key intermediate **38** [16], which was converted into the 6-*S*-acetyl derivative **45**. The 1-OH group of the latter was activated by mesylation, and treatment of the obtained mesylate **48** with sodium methoxide in methanol afforded thioanhydride **51**. However, the conversion of **51** into **15**, i.e., the removal of the allyl protecting groups proved to be problematic, as neither basic [17] or acidic conditions [18], nor the reductive cleavage with sodium

[2] Compound **4** had been produced by Chinoin (Budapest, Hungary) and sold under the tradename *Myelobromol* as a cytostatic.

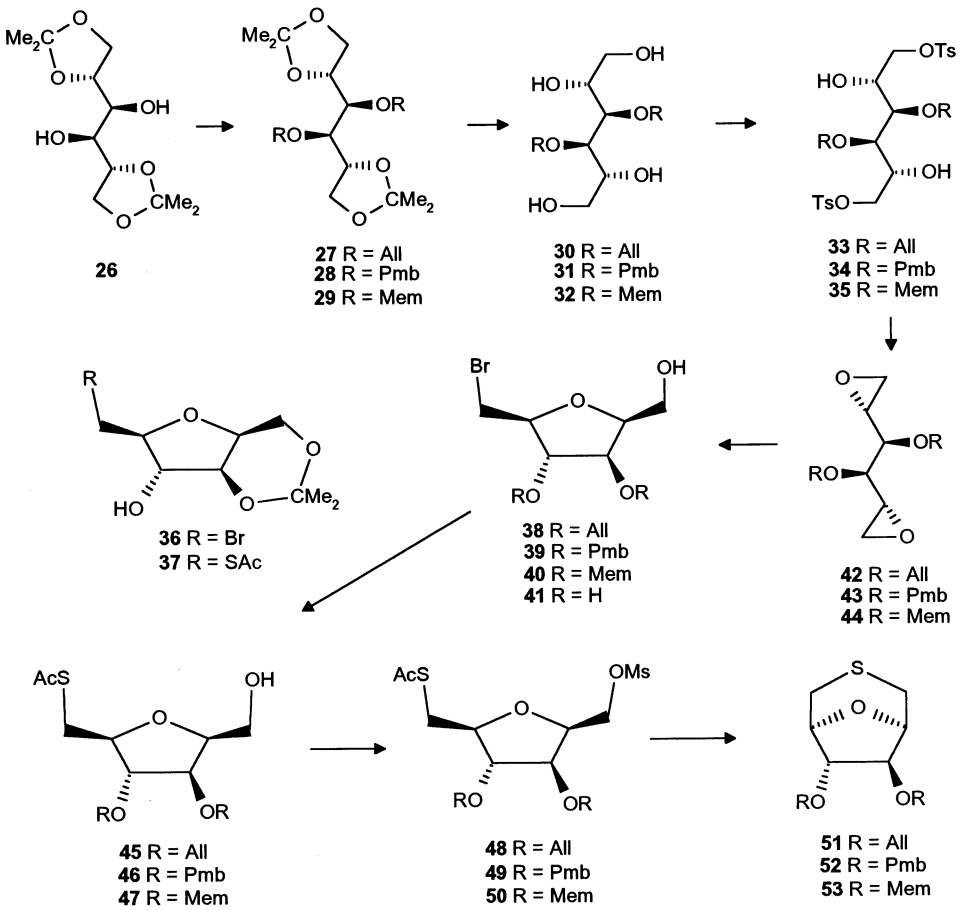
borohydride/iodide, described recently [19], led to the desired result. Finally the boron tribromide method, which was successfully used [20] for the O-debenzylation of similar 1,6-thioanhydro-derivatives was applied, and although according to thin-layer chromatography (TLC) the deallylation took place, the resulting dihydroxy derivative **15** could be separated in traces only.

To overcome these difficulties, the whole reaction sequence was repeated using the more easily removable 4-methoxybenzyl group for the protection of the corresponding hydroxyl groups. Accordingly, **26** was converted via the **28** → **31** → **34** → **43** → **39** → **46** → **49** reaction sequence into **52**, the 4-methoxybenzyl blocking groups of which could be removed either by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone or by acidic hydrolysis (MeOH–water–HCl). In both cases the dihydroxy derivative **15** had to be purified by column chromatography. The overall yield of this reaction sequence estimated from **26** was ~9%.

Finally, we tried to avoid this last purification step by applying the 2-methoxyethoxymethyl group for the protection of the 3,4-OH groups of **26** converting it via **29** → **32** → **35** into diepoxide **44**. Treatment of this latter with concentrated hydrogen bromide in acetone — the usual conditions used for converting the corresponding diepoxides into the monobromo-2,5-anhydro compounds — led to the simultaneous cleavage of the O-methoxyethoxymethyl groups, and the trihydroxy derivative **41** formed was partially converted into its 1,3-*O*-isopropylidene derivative **36**. This was isolated and characterised as its 6-*S*-acetate **37**. To avoid this untimely cleavage of the O-protecting groups, the addition of hydrobromic acid was carried out in the presence of potassium bromide by slowly adding one equivalent of sulfuric acid. In this way the formed anhydro derivative **40** could be isolated in a yield of 58%. Its conversion via the **40** → **47** → **50** reaction sequence into the protected thioanhydride **53** caused no problems. The protecting groups of **53** could be split off easily by treatment with acid, but the overall yield of the obtained dihydroxy derivative **15** remained below 5% (Scheme 3).

Among the further reactions needed for the conversion of the thioanhydro-glucitol derivative **15** into the desired glucothioseptanose donor molecule **13**, the acetylation and subsequent oxidation **15** → **18** → **14** caused no problems; however, the Pummerer rearrangement of sulfoxide **14** led to a syrupy mixture containing the L-gulo **12** and the D-gluco **13** isomer in a ratio of 1:9. Because of their very similar R_f values, they could only be partially separated by repeated column chromatography, but for the synthesis of the corresponding thioglucosides it was not necessary to separate them, as the glycosides resulting after deacetylation could be easily purified by crystallisation.

Glycosidation reactions.—For the synthesis of the glucoseptanoside **61**, the glucotriacetate **13** was used as donor, 4-cyanobenzenethiol as acceptor and trimethylsilyl triflate as promoter. Despite the fact that the isolated glycoside gave on TLC only one spot, according to NMR spectroscopy it contained, besides **61**, ~10% of the corresponding gulo isomer **58**. This fact led to the suppositions that during the condensation reaction, the primarily formed sulfonium ion **55** might undergo a heteroallylic rearrangement, affording in an equilibrium reaction the isomeric ion **54**. Both ions can be attacked by the bulky aglycon only from the less hindered 'exo' side, yielding the corresponding α anomers **58** and **61**, respectively. This supposition was backed by the fact that when the pure *gulo*-triacetate **12** was applied as donor, again both thioglycosides **58** and **61** were formed, but their ratio was 6:1. That means that the rate of the isomerisation cannot be faster than that of the glycosidation, otherwise the same 1:9 ratio should have been reached as in the first case. On the other hand, the isomerisation made the tedious separation of the two triacetate donors **12** and **13** unnecessary, as when their 1:9 mixture — obtained in the Pummerer reaction — was used, the resulting thioglycoside mixture contained the gulo **58** and the gluco **61** isomers in the same 1:9 ratio, as in the first case when pure **13** was applied as donor. As the acetylated thioglycosides possessed identical R_f values, they could not be separated by column chromatography, but during deacetylation ac-



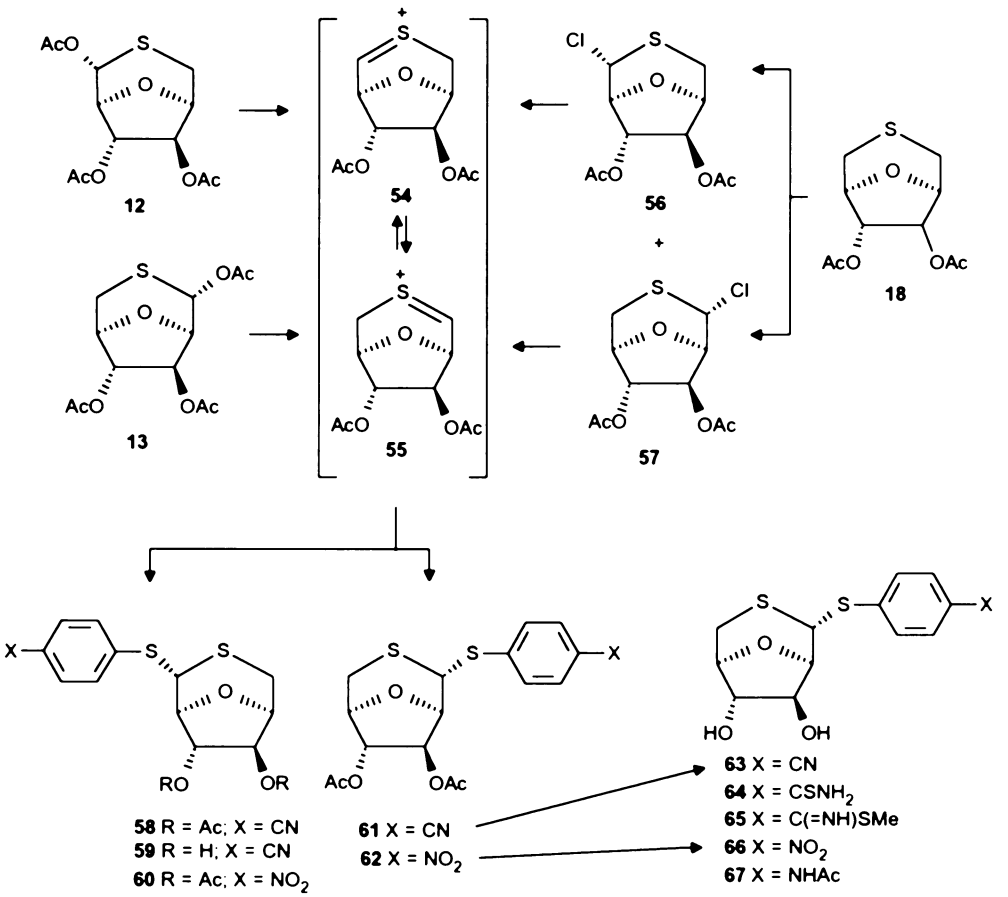
Scheme 3.

cording to Zemplén the main component crystallised spontaneously and could be purified further by recrystallisation from methanol. In this way, both **59** and **63** were obtained in pure isomer-free form.

As is known from the literature [21] that cyclic thioethers, in which the sulfur atom is flanked by methylene groups, can be converted into α-chloro derivatives on treatment with *N*-chlorosuccinimide, this reaction was applied to the thioanhydro glucitol **18**. Theoretically both the gulo **56** and the gluco-acetochloro isomer **57** can be formed this way, and although two distinct spots could be detected on TLC, the individual compounds could not be isolated because of their instability. Nevertheless if their solution was used directly for the glycosylation of the aglycon in the presence of zinc oxide as promoter, the two isomeric glycosides **58** and **61** were formed in the same ratio (1:9) as in the case when a 1:9 mixture of triacetates **12** + **13** was used as donor in the presence of trimethylsilyl triflate. Accordingly, it could be assumed that both chloro compounds **56** and **57** were formed and reacted further via the sulfonium intermediates **54** and **55**, mentioned above.

For investigating the influence of the 4′-substituent of the aglycon on the biological activity, transformations of the 4′-cyano group of **63**, which increased the biological activity in the case of the corresponding thioxylopyranoside [22], were carried out. Accordingly, **63** was transformed into the thioamide **64** by treatment with hydrogen sulfide in pyridine-triethylamine solution. Methylation of **64** with methyl iodide in acetone afforded the methylthioimine **65**.

When 4-nitrobenzenethiol was used as aglycon in the glycosylation reaction and boron trifluoride etherate as promoter, according to NMR spectroscopy, a 1:4 mixture of the corresponding L-gulo- **60** and D-glucothioheptanoside **62** was obtained in a yield of 90%, which could not be separated. Deacetylation of this mixture afforded crystalline **66**. The



Scheme 4.

Table 1
Oral antithrombotic activity of 4-substituted phenyl 2,5-anhydro-1,6-dithio-α-L-gulo- (**59**) and -α-D-glucoseptanosides (**63**–**67**) in rats using Pescador's model [23] compared with beciparcil

Compound	Ref [a]	**59**	**63**	**64**	**65**	**66**	**67**
R [b]	CN	CN	CN	$CSNH_2$	C(NH)SMe	NO_2	NHAc
ED_{50} (mg/kg)	25	3	3.5	2	3	2	2

[a] Ref, reference compound (beciparcil = 4-cyanophenyl 1,5-dithio-β-D-xylopyranoside) [3].
[b] 4′-Sustituent of the aglycon.

4-nitro group of the latter was reduced with sodium borohydride to give after acetylation and subsequent O-deacetylation, according to Zemplén, the 4-acetamido derivative **67** (Scheme 4).

Biological results.—The oral antithrombotic activity of **59**, **63**, **64**, **65**, **66**, and **67** was determined in rats using Pescador's model [23]. All compounds were administered orally 3 h before ligation. From the data listed in Table 1, it can be seen that all thioglycosides were ~10-fold active as beciparcil [3] used as reference compound, but transformations of the 4′-substituent of the aglycon had no significant influence on the biological effect.

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 60 F_{254} plates with EtOAc (A), EtOAc–hexane mixtures (B, 1:1; C, 1:2; D, 1:3; E, 1:4; F, 2:1; G, 3:1; H,

2:3), EtOAc–EtOH mixture (I 9:1), toluene–MeOH mixture (J, 4:1), CH_2Cl_2–MeOH mixtures (K, 9:1, L 95:5), CH_2Cl_2–acetone mixture (M, 9:1) and $CHCl_3$–MeOH mixture (N, 95:5); detection by spraying the plates with a 0.02 M solution of I_2 and a 0.3 M solution of KI in 10% aq H_2SO_4 soln, followed by heating at ca. 200 °C. For column chromatography Kieselgel 60 was used. The melting points are uncorrected. Optical rotations were determined on 1.0% solutions in $CHCl_3$ at 20 °C unless stated otherwise. NMR spectra were recorded with a Bruker AC 250 spectrometer at 250 MHz (^{1}H) and 62.9 MHz (^{13}C) for solutions 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 experiments. The ratio of α:β anomeric mixtures was determined by ^{1}H NMR.

*2,5-Anhydro-1,6-dibromo-1,6-dideoxy-4-*O*-methanesulfonyl-3-*O*-tetrahydropyranyl-*D*-glucitol* (**8**).—To a stirred solution of **5** [6] (26.5 g, 72 mmol) in CH_2Cl_2 (240 mL), 3,4-dihydro-2-*H*-pyran (8.45 mL, 93 mmol) and subsequently p-TsOH (70 mg) were added. The solution was kept at 20 °C for 1 h during which time it turned blue. Thereafter it was washed with 5% aq $NaHCO_3$ and water, dried and concentrated to give **8** (32.5 g, 100%) as a colourless oil. R_f 0.4 + 0.45 (solvent C); ^{1}H NMR: δ 5.30 (m, 1 H, H-2′), 5.06, 4.86, 4.74, 4.52 (4m, 2 H, H-3,4), 4.50–4.25 (m, 2 H, H-2,5), 3.92, 3.50 (m, 2 H, H-6′), 3.70–3.35 (m, 4 H, H-1a,1b,6a,6b), 3.13 (s, 3 H, OMs), 1.85–1.45 (m, 6 H, H-3′,4′,5′); ^{13}C NMR: δ 102.5, 96.7 (C-2′), 85.1, 84.2, 83.4, 83.0, 82.2, 81.8, 81.5, 77.8 (C-2,3,4,5), 63.8, 63.0 (C-6′), 38.8, 38.2 (OMs), 30.8, 30.5, 30.3, 28.0, 26.9, 25.0, 19.9, 19.2 (C-1,6,3′,4′,5′). Anal. Calcd for $Br_2C_{12}H_{20}O_6S$: Br, 35.34; C, 31.88; H, 4.46; S, 7.09. Found: Br, 35.23; C, 31.57; H, 4.50; S, 7.00.

*1,6:2,5-Dianhydro-4-*O*-methanesulfonyl-3-*O*-tetrahydropyranyl-1-thio-*D*-glucitol* (**11**).—To a stirred solution of **8** (30.1 g, 66.6 mmol) in acetone (500 mL), potassium thiobenzoate (14 g, 79.4 mmol) was added and the reaction mixture was boiled for 4 h. The formed slurry was cooled, filtered and the salts were washed with acetone (200 mL). The filtrate was concentrated, the residue dissolved in CH_2Cl_2, washed with 5% aq $NaHCO_3$ and water, dried and concentrated to a volume of ~500 mL. This solution contained according to TLC (solvent C) and NMR measurements several components, most probably the diastereomers of **20**, **21** and **22** [10] and afforded on evaporation a syrup (33.9 g). As the individual components could not be separated by column chromatography, the original solution was used in the further reaction. It was cooled with ice, MeOH (100 mL) and subsequently 3 M NaOMe in MeOH (24.5 mL) was added with stirring. The mixture was kept at 20 °C for 3 h and was then neutralised with solid CO_2. The formed precipitate was filtered off and washed with $CHCl_3$ (50 mL). The residue, obtained on concentration of the filtrate was dissolved in $CHCl_3$, washed with water, dried and concentrated. The residue was purified by column chromatography (solvent C containing 0.1% triethylamine) to give after concentration of the fractions having R_f 0.5 (solvent C) **11** (10.7g, 50%) as a syrup; ^{1}H NMR: δ 5.62–5.55 (m, 1 H, H-4), 4.75 (m, 1 H, H-2′), 4.65–4.35 (m, 3 H, H-2,3,5), 4.10, 3.80, 3.65–3.45 (m, 2 H, H-6′), 3.25–3.05 (m, 2 H, H-1ax,6ax), 3.13, 3.10 (2 s, 6 H, OMs) 2.50–2.30 (m, 2 H, H-1eq,6eq), 2.00–1.40 (m, 6 H, H-3′,4′,5′); ^{13}C NMR: δ 100.1, 100.0 (C-2′), 87.8, 86.8, 84.1, 82.1, 80.1, 78.8, 76.9, 76.1 (C-2,3,4,5), 63.8, 62.7 (C-6′), 39.1, 37.9 (OMs), 30.8, 30.6, 28.0, 27.8, 25.3, 25.0, 24.6, 24.5 (C-1,6,3′,5′), 20.1, 19.0 (C-4′). Anal. Calcd for $C_{12}H_{20}O_6S_2$: C, 44.43; H, 6.21; S, 19.77. Found: C, 44.48; H, 6.37; S, 19.56.

*1,3,4-Tri-*O*-acetyl-2,5-anhydro-6-thio-α-*L*-guloseptanose* (**12**) *and 1,3,4-tri-*O*-acetyl-2,5-anhydro-6-thio-α-*D*-glucoseptanose* (**13**).—A solution of sulfoxide **14** [5,11] in Ac_2O was kept at 100 °C for 8 h and was then concentrated. The residue was dissolved in EtOH (100 mL), concentrated and this was repeated once more. The residue was dissolved in CH_2Cl_2, washed with 5% aq $NaHCO_3$ and water, dried and concentrated to give a syrup (30 g, 100%) containing, according to NMR spectroscopy, **12** and **13** in a ratio of 1:9. This mixture could be partially separated by column chromatography (solvent C). Concentration of the first fraction yielded **12** (2 g); $[\alpha]_D$ −92° (*c* 0.4, $CHCl_3$); R_f 0.45 (solvent C);

^{1}H NMR: δ 5.97 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 5.72 (d, $J_{2,3}$ 0, $J_{3,4}$ 2.9 Hz, H-3), 5.30 (dd, $J_{4,5}$ 6.4 Hz, H-4), 4.78 (ddd, 1 H, $J_{5,6ax}$ 3.2, $J_{5,6eq}$ 1.0 Hz, H-5), 4.29 (d, 1 H, H-2), 3.28 (dd, 1 H, $J_{6ax,6eq}$ 13.7 Hz, H-6ax), 2.35 (dd, 1 H, H-6eq), 2.13, 2.12, 2.11 (3s, 9 H, COMe); ^{13}C NMR: δ 170.3, 170.2, 169.3 (*C*OMe), 80.1, 78.8, 78.2, 75.1 (C-2,3,4,5), 68.2 (C-1), 27.3 (C-6), 20.9, 20.7, 20.6 (CO*Me*). Anal. Calcd for $C_{12}H_{16}O_7S$: C, 47.35; H, 5.30; S, 10.53. Found: C, 47.16; H, 5.15; S, 10.32.

Concentration of the second fraction gave a mixture of **12** and **13** (7 g), while concentration of the third fraction yielded **13** (19 g); $[\alpha]_D$ +112° (*c* 0.6, $CHCl_3$); lit. $[\alpha]_D$ +95° (*c* 1, $CHCl_3$) [5]; R_f 0.4 (solvent C); ^{1}H NMR: δ 5.59 (d, 1 H, $J_{3,4}$ 3.2, $J_{4,5}$ 0 Hz, H-4), 5.36 (dd, $J_{2,3}$ 7.3 Hz, H-3), 5.34 (d, $J_{1,2}$ 1.8 Hz, H-1), 4.68 (dd, 1 H, H-2), 4.38 (dd, 1 H, $J_{5,6ax}$ 2.9, $J_{5,6eq}$ 2.2 Hz, H-5), 3.40 (dd, 1 H, $J_{6ax,6eq}$ 13.2 Hz, H-6ax), 2.51 (dd, 1 H, H-6eq), 2.16, 2.15, 2.10 (3s, 9 H, COMe); ^{13}C NMR: δ 170.8, 170.1, 169.7 (*C*OMe), 80.5, 79.0, 77.8, 77.6 (C-2,3,4,5), 67.6 (C-1), 26.3 (C-6), 21.1, 20.7, 20.6 (CO*Me*).

3,4-Di-O-*acetyl-1,6:2,5-dianhydro-1-thio*-D-*glucitol* S-*oxide* (**14**).—To a solution of **18** (24.6 g, 0.1 mol) in AcOH (250 mL), 33% aq H_2O_2 (10 mL) was added, the mixture was kept at 20 °C for 20 h and concentrated. The residue was dissolved in EtOH (100 mL), concentrated and this was repeated twice. The residue was crystallised with ether to give **14** (24.4 g, 93%); mp 126–128 °C; lit. 126–127 °C [10]; lit.128–130 °C [11]; R_f 0.3 (solvent A); ^{1}H NMR: δ 5.12 (dd, 1 H, $J_{2,3}$ 6.9, $J_{3,4}$ 2.2 Hz, H-3), 4.94 (d, $J_{4,5}$ 0 Hz, H-4), 4.86 (ddd, 1 H, $J_{1eq,2} \sim 2$, $J_{1ax,2}$ 2.9 Hz, H-2), 4.47 (dd, 1 H, $J_{5,6eq}$ 1.5, $J_{5,6ax}$ 3.1 Hz, H-5), 3.75 (dd, 1 H, $J_{6eq,6ax}$ 12.5 Hz, H-6eq), 3.50 (dd, 1 H, H-1eq), 2.66 (dd, 2 H, $J_{1ax,1eq}$ 12.5 Hz, H-1ax,6ax), 2.12, 2.05 (2s, 6 H, COMe); ^{13}C NMR: δ 170.0, 169.9 (*C*OMe), 79.3 (C-4), 78.6 (C-3), 78.5 (C-5), 74.0 (C-2), 53.5 (C-6), 51.1 (C-1) 20.7, 20.6 (CO*Me*).

1,6:2,5-Dianhydro-1-thio-D-*glucitol* (**15**).—(i) To a stirred solution of **52** (1 g, 2.5 mmol) in CH_2Cl_2 (20 mL), water (1 mL) and subsequently DDQ (1.7 g, 7.5 mmol) was added. The precipitated DDQH was filtered after 1 h and the residue of the concentrated filtrate was purified by column chromatography (solvent K) to give **15** (0.24 g, 59%): mp 113–115 °C (acetone); lit. mp 113–115 °C [10]; ^{1}H NMR: δ 5.16 and 5.10 (2s, 2 H, OH-3,4), 4.35 (d,1 H, $J_{3,4}$ 2.9, $J_{4,5}$ 0 Hz, H-4), 4.28 (ddd, $J_{1eq,2}$ 1, $J_{1ax,2}$ 1, $J_{2,3}$ 7.1 Hz, H-2), 3.96 (dd, 1 H, $J_{4,5}$ 0, $J_{5,6eq}$ 1, $J_{5,6ax}$ 2.7 Hz, H-5), 2.94 (dd, 1 H, $J_{6eq,6ax}$ 12.9 Hz, H-6ax), 2.86 (dd, 1 H, $J_{1ax,1eq}$ 13 Hz, H-1ax), 2.35 (dd, 1 H, H-6eq), 2.25 (dd, 1 H, H-1eq); ^{13}C NMR: δ 77.0, 80.4, 81.1, 81.3 (C-2,3,4,5), 23.7, 28.3 (C-1,6).

(ii) A solution of **52** (250 mg) in MeOH (5 mL), water (4 mL) and concd HCl (1 mL) was stirred at 60 °C for 6 h, cooled and neutralized with $NaHCO_3$. The residue obtained on concentration was submitted to column chromatography (solvent A) to give **15** (100 mg, 99%), identical with that described above.

(iii) A solution of **53** (0.78 g) in MeOH (8 mL), water (6 mL) and concd HCl (1.5 mL) was stirred at 60 °C for 2 h and was worked up as described in (ii) to give **15** (330 mg, 88%), identical with that described above.

3,4-Di-O-*acetyl-1,6:2,5-dianhydro-1-thio*-D-*glucitol* (**18**) *and 3,6-di*-O-*acetyl-1,4:2,5-dianhydro-1-thio*-D-*galactitol* (**25**).—To a solution of crude **19** (9.5 g, 33 mmol) in MeOH (290 mL), Dowex 50 WX2 (H^+) (6 g) was added and the mixture was stirred at 20 °C for 3 h. The filtered solution was concentrated, the residue dissolved in pyridine (50 mL) and Ac_2O (20 mL) was added at rt. After 3 h the mixture was poured onto ice to give, after extraction with CH_2Cl_2, and usual processing, a semisolid residue. This was dissolved in ether (20 mL) and gradually triturated with hexane (50 mL) to give crystalline **18** (4.95 g, 61%). Concentration of the filtrate and column chromatography (solvent C) of the residue yielded a second crop of **18** (0.45 g, 5%); mp 76–77 °C, lit. mp 77–79 °C [10]; R_f 0.6 (solvent C); ^{1}H NMR: δ 5.62 (d, 1 H, $J_{3,4}$ 2.2, $J_{4,5}$ 0 Hz, H-4), 5.30 (dd, $J_{2,3}$ 6.8 Hz, H-3), 4.74 (ddd, 1 H, $J_{1eq,2}$ 1.5, $J_{1ax,2}$ 2.7 Hz, H-2), 4.25 (dd, 1 H, $J_{5,6eq}$ 1.5, $J_{5,6ax}$ 2.5 Hz, H-5), 3.16 (dd, 1 H, $J_{6eq,6ax}$ 13.9 Hz, H-6ax), 3.15 (dd, 1 H, $J_{1ax,1eq}$ 12.5 Hz H-1ax), 2.45 (dd, 1 H, H-6eq), 2.10 (dd, 1 H, H-1eq), 2.14, 2.12 (2s, 6 H, COMe); ^{13}C NMR: δ 170.9, 170.4 (*C*OMe), 81.0, 79.2, 78.6, 75.4 (C-2,3,4,5), 28.2, 24.7 (C-1,6) 20.8, 20.6 (CO*Me*).

Concentration of the fractions having R_f 0.5 (solvent C) gave **25** (0.45 g, 5%) as a syrup; $[\alpha]_D$ −33° (*c* 0.4, $CHCl_3$); ^{1}H NMR: δ 5.17 (m, 1 H, H-3), 4.45–4.33 (m, 4 H, H-2,5,6a,6b), 3.66 (m, 1 H, H-4), 2.95–2.75 (m, 2 H, H-1a,1b), 2.08, 1.98 (2s, 6 H, COMe); ^{13}C NMR: δ 170.2, 169.9 (*C*OMe), 79.7, 76.3, 76.2 (C-2,3,5), 64.9 (C-6), 48.5 (C-4), 35.6 (C-1), 20.5, 20.5 (CO*Me*). Anal. Calcd for $C_{10}H_{14}O_5S$: C, 48.77; H, 5.73; S, 13.02. Found: C, 48.61; H, 5.87; S, 12.96.

*4-O-Acetyl-1,6:2,5-dianhydro-3-O-tetrahydropyranyl-1-thio-*D*-glucitol* (**19**).—To a solution of **11** (10.7 g, 33 mmol) in DMF (110 mL), sodium acetate (10.7 g, 130 mmol) was added and the mixture was stirred at 100 °C for 5 h. The cooled mixture was filtered and the residue obtained on concentration was dissolved in CH_2Cl_2, washed with water, dried and concentrated to give **19** (9.5 g, 100%) as a syrup, which contained less than 10% of 6-*O*-acetyl-1,4:2,5-dianhydro-3-*O*-tetrahydropyranyl-1-thio-D-galactitol (**24**) and was pure enough for the subsequent reaction. Purification by column chromatography (solvent C) yielded **19** (6 g, 63%), R_f 0.6 + 0.65; ^{1}H NMR: δ 5.63, 5.53 (m, 1 H, H-4), 4.72 (m, H-2′), 4.60–4.40 (m, 1 H, H-3), 4.55 (m, 1 H, H-2), 4.02, 3.82, 3.60–3.45 (m, 2 H, H-6′), 3.20–3.05 (m, 2 H, H-1ax,6ax), 2.55–2.33 (m, 2 H, H-1eq,6eq), 2.08 (s, 3 H, COMe), 1.90–1.40 (m, 6 H, H-3′,4′,5′); ^{13}C NMR: δ 171.1, 171.0 (*C*OMe), 99.6, 99.1 (C-2′), 82.6, 82.2, 81.8, 81.7, 79.9, 79.5, 76.8, 75.9 (C-2,3,4,5), 63.4, 62.1 (C-6′), 30.6, 30.5, 28.2, 28.1, 25.3, 25.1, 24.8, 24.7 (C-1,6,3′,5′), 20.9, 20.8 (CO*Me*), 19.9, 18.8 (C-4′). Anal. Calcd for $C_{13}H_{20}O_5S$: C, 54.15; H, 6.99; S, 11.12. Found: C, 54.10; H, 6.92; S, 11.07.

*1,2:5,6-Di-O-isopropylidene-3,4-di-O-(4-methoxybenzyl)-*D*-mannitol* (**28**).—To a stirred suspension of NaH (50% in mineral oil, 20 g) in Me_2SO (340 mL), a solution of **26** (52.4 g, 0.2 mol) in Me_2SO (160 mL) and after 30 min 4-methoxybenzyl chloride (74 mL, 0.48 mol) were added. The mixture was stirred at 50 °C for 3 h, then cooled, diluted with water and extracted with CH_2Cl_2. The organic soln was washed with water, dried and concentrated to give crude **28** (110 g, 109%). An aliquot part (2 g) was purified by column chromatography (solvent E) to give **28** (1.3 g, 65%); $[\alpha]_D$ +38° (*c* 0.5, $CHCl_3$); R_f 0.4 (solvent E); ^{1}H NMR: δ 7.15 (d, 4 H, aromatic), 6.76 (d, 4 H, aromatic), 4.52 (s, 4 H, O–CH_2–Ar), 4.11 (m, 2 H, H-2,5), 3.89 (dd, 2 H, $J_{1a,2}$ 6.4, $J_{1a,1b}$ 8.3 Hz, H-1a,6a), 3.73 (dd, 1 H, $J_{1b,2}$ 7.1 Hz, H-1b,6b), 3.66 (s, 6 H, OMe), 3.65 (m, 2 H, H-3,4), 1.20, 1.30 (2s, 12 H, CMe_2); ^{13}C NMR: δ 159.2, 130.3, 129.6, 113.6 (C-aromatic), 108.4 (*C*Me_2), 79.5 (C-3,4), 75.8 (C-2,5), 74.0 (O–*C*H_2–Ar), 66.7 (C-1,6), 55.1 (OMe), 25.1, 26.6 (C*Me*$_2$). Anal. Calcd for $C_{28}H_{38}O_8$: C, 66.92; H, 7.62. Found: C, 66.77; H, 7.54.

*1,2:5,6-Di-O-isopropylidene-3,4-di-O-(2-methoxyethoxymethyl)-*D*-mannitol* (**29**).—To a stirred suspension of NaH (50%, 10 g) in DMF (40 mL), a solution of **26** (20 g, 76 mmol) in DMF (60 mL) and after 30 min 2-methoxyethoxymethyl chloride (20.7 mL, 182 mmol) were added. The mixture was stirred at 20 °C for 1 h then poured onto ice and extracted with CH_2Cl_2. The organic soln was washed with 5% aq $NaHCO_3$ and water, dried and concentrated to give crude **29** (33.2 g, 99%). An aliquot part (2 g) was purified by column chromatography (solvent B) to give **29** (1.4 g, 69%); $[\alpha]_D$ +72° (*c* 0.5, $CHCl_3$); R_f 0.4 (solvent B); ^{1}H NMR: δ 4.97 and 4.80 (2d, 4 H, *J* 7.1 Hz, O–CH_2–O) 3.50–4.20 (m, 16 H, H-1a,1b,2,3,4,5,6a,6b, O–CH_2–CH_2–O), 3.37 (s, 6 H, OMe), 1.28 and 1.36 (2s, 12 H, CMe_2); ^{13}C NMR: δ 108.8 (*C*Me_2), 96.7 (O–CH_2–O), 79.3 (C-3,4), 73.9 (C-2,5), 71.4, 67.5 (O-CH_2–CH_2–O), 67.6 (C-1,6), 58.8 (OMe), 26.4, 25.2 (C*Me*$_2$). Anal. Calcd for $C_{20}H_{38}O_{10}$: C, 54.78; H, 8.73. Found: C, 54.92; H, 8.61.

*3,4-Di-O-(4-methoxybenzyl)-*D*-mannitol* (**31**).—To a solution of crude **28** (12.3 g) in MeOH (120 mL), water (36 mL) was added and the pH of the mixture was adjusted to 4 by adding 1 M HCl (1.2 mL). The mixture was boiled for 1.5 h and the resulting clear solution was neutralised with $NaHCO_3$ after cooling. The residue obtained on concentration was dissolved in $CHCl_3$, the insoluble salts were filtered off and the residue of the evaporated filtrate was recrystallized from EtOH–Et_2O to yield **31** (9.46 g, 91%); mp 91–92 °C; $[\alpha]_D$ +38° (*c* 0.5, MeOH); R_f 0.5

(solvent I); ^{1}H NMR (Me_2SO-d_6): δ 7.20 (d, 4 H, aromatic), 6.86 (d, 4 H, aromatic), 4.68 (d, 2 H, *J* 5.2 Hz, 2-OH and 5-OH), 4.56, 4.46 (2d, 4 H, *J* 10.5 Hz, O–CH_2–Ar), 4.48 (t, 2 H, *J* 5.7 Hz, 1-OH, 6-OH), 3.65 (s, 6 H, OMe), 3.40–3.80 (m, 8 H, H-1a,1b,2,3,4,5,6a,6b). Anal. Calcd for $C_{22}H_{30}O_8$: C, 62.55; H, 7.16. Found: C, 62.48; H, 7.28.

*3,4-Di-O-(2-methoxyethoxymethyl)-*D*-mannitol* (**32**).—A solution of crude **29** (15 g) in AcOH (120 mL) and water (60 mL) was stirred at 50 °C for 4 h and was then concentrated. Ethanol (100 mL) and subsequently toluene (100 mL) were evaporated from the residue, which solidified. Recrystallisation from EtOH–Et_2O gave **32** (5.87 g, 48%): mp 77–79 °C; $[\alpha]_D$ +30° (*c* 0.5, MeOH); R_f 0.3 (solvent J); ^{1}H NMR (Me_2SO-d_6): δ 4.70 (s, 4 H, O–CH_2–O), 4.54 (d, 2 H, *J* 5.6 Hz, 2-OH and 5-OH), 4.37 (t, 2 H, *J* 5.4 Hz, 1-OH and 6-OH), 3.25–3.70 (m, 16 H, H-1a,1b,2,3,4,5,6a,6b, O–CH_2–CH_2–O), 3.24 (s, 6 H, OMe); ^{13}C NMR: δ 96.4 (O–CH_2–O), 77.3, 70.8 (C-2,3,4,5), 71.4, 67.4 (O–CH_2–CH_2–O), 63.1 (C-1,6), 58.3 (OMe). Anal. Calcd for $C_{14}H_{30}O_{10}$: C, 46.92; H, 8.43. Found: C, 46.73; H, 8.48.

*2,5-Anhydro-6-S-acetyl-1,3-O-isopropylidene-6-thio-*D*-glucitol* (**37**).—A solution of **44** (400 mg, 1.24 mmol) in acetone (2 mL) was added dropwise to a stirred, ice cooled soln of HBr in AcOH (33%, 0.5 mL) and acetone (2 mL). After 30 min the solution was neutralised with solid $NaHCO_3$, the precipitated salts were filtered off, washed with acetone and the filtrate was concentrated. The residue containing **36** was dissolved in DMF (2 mL), KSAc (170 mg) was added and the mixture was stirred for 1 h at 80 °C. The residue obtained on concentration was dissolved in CH_2Cl_2, washed with water dried and concentrated to give after purification by column chromatography (solvent L) **37** (70 mg, 21.5%) as a syrup: $[\alpha]_D$ +13° (*c* 0.5, $CHCl_3$); R_f 0.5 (solvent L); ^{1}H NMR: δ 3.50–4.25 (m, 6 H, H1a,1b,2,3,4,5), 3.15–3.35 (m, 2 H, H-6a,6b), 2.36 (s, 3 H, SAc), 1.38 and 1.43 (2s, 6 H, CMe_2); ^{13}C NMR: δ 195.8 (S*C*OMe), 97.5 (*C*Me_2), 85.4, 80.2, 76.2 and 73.1 (C-2,3,4,5), 60.6 (C-1), 32.0 (C-6), 30.5 (SCO*Me*), 28.6 and 19.1 (C*Me*$_2$). Anal. Calcd for $C_{11}H_{18}O_5S$: C, 50.37; H, 6.92; S, 12.22. Found: C, 50.51; H, 6.82; S, 6.85.

*2,5-Anhydro-6-bromo-6-deoxy-3,4-di-*O*-(4-methoxybenzyl)-*D*-glucitol* (**39**).—A solution of **43** (3.86 g, 10 mmol) in acetone (12 mL) was added dropwise to a stirred, ice cooled solution of HBr in AcOH (33%, 3 mL) and acetone (10 mL). After 15 min the solution was neutralised with solid $NaHCO_3$, the precipitated salts were filtered off, washed with acetone and the filtrate was concentrated. Ethanol and subsequently toluene were evaporated from the residue, which was dissolved in CH_2Cl_2, filtered and concentrated to give crude **39** (4.6 g, 98.5%). Column chromatography (solvent H) afforded **39** (3 g, 64%) as a syrup: $[\alpha]_D$ +8° (*c* 0.5, $CHCl_3$); R_f 0.5 (solvent H); ^{1}H NMR: δ 7.15–7.30 (m, 4 H, aromatic), 6.80–6.95 (m, 4 H, aromatic), 4.56, 4.48 (2d, 2 H, *J* 11.7 Hz, O–C*H*$_2$–Ar), 4.51, 4.33 (2d, 2 H, *J* 11.5 Hz, O–C*H*$_2$–Ar), 4.13–4.32 (m, 2 H, H-2,5), 4.01–4.08 (m, 2 H, H-3,4), 3.75–3.90 (m, 2 H, H-1a,1b), 3.82 (s, 6 H, OMe), 3.37–3.52 (m, 2 H, H-6a,6b); ^{13}C NMR: δ 159.6, 159.5, 129.5, 129.4, 129.3, 129.1, 114.1, 113.9 (C-aromatic), 83.6, 83.2, 82.9, 81.4 (C-2,3,4,5), 71.8, 71.3 (O–CH_2–Ar), 61.7 (C-1), 55.3 (OMe), 32.4 (C-6). Anal. Calcd for $BrC_{22}H_{27}O_6$: Br, 17.10; C, 56.54; H, 5.82. Found: Br, 17.00; C, 56.62; H, 6.05.

*2,5-Anhydro-6-bromo-6-deoxy-3,4-di-*O*-(2-methoxyethoxymethyl)-*D*-glucitol* (**40**).—To an ice cooled stirred soln of **44** (400 mg, 1.25 mmol) in acetone (10 mL) was added dropwise a soln of KBr (295 mg, 2.5 mmol) in water (2 mL), and subsequently 1 M H_2SO_4 (2.5 mL) in acetone (10 mL). The mixture was kept at 20 °C for 20 h and was then neutralised with solid $NaHCO_3$ and concentrated. The residue gave after column chromatography (solvent M) **40** (292 mg, 58%) as a syrup; $[\alpha]_D$ +55° (*c* 0.5, $CHCl_3$); R_f 0.4 (solvent M); ^{1}H NMR: δ 4.70–4.85 (m, 4 H, O–CH_2–O), 4.05–4.30 (m, 4 H) 3.60–3.85 (m, 6 H) and 3.50–3.60 (m, 4 H) (H-1a,1b,2,3,4,5, O–CH_2–CH_2–O), 3.40–3.50 (m, 2 H, H-6a,6b), 3.37 (s, 6 H, O–Me); ^{13}C NMR: δ 94.8, 94.5 (O–CH_2–O), 83.6, 83.0, 81.6, 80.9 (C-2,3,4,5), 71.6, 71.5, 67.5, 67.2 (O–CH_2–CH_2–O), 60.3 (C-1), 58.9 (OMe),

32.1 (C-6). Anal. Calcd for $BrC_{14}H_{27}O_8$: Br, 19.80; C, 41.70; H, 6.75. Found: Br, 19.99; C, 41.99; H, 6.94.

*1,2:5,6-Dianhydro-3,4-di-*O*-(4-methoxybenzyl)-*D*-mannitol* (**43**).—To a stirred solution of **31** (24.5 g, 58 mmol) in pyridine (170 mL), a soln of tosyl chloride (30.2 g, 158 mmol) in a mixture of CH_2Cl_2 (60 mL) and pyridine (15 mL) was added at 0 °C over a period of 30 min. The mixture was kept at 20 °C for 20 h to give, after usual processing, crude **34** as a syrup (47 g). This was dissolved in CH_2Cl_2 (100 mL) and MeOH (25 mL), cooled to 0 °C and 4.3 M methanolic NaOMe (25 mL) was added. After 30 min the mixture was diluted with CH_2Cl_2, the organic soln was washed with water, dried and concentrated. The residue was purified by column chromatography (solvent E) to give **43** (6 g, 27.6%) as a syrup; $[\alpha]_D$ −5° (*c* 0.5, $CHCl_3$); R_f 0.3 (solvent E); ^{1}H NMR: δ 7.20 (d, 4 H, aromatic), 6.83 (d, 4 H, aromatic), 4.63, 4.52 (2d, 4 H, *J* 11.5 Hz, O–CH_2–Ar), 3.77 (s, 6 H, OMe), 3.40 (d, 2 H, $J_{2,3}$ 4.6 Hz, H-3,4), 3.13 (m, 2 H, H-2,5), 2.76 (dd, 2 H, $J_{1a,2}$ 3.9, $J_{1a,1b}$ 5.4 Hz, H-1a,6a), 2.63 (dd, 2 H, $J_{1b,2}$ 2.4 Hz, H-1b,6b); ^{13}C NMR: δ 159.2, 130.0, 129.5, 113.6 (C-aromatic), 78.0 (C-3,4), 73.0 (O–CH_2–Ar), 55.1 (OMe), 50.6 (C-2,5), 46.0 (C-1,6). Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 62.39; H, 6.90.

*1,2:5,6-Dianhydro-3,4-di-*O*-(2-methoxyethoxymethyl)-*D*-mannitol* (**44**).—To a stirred solution of **32** (6.1 g, 17 mmol) in pyridine (40 mL), a soln of tosyl chloride (7.7 g, 41 mmol) in a mixture of CH_2Cl_2 (14 mL) and pyridine (3 mL) was added at 0 °C over a period of 30 min. The mixture was kept at 20 °C for 20 h to give, after usual processing, crude **35** as a syrup (10 g); R_f 0.4 (solvent J). This was dissolved in CH_2Cl_2 (50 mL) and MeOH (50 mL), cooled to 0 °C and 4.3 M methanolic NaOMe (6.5 mL) was added. After 30 min the mixture was diluted with CH_2Cl_2, the organic soln was washed with water, dried and concentrated. The residue (6.2 g) was purified by column chromatography (solvent A) to give **44** (2.8 g, 51%); mp 40–42 °C (ether–hexane); $[\alpha]_D$ −6° (*c* 0.5, $CHCl_3$); R_f 0.5 (solvent A); ^{1}H NMR: δ 4.88, 4.78 (2d, 4 H, *J* 7.1 Hz, O–CH_2–O), 3.74 (m, 4 H, O–CH_2–CH_2–O), 3.55 (m, 4 H, O–CH_2–CH_2–O), 3.63 (d, 2 H, $J_{2,3}$ 5.4 Hz, H-3,4), 3.38 (s, 6 H, OMe), 3.15 (m, 2 H, H-2,5), 2.86 (dd, 2 H, $J_{1a,2}$ 3.7, $J_{1a,1b}$ 5.4 Hz, H-1a,6a), 2.81 (dd, 2 H, $J_{1b,2}$ 2.7 Hz, H-1b,6b); ^{13}C NMR: δ 95.0 (O–CH_2–O), 76.3 (C-3,4), 71.4, 67.1 (O–CH_2–CH_2–O), 58.8 (OMe), 49.8 (C-2,5), 46.4 (C-1,6). Anal. Calcd for $C_{14}H_{26}O_8$: C, 46.92; H, 8.43. Found: C, 47.14; H, 8.25.

*2,5-Anhydro-6-*S*-acetyl-3,4-di-*O*-allyl-6-thio-*D*-glucitol* (**45**).—A solution of crude **38** [15] (24.5 g) and KSAc (8 g) in DMF (100 mL) was stirred for 1 h at 80 °C. The residue obtained on concentration was dissolved in CH_2Cl_2, washed with water, dried and concentrated to give after purification by column chromatography (solvent D) **45** (20.2 g, 84%) as a syrup; $[\alpha]_D$ +44°; R_f 0.4 (solvent C); ^{1}H NMR: δ 5.85 (m, 2 H, O–CH_2–C*H*=CH_2), 5.15–5.35 (m, 4 H, O–CH_2–CH=CH_2), 3.70–4.15 (m, 10 H, H-1a,1b, H-2, H-3, H-4, H-5, O–CH_2–CH=CH_2), 3.22 (dd, 1 H, $J_{5,6a}$ 6.1, $J_{6a,6b}$ 13.7 Hz, H-6a), 3.10 (dd, 1 H, $J_{5,6b}$ 6.8 Hz, H-6b), 2.33 (s, 3 H, SAc); ^{13}C NMR: δ 194.9 (S*C*OMe), 133.9, 133.8 (O–CH_2–*C*H=CH_2), 117.1 (O–CH_2–CH=*C*H_2), 84.6, 83.1, 81.7, 80.8 (C-2,3,4,5), 70.4, 70.2 (O–*C*H_2–CH=CH_2), 60.9 (C-1), 31.8 (C-6), 30.3 (SCO*Me*). Anal. Calcd for $C_{14}H_{22}O_5S$: C, 55.61; H, 7.33; S, 10.60. Found: C, 55.66; H, 7.20; S, 10.44.

*2,5-Anhydro-6-*S*-acetyl-3,4-di-*O*-(4-methoxybenzyl)-6-thio-*D*-glucitol* (**46**).—A solution of crude **39** (3.5 g) and KSAc (1.02 g) in DMF (15 mL) was stirred for 1 h at 80 °C. The residue obtained on concentration was dissolved in CH_2Cl_2, washed with water, dried and concentrated to give after purification by column chromatography (solvent H) **46** (3.2 g, 93%) as a syrup: $[\alpha]_D$ +38° (*c* 0.5, $CHCl_3$); R_f 0.4 (solvent H); ^{1}H NMR: δ 7.18–7.28 (m, 4 H, aromatic), 6.85–6.92 (m, 4 H, aromatic), 4.54, 4.26 (2d, 2 H, *J* 11.5 Hz, O–CH_2–Ar), 4.48 (s, 2 H, O–CH_2–Ar), 3.75–4.15 (m, 6 H, H-1a,1b,2,3,4,5), 3.80, 3.79 (2s, 6 H, OMe), 3.22 (dd, 1 H, $J_{5,6a}$ 6.1, $J_{6a,6b}$ 13.7 Hz, H-6a), 3.10 (dd, 1 H, $J_{5,6b}$ 6.6 Hz, H-6b), 2.32 (s, 3 H, SAc); ^{13}C NMR: δ 195.1 (S*C*OMe), 159.4, 159.3, 129.5, 129.3, 129.3, 129.2, 113.9, 113.8 (C-aromatic), 84.5, 83.4, 82.0 and 80.8 (C-

2,3,4,5), 71.5 and 71.3 (O–CH_2–Ar), 61.5 (C-1), 55.2 (OMe), 32. (C-6), 30.4 (SCO*Me*). Anal. Calcd for $C_{24}H_{30}O_7S$: C, 62.32; H, 6.54; S, 6.93. Found: C, 62.36; H, 6.78; S, 6.90.

*2,5-Anhydro-6-*S*-acetyl-3,4-di-*O*-(2-methoxyethoxymethyl)-6-thio-*D*-glucitol* (**47**).—A solution of crude **40** (2.4 g) and KSAc (0.82 g) in acetone (50 mL) was stirred for 16 h at 20 °C. The residue obtained on concentration was dissolved in CH_2Cl_2, washed with water, dried and concentrated to give after purification by column chromatography (solvent N) **47** (1.65 g, 70%) as a syrup: $[\alpha]_D$ +81° (*c* 0.5, $CHCl_3$); R_f 0.5 (solvent N). ^{1}H NMR: δ 4.70–4.85 (m, 4 H, O–CH_2–O), 3.50–4.25 (m, 14 H, H-1a,1b,2,3,4,5, O–CH_2–CH_2–O), 3.39 (s, 6 H, OMe), 3.25 (dd, 1 H, $J_{5,6a}$ 6.1, $J_{6a,6b}$ 13.7 Hz, H-6a), 3.08 (dd, 1 H, $J_{5,6b}$ 7.1 Hz, H-6b); ^{13}C NMR: δ 195.1 (S*C*OMe), 94.6, 94.5 (O–CH_2–O), 83.7, 82.6, 81.1, 81.0 (C-2,3,4,5), 71.5, 71.5, 67.4, 67.1 (O–CH_2–CH_2–O), 60.2 (C-1), 58.9 (OMe), 31.8 (C-6), 30.3 (SCO*Me*). Anal. Calcd for $C_{16}H_{30}O_9S$: C, 48.23; H, 7.59; S, 8.04. Found: C, 48.01; H, 7.60; S, 7.90.

*2,5-Anhydro-6-*S*-acetyl-1-*O*-methanesulfonyl-3,4-di-*O*-allyl-6-thio-*D*-glucitol* (**48**).—To a stirred solution of **45** (4 g) in CH_2Cl_2 (20 mL) and pyridine (4 mL), mesyl chloride (1.5 mL) was added at 0 °C and was kept for 1 h at 20 °C to give, after usual processing and column chromatography, (solvent C) **48** (3.7 g, 73%) as a syrup: $[\alpha]_D$ +39° (*c* 0.5, $CHCl_3$); R_f 0.4 (solvent C); ^{1}H NMR: δ 5.80–6.00 (m, 2 H, O–CH_2–C*H*=CH_2), 5.15–5.35 (m, 4 H, O–CH_2–CH=CH_2), 4.35–4.50 (m, 2 H, H-1a,1b), 4.31 (m, 1 H, H-2), 3.75–4.25 (m, 7 H, H-3, H-4, H-5, O–CH_2–CH=CH_2), 3.22 (dd, 1 H, $J_{5,6a}$ 6.6, $J_{6a,6b}$ 13.7 Hz, H-6a), 3.08 (dd, 1 H, $J_{5,6b}$ 7.1 Hz, H-6b), 3.06 (s, 3 H, OMs), 2.35 (s, 3 H, SAc); ^{13}C NMR: δ 194.8 (S*C*OMe), 133.8, 133.7 (O–CH_2–*C*H=CH_2), 117.6, 117.5 (O–CH_2–CH=*C*H_2), 83.9, 83.0, 82.0, 78.7 (C-2,3,4,5), 70.6, 70.4 (O–*C*H_2–CH=CH_2), 68.5 (C-1), 37.4 (OMs), 31.8 (C-6), 30.4 (SCO*Me*). Anal. Calcd for $C_{15}H_{24}O_7S_2$: C, 47.35; H, 6.36; S, 16.85. Found: C, 47.22; H, 6.43; S, 16.66.

*2,5-Anhydro-6-*S*-acetyl-1-*O*-methanesulfonyl-3,4-di-*O*-(4-methoxybenzyl)-6-thio-*D*-glucitol* (**49**).—To a stirred solution of **46** (3.2 g) in pyridine 20 (mL), mesyl chloride (1.1 mL) was added at 0 °C, the solution was kept for 1 h at 20 °C to give, after usual processing and column chromatography, (solvent H) **49** (3.3 g, 89%) as a syrup: $[\alpha]_D$ +21° (*c* 0.5, $CHCl_3$); R_f 0.6 (solvent H); ^{1}H NMR: δ 7.17–7.27 (m, 4 H, aromatic), 6.85–6.93 (m, 4 H, aromatic), 4.20–4.55 (m, 7 H, O–CH_2–Ar, H-1a,1b, H-2), 4.03 (m, 1 H, H-5), 3.95 (d, 1 H, $J_{2,3}$ 3.9 Hz, H-3), 3.81 (m, 1 H, H-4), 3.80 (s, 6 H, OMe), 3.20 (dd, 1 H, $J_{5,6a}$ 6.6, $J_{6a,6b}$ 13.7 Hz, H-6a), 3.06 (dd, 1 H, $J_{5,6b}$ 6.6 Hz, H-6b), 3.00 (s, 3 H, OMs), 2.32 (s, 3 H, SAc); ^{13}C NMR: δ 194.9 (S*C*OMe), 159.4, 159.3, 129.5, 129.3, 129.2, 129.0, 113.9, 113.8 (C-aromatic), 83.6, 83.2, 81.9, 78.8 (C-2,3,4,5), 71.4, 71.2 (O–*C*H_2–Ar), 68.6 (C-1), 55.2 (OMe), 37.4 (OMs), 31.8 (C-6), 30.4 (SCO*Me*). Anal. Calcd for $C_{25}H_{32}O_9S_2$: C, 55.54; H, 5.97; S, 11.86. Found: C, 55.62; H, 5.63; S, 11.66.

*2,5-Anhydro-6-*S*-acetyl-1-*O*-methanesulfonyl-3,4-di-*O*-(2-methoxyethoxymethyl)-6-thio-*D*-glucitol* (**50**).—To a stirred solution of **47** (1.4 g) in pyridine (10 mL), mesyl chloride (0.54 mL) was added at 0 °C. After 1 h at 20 °C, the mixture was processed the usual way to give **50** (1.59 g, 95%) as a syrup; $[\alpha]_D$ +50°; R_f 0.3 (solvent F); ^{1}H NMR: δ 4.70–4.90 (m, 4 H, O–CH_2–O), 4.35–4.50 (m, 2 H, H-1a,1b), 4.32 (m, 1 H, H-2), 4.24 (d, 1 H, $J_{2,3}$ 3.9 Hz, H-3), 4.05 (d, 1 H, $J_{4,5}$ 2.2 Hz, H-4), 3.96 (ddd, 1 H, $J_{5,6a}$ 6.3, $J_{5,6b}$ 7.3 Hz, H-5), 3.62–3.80 (m, 4 H) and 3.50–3.62 (m, 4 H) (O–CH_2–CH_2–O), 3.38 (s, 6 H, OMe), 3.25 (dd, 1 H, $J_{6a,6b}$ 13.4 Hz, H-6a), 3.09 (dd, 1 H, H-6b), 3.08 (s, 3 H, OMs), 2.35 (s, 3 H, SAc); ^{13}C NMR: δ 194.6 (S*C*OMe), 94.4, 94.6 (O–CH_2–O), 83.4, 82.8, 80.5, 78.6 (C-2,3,4,5), 68.4 (C-1), 71.4, 71.4, 67.5, 67.1 (O–CH_2–CH_2–O), 58.7, 58.8 (OMe), 37.4 (OMs), 31.5 (C-6), 30.3 (SCO*Me*). Anal. Calcd for $C_{17}H_{32}O_{11}S_2$: C, 42.85; H, 6.77; S, 13.45. Found: C, 42.90; H, 6.82; S, 13.28.

*1,6:2,5-Dianhydro-3,4-di-*O*-allyl-1-thio-*D*-glucitol* (**51**).—To a stirred solution of **45** (15.1 g, 50 mmol) in CH_2Cl_2 (50 mL), pyridine (10 mL) and mesyl chloride (6 mL) were added at 0 °C and the mixture was processed after 1 h at 20 °C in the usual way. The CH_2Cl_2 soln containing **48** (R_f 0.5, solvent C)

was concentrated to 100 mL and 4.5 M methanolic NaOMe (15 mL) was added at 0 °C. The mixture was neutralised with solid CO_2 after 1 h to give on concentration and column chromatography (solvent D) **51** (8.8 g, 73%) as liquid; $[\alpha]_D$ −5°; R_f 0.7 (solvent C). ^{1}H NMR: δ 5.85–6.05 (m, 2 H, O–CH_2–C*H*=CH_2), 5.15–5.40 (m, 4 H, O–CH_2–CH=C*H*$_2$), 4.45–4.55 (m, 2 H, H-2,4), 4.28 (br, 1 H, H-5), 3.95–4.25 (m, 5 H, H-3 and O–C*H*$_2$–CH=CH_2), 3.20 (dd, 1 H, $J_{5,6ax}$ 2.7, $J_{6ax,6eq}$ 12.9 Hz, H-6ax), 3.12 (dd, $J_{1ax,2}$ 3.2, $J_{1ax,1eq}$ 13.2 Hz, H-1ax), 2.30 (ddd, 1 H, $J_{1eq,6eq} \sim 1$, $J_{1eq,2} \sim 1$ Hz, H-1eq), 2.20 (ddd, $J_{5,6eq}$ 2.2 Hz, H-6eq); ^{13}C NMR: δ 134.3, 134.2 (O–CH_2–*C*H=CH_2), 117.6, 117.4 (O–CH_2–CH=*C*H_2), 86.5, 86.3, (C-3,4), 78.5 (C-5), 76.0 (C-2), 71.8, 70.6 (O–*C*H_2–CH=CH_2), 29.0 (C-6), 24.6 (C-1). Anal. Calcd for $C_{12}H_{18}O_3S$: C, 59.48; H, 7.49; S, 13.23. Found: C, 59.51; H, 7.42; S, 13.12.

1,6:2,5-Dianhydro-3,4-di-O-*(4-methoxybenzyl)-1-thio*-D-*glucitol* (**52**).—To a stirred solution of **49** (3 g) in CH_2Cl_2 (10 mL), 1 M methanolic NaOMe (20 mL) was added at 0 °C. After 5 h, the mixture was neutralised with solid CO_2 to give after concentration and column chromatography (solvent C) **52** (1.5 g, 67%): mp 50–51 °C (ether–hexane); $[\alpha]_D$ +10° (*c* 0.5, $CHCl_3$); R_f 0.5 (solvent C). ^{1}H NMR ($CDCl_3$): δ 7.20–7.28 (m, 4 H, aromatic), 6.84–6.90 (m, 4 H, aromatic), 4.48–4.62 (m, 3 H, O–CH_2–O and H-4), 4.35–4.45 (m, 3 H, O–CH_2–O and H-2), 4.20–4.28 (m, 2 H, H-3 and H-5), 3.78 (s, 6 H, OMe), 3.15 (dd, 1 H, $J_{5,6ax} \sim 2.5$, $J_{6ax,6eq}$ 12.9 Hz, H-6ax), 3.05 (dd, $J_{1ax,2} \sim 3.0$, $J_{1ax,1eq}$ 13.2 Hz, H-1ax), 2.25 (ddd, 1 H, $J_{1eq,6eq} \sim 1$, $J_{1eq,2} \sim 1$ Hz, H-1eq), 2.12 (ddd, $J_{5,6eq} \sim 2.0$ Hz, H-6eq); ^{13}C NMR: δ 159.3, 159.2, 129.8, 129.7, 129.5, 129., 113.7 (C-aromatic), 86.2 (C-4), 86.0 (C-3), 78.5 (C-5), 75.9 (C-5), 72.4, 71.3 (O–*C*H_2–Ar), 55.2 (OMe), 28.9 (C-6), 24.6 (C-1); Anal. Calcd for $C_{22}H_{26}O_5S$: C, 65.65; H, 6.51; S, 7.97. Found: C, 65.71; H, 6.77; S, 7.88.

1,6:2,5-Dianhydro-3,4-di-O-*(2-methoxyethoxymethyl)-1-thio*-D-*glucitol* (**53**).—To a stirred solution of **50** (1.5 g) in CH_2Cl_2 (10 mL) 4 M methanolic NaOMe (4 mL) was added at 0 °C. After 5 h, the mixture was neutralised with solid CO_2 to give after concentration and column chromatography (solvent F) **53** (0.88 g, 83%) as a syrup; $[\alpha]_D$ +44° (*c* 0.5, $CHCl_3$); R_f 0.4 (solvent F); ^{1}H NMR: δ 4.75–4.75 (m, 4 H, O–CH_2–O), 4.71 (d, 1 H, $J_{3,4}$ 3.2, $J_{4,5} \sim 0$ Hz, H-4), 4.52 (m, 1 H, H-2), 4.38 (dd, 1 H, $J_{2,3}$ 6.7 Hz, H-3), 4.31 (br, 1 H, H-5), 3.65–3.85 and 3.50–3.60 (m, 8 H, O–CH_2–CH_2–O), 3.38 (s, 6 H, OMe), 3.27 (dd, 1 H, $J_{5,6ax}$ 2.4, $J_{6ax,6eq}$ 12.5 Hz, H-6ax), 3.11 (dd, $J_{1ax,2}$ 3.2, $J_{1ax,1eq}$ 13.2 Hz, H-1ax), 2.33 (ddd, 1 H, $J_{1eq,6eq} \sim 1$, $J_{1eq,2} \sim 1$ Hz, H-1eq), 2.19 (ddd, $J_{5,6eq}$ 2.2 Hz, H-6eq); ^{13}C NMR: δ 95.9, 95.4 (O–CH_2–O), 85.3 (C-4), 85.1 (C-3), 79.1 (C-5), 75.8 (C-5), 71.5, 71.4, 67.4, 67.1 (O–*C*H_2–CH_2–O), 58.7 (OMe), 28.5 (C-6), 24.6 (C-1). Anal. Calcd for $C_{14}H_{26}O_7S$: C, 49.69; H, 7.74; S, 9.47. Found: C, 49.71; H, 7.70; S, 9.40.

4-Cyanophenyl 3,4-di-O-*acetyl-2,5-anhydro-1,6-dithio-α*-L-*gulo*- (**58**) *and* -α-D-*glucoseptanoside* (**61**).—(i) Under argon, a solution of a 1:9 mixture of **12** and **13** (4.4 g, 14.5 mmol) and 4-cyanobenzenethiol (3.9 g, 28.8 mmol) in 1,2-dichloroethane (100 mL) was cooled to −10 °C. Thereafter Me_3SiOTf (2.9 mL, 16 mmol) was added and the mixture was stirred for 1 h at 20 °C. The reaction was quenched with Et_3N (4.5 mL), concentrated and the residue purified by column chromatography (solvent C). The syrup, obtained on concentration of the fractions having R_f 0.5 (solvent C) was, according to NMR spectroscopy, a 1:9 mixture of **58** + **61** (5.48 g, ∼100%); ^{1}H NMR: δ (**58**) 7.58–7.44 (m, 4 H, aromatic), 5.53 (d, 1 H, $J_{2,3}$ 0, $J_{3,4}$ 3.4 Hz, H-3), 5.33 (dd, $J_{4,5}$ 6.8 Hz, H-4), 4.85 (dd, 1 H, $J_{5,6eq}$ 1.5, $J_{5,6ax}$ 3.2 Hz, H-5), 4.45 (dd, 1 H, $J_{1,2}$ 1.5, $J_{1,6eq} \sim 1$ Hz, H-1), 4.30 (d, 1 H, H-2), 3.43 (dd, 1 H, $J_{6ax,6eq}$ 13.1 Hz, H-6ax), 2.15 (ddd, 1 H, H-6eq), 2.12, 2.09 (2s, 6 H, OAc); (**61**) 7.60–7.45 (m, 4 H, aromatic) 5.61 (d, 1 H, $J_{3,4}$ 3.2, $J_{4,5}$ 0 Hz, H-4), 5.33 (dd, $J_{2,3}$ 7.1 Hz, H-3), 4.80 (dd, 1 H, $J_{1,2}$ 2.4, H-2), 4.37 (dd, 1 H, $J_{5,6eq}$ 2.6, $J_{5,6ax}$ 2.4 Hz, H-5), 4.04 (dd, 1 H, $J_{1,6eq} \sim 1$ Hz, H-1), 3.45 (dd, 1 H, $J_{6ax,6eq}$ 13.2 Hz, H-6ax), 2.51 (ddd, 1 H, H-6eq), 2.16, 2.10 (2s, 6 H, COMe); ^{13}C NMR: δ (**58**) 171.3, 170.3 (*C*OMe), 141.9 (C-1′), 132.4, 129.4 (C-2′,3′,5′,6′), 118.5 (CN), 110.0 (C-4′), 81.8 (C-2), 81.4 (C-3), 77.6 (C-4), 75.6 (C-5), 47.6 (C-1),

22.9 (C-6) 20.7, 20.6 (CO*Me*); (**61**) 170.9, 170.3 (*C*OMe), 141.8 (C-1′), 136.1, 132.4 (C-2′,3′,5′,6′), 118.4 (CN), 110.3 (C-4′), 80.5 (C-4), 79.6 (C-5), 78.9 (C-3), 78.6 (C-2), 45.8 (C-1), 26.5 (C-6) 20.8, 20.7 (CO*Me*). Anal. Calcd for $C_{17}H_{17}NO_5S_2$: C, 53.81; H, 4.52; N, 3.69; S, 16.90. Found: C, 53.90; H, 4.63; N, 3.58; S, 16.85.

(ii) The ratio of **58**:**61** remained unchanged when pure **13** was used as donor.

(iii) When pure **12** was used as donor, the ratio of **58**:**61** was 6:1.

(iv) To a slurry of **18** (6.6 g, 26.8 mmol) in toluene (100 mL), NCS (3.5 g, 26.2 mmol) was added and the mixture was stirred for 1 h at 20 °C. During this period **18** was gradually dissolved and succinimide precipitated. This was filtered off and was washed with toluene (50 mL). The filtrate, containing **56** and **57** (R_f 0.7 solvent C) was added dropwise over a period of 30 min to a stirred slurry of freshly fused ZnO (2.8 g, 34.4 mmol) and 4-cyanobenzenethiol (4.4 g, 32.5 mmol) in MeCN (150 mL). Stirring was continued for 30 min at 20 °C, then the mixture was filtered through Celite. The residue obtained on concentration of the filtrate was freed from 4-cyanobenzenethiol disulfide (R_f 0.8) by column chromatography (solvent C) to give after concentration of the fractions having R_f 0.5, a mixture of **58** + **61** (8 g, 79%), identical to that obtained according to method (i).

*4-Cyanophenyl 2,5-anhydro-1,6-dithio-α-*L*-guloseptanoside* (**59**).—To a solution of a 6:1 mixture of **58** and **61** (450 mg, 1.2 mmol), obtained according to method (iii), in MeOH (15 mL) 1 M methanolic NaOMe (0.1 mL) was added and the mixture was kept for 1 h at 20 °C. After neutralization with solid CO_2, the precipitated material was filtered and washed with Et_2O to give **59** (160 mg, 46%), mp 148–150 °C; $[\alpha]_D$ −442° (*c* 0,5, MeOH); R_f 0.3 (solvent G); ^{1}H NMR: δ 7.58–7.43 (m, 4 H, aromatic), 5.38, 5.35 (2s, 2 H, OH), 4.76 (d, 1 H, $J_{1,2}$ 2 Hz, H-1), 4.38 (ddd, $J_{4,5}$ 6.8, $J_{5,6ax}$ 3.2, $J_{5,6eq}$ 1.5 Hz, H-5), 4.35 (d, 1 H, $J_{2,3}$ 0, $J_{3,4}$ 2.9 Hz, H-3), 4.15 (dd, 1 H, H-4), 3.98 (d, 1 H, H-2), 3.06 (dd, 1 H, $J_{6ax,6eq}$ 13.2 Hz, H-6ax), 2.30 (dd, 1 H, H-6eq). Anal. Calcd for $C_{13}H_{13}NO_3S_2$: C, 52.86; H, 4.44; N, 4.72; S, 21.71. Found: C, 52.89; H, 4.48; N, 4.63; S, 21.59.

The mother liquor gave on concentration a 2:1 mixture of **59** + **61** (120 mg, 34.5%).

*4-Nitrophenyl 3,4-di-*O*-acetyl-2,5-anhydro-1,6-dithio-α-*L*-gulo-* (**60**) *and -α-*D*-glucoseptanoside* (**62**).—Under argon, to a solution of a 1:9 mixture of **12** and **13** (0.9 g, 2.96 mmol) and 4-nitrobenzenethiol (0.48 g, 3.1 mmol) in 1,2-dichloroethane (15 mL) $BF_3{\cdot}Et_2O$ (0.35 mL, 2.9 mmol) was added, and the mixture was stirred for 24 h at 20 °C. It was then poured into ice cooled 6% aq $NaHCO_3$ (25 mL) and extracted with 1,2-dichloroethane (15 mL). The organic solution was washed with water, dried, concentrated and the residue purified by column chromatography (solvent C). Concentration of the fractions having R_f 0.6 afforded, according to NMR spectroscopy, a 1:4 mixture of **60** + **62** (1.05 g, 89%). ^{1}H NMR: δ (**60**) 8.12 (d, 2 H, aromatic), 7.45 (d, 2 H, aromatic), 5.50 (d, 1 H, $J_{2,3}$ 0, $J_{3,4}$ 3.4 Hz, H-3), 5.32 (dd, 1 H, $J_{4,5}$ 6.5 Hz, H-4), 4.84 (m, 1 H, H-5), 4.49 (dd, 1 H, $J_{1,2}$ 1.7, $J_{1,6eq} \sim 1$ Hz, H-1), 4.30 (d, 1 H, H-2), 3.42 (dd, 1 H, $J_{5,6ax}$ 2.9, $J_{6ax,6eq}$ 13.9 Hz, H-6ax), 2.15 (m, 1 H, H-6eq), 2.12, 2.08 (2s, 6 H, COMe). Anal. Calcd for $C_{16}H_{17}NO_7S_2$: C, 48.11; H, 4.29; N, 3.51; S, 16.05. Found: C, 48.02; H, 4.45; N, 3.48; S, 15.87.

*4-Cyanophenyl 2,5-anhydro-1,6-dithio-α-*D*-glucoseptanoside* (**63**).—To a solution of a 1:9 mixture of **58** and **61** (5.48 g, 14.4 mmol) obtained according to method (i) or (iv) in MeOH (50 mL), 3 M methanolic NaOMe (0.5 mL) was added and the mixture was kept for 2 h at 20 °C. Thereafter it was neutralised with solid CO_2 and the precipitated crude thioglucoside was recrystallized from MeOH (32 mL) to give **63** (3.2 g, 75%), mp 152–154 °C; $[\alpha]_D$ + 553° (*c* 0.5, MeOH); R_f 0.3 (solvent G); ^{1}H NMR: δ 7.80–7.54 (m, 4 H, aromatic) 5.38, 5.35 (2s, 2 H, OH), 4.55 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1), 4.40 (d, 1 H, $J_{3,4}$ 2.9, $J_{4,5}$ 0 Hz, H-4), 4.37 (dd, $J_{2,3}$ 6.8 Hz, H-2), 4.19 (d, 1 H, H-3), 4.12 (dd, 1 H, $J_{5,6ax}$ 2.7, $J_{5,6eq}$ 2.3 Hz, H-5), 3.17 (dd, $J_{6ax,6eq}$ 13.1 Hz, H-6ax), 2.38 (dd, 1 H, H-6eq); ^{13}C NMR: δ 143.4 (C-1′), 132.8, 128.5 (C-2′,3′,5′,6′), 118.9 (CN), 108.2 (C-4′), 81.7, 81.7, 80.4, 79.8 (C-2,3,4,5), 44.4 (C-1), 26.9 (C-6). Anal. Calcd for $C_{13}H_{13}NO_3S_2$: C, 52.86; H, 4.44; N, 4.72; S, 21.71. Found: C, 52.84; H, 4.52; N, 4.66; S, 21.62.

4-(Aminothiocarbonyl)phenyl 2,5-anhydro-1,6-dithio-α-D-glucoseptanoside (**64**).—A stirred solution of **63** (1.3 g, 4.4 mmol) in dry pyridine (30 mL) and Et_3N (30 mL) was saturated with a slow stream of dry hydrogen sulfide for 2 h. The mixture was kept at rt overnight and was then concentrated. Toluene was evaporated from the residue, which was subsequently recrystallized from MeOH to yield **64** (1.2 g, 83%): mp 195–202 °C; $[\alpha]_D$ +251° (*c* 0.4, Me_2SO); R_f 0.4 (solvent J); ^1H NMR (Me_2SO-d_6): δ 9.84 and 9.48 (2 br., 2 H, NH_2), 7.87 and 7.37 (2d, 4 H, aromatic), 5.42 and 5.30 (2d, 2 H, OH), 4.45 (br., 1 H, $J_{1,2} \sim 1$, $J_{1,6eq} \sim 1$ Hz, H-1), 4.25–4.42 (m, 2 H, H-2,4), 4.05–4.20 (m, 2 H, H-3,5), 3.17 (dd, 1 H, $J_{5,6ax}$ 2.6, $J_{6ax,6eq}$ 13.2 Hz, H-6ax), 2.35 (ddd, 1 H, $J_{5,6eq} \sim 1$ Hz, H-6eq). Anal. Calcd for $C_{13}H_{15}NO_3S_3$: C, 47.40; H, 4.59; N, 4.25; S, 29.19. Found: C, 47.38; H, 4.56; N, 4.20; S, 29.11.

4-[(Imino)(methylthio)methyl]phenyl 2,5-anhydro-1,6-dithio-α-D-glucoseptanoside (**65**).—To a stirred solution of **34** (0.9 g, 2.7 mmol) in dry acetone (130 mL), MeI (2 mL) was added and the mixture was refluxed for 4 h. After cooling to 5 °C, the precipitated crystals were filtered off and washed with ether to give **65** (1.03 g, 80%) as its hydroiodide: mp 193–196 °C; $[\alpha]_D$ +278° (*c* 0.5, Me_2SO); R_f 0.3 (solvent A); ^1H NMR (Me_2SO-d_6): δ 10.5–12.5 (br., 2 H, NH_2^+), 7.84 and 7.54 (2d, 4 H, aromatic), 4.55 (br., 1 H, $J_{1,2} \sim 1$, $J_{1,6eq} \sim 1$ Hz, H-1), 4.32–4.45 (m, 2 H, H-2 and H-4), 4.15 (dd, 1 H, $J_{2,3}$ 7.2, $J_{3,4}$ 3.2 Hz, H-3), 4.12 (br., 1 H, $J_{4,5} \sim 0$ Hz, H-5), 3.16 (dd, 1 H, $J_{5,6ax}$ 2.7, $J_{6ax,6eq}$ 12.9 Hz, H-6ax), 2.39 (ddd, 1 H, $J_{5,6eq} \sim 1$ Hz, H-6eq). Anal. Calcd for $C_{14}H_{18}INO_3S_3$: C, 35.67; H, 3.85; I, 26.92; N, 2.97; S, 20.40. Found: C, 35.61; H, 3.90; I, 26.78; N, 2.92; S, 20.27.

4-Nitrophenyl 2,5-anhydro-1,6-dithio-α-D-glucoseptanoside (**66**).—To a solution of a 1:4 mixture of **60** and **62** (1.0 g, 2.5 mmol) in MeOH (20 mL), 3 M NaOMe (0.1 mL) was added at 20 °C. After 1 h the solution was neutralised with solid CO_2 and the residue obtained on concentration was purified by column chromatography (solvent J) to give **66** (0.60 g, 76%), mp 174–178 °C (Et_2O); $[\alpha]_D$ +441° (*c* 0.5, MeOH); R_f 0.5 (solvent J); ^1H NMR (Me_2SO-d_6): δ 8.18 (d, 2 H, aromatic), 7.55 (d, 2 H, aromatic), 5.49 and 5.33 (2d, 2 H, OH), 4.61 (br., 1 H, $J_{1,2} \sim 1$, $J_{1,6eq} \sim 1$ Hz, H-1), 4.36–4.42 (m, 2 H, H-2 and H-4), 4.18 (m, 1 H, $J_{2,3}$ 6.8, $J_{3,4}$ 2.4 Hz, H-3), 4.14 (dd, 1 H $J_{4,5} \sim 0$ Hz, H-5), 3.17 (dd, 1 H, $J_{5,6ax}$ 2.7, $J_{6ax,6eq}$ 12.9 Hz, H-6ax), 2.40 (ddd, 1 H, $J_{5,6eq} \sim 1$ Hz, H-6eq); Anal. Calcd for $C_{16}H_{17}NO_7S_2$: C, 45.70; H, 4.16; N, 4.44; S, 20.33. Found: C, 45.66; H, 4.15; N, 4.41; S, 20.29.

4-Acetamidophenyl 2,5-anhydro-1,6-dithio-α-D-glucoseptanoside (**67**).—To a stirred solution of **66** (310 mg, 1 mmol) in EtOH (30 mL), $NaBH_4$ (150 mg, 4 mmol) and subsequently $NiCl_2 \cdot 6\ H_2O$ (10 mg) were added at 20 °C. After 30 min the slurry was neutralized with 1 M HCl, filtered and the residue obtained on concentration was treated with Ac_2O (5 mL) and pyridine (10 mL). The mixture was kept at rt for 20 h to give, after usual processing, a syrup, which was dissolved in MeOH (10 mL), and 1 M methanolic NaOMe (0.1 mL) was added. After 1 h at 20 °C the mixture was neutralized with solid CO_2 and the residue obtained on concentration was submitted to column chromatography (solvent J) to yield **67** (190 mg, 59%); mp 55–58 °C (Et_2O); $[\alpha]_D$ +229° (*c* 1, MeOH); R_f 0.4 (solvent J). ^1H NMR (Me_2SO-d_6): δ 10.03 (s, 1 H, N*H*Ac), 7.57, 7.38 (2d, 4 H, aromatic), 5.34, 5.25 (2d, 2 H, OH), 4.35 (m, 1 H, $J_{3,4}$ 2.7, $J_{4,5} \sim 0$ Hz, H-4), 4.22 (dd, 1 H, $J_{1,2} \sim 1$, $J_{2,3}$ 6.5 Hz, H-2), 4.00–4.15 (m, 3 H, H-1,3,5), 3.14 (dd, 1 H, $J_{5,6ax}$ 2.2, $J_{6ax,6eq}$ 13.2 Hz, H-6ax), 2.30 (ddd, 1 H, $J_{5,6eq} \sim 1.5$, $J_{1,6eq} \sim 1$ Hz, H-6eq), 2.04 (s, 3 H, NAc). Anal. Calcd for $C_{14}H_{17}NO_4S_2$: C, 51.36; H, 5.23; N, 4.28; S, 19.58. Found: C, 51.30; H, 5.29; N, 4.21; S, 19.44.

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