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1,6-ANHYDRO-1(6)-THIO-L-IDITOL AND -D-MANNITOL, AND SOME DERIVATIVES THEREOF*

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ABSTRACT

Starting from 1,2:5,6-dianhydro-3,4-*O*-isopropylidene-L-iditol (**1**) and -D-mannitol (**6**), respectively, the corresponding 1,6-anhydro-1(6)-thio derivatives (**2a** and **7a**) were synthesized. The discrepancy in the yields obtained, as well as the different behavior of their methylated derivatives (**2e** and **7c**) towards acid hydrolysis, could be explained by steric factors. The di-*O*-mesyl derivatives **3d** and **12c** were unstable compounds, and showed no ulcerostatic activity, unlike the D-glucitol analog[1].

INTRODUCTION

Recently, we described[1] the synthesis of 1,6-anhydro-2,5-di-*O*-methyl-3,4-di-*O*-(methylsulfonyl)-1(6)-thio-D-glucitol, which showed ulcerostatic activity similar to that of the corresponding 2,5-anhydro derivative[2–4]. In order to study the structure–activity relationships in this type of hexitol derivative, the synthesis of 1,6-anhydro-2,5-di-*O*-methyl-3,4-di-*O*-(methylsulfonyl)-1(6)-thio-L-iditol and -D-mannitol was undertaken.

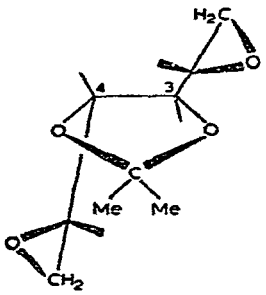
RESULTS AND DISCUSSION

In our previous paper[1], we showed that 3,4-*O*-isopropylidene-D-glucitol derivatives carrying reactive groups at C-1 and C-6 readily form 1,6-anhydro-1(6)-thio derivatives on treatment with sodium sulfide; therefore, the same reaction was applied to the synthesis of the corresponding L-iditol derivative **2a**. When the diepoxide **1** was treated with sodium sulfide, besides some polymeric material, **2a** was formed as the main component, which was separated as its di-*O*-acetyl derivative **2b** in satisfactory yield (73%). Deacetylation of **2b** with a catalytic amount of sodium methoxide was a slow process and, when the reaction was stopped after 2 h, gave, besides **2a**, some mono-*O*-acetyl derivative **2c**.

*1,6-Anhydro-1(6)-thiohexitols VIII. For Part VII, see ref. 1.

Mesylation of **2a** afforded **2d**, the isopropylidene group of which could not be split off by hydrolysis without further decomposition of the molecule.

When methylation of **2a** was conducted with dimethyl sulfate–sodium hydroxide as described for the D-glucitol analog[1], the di-*O*-methyl derivative **2e** was obtained only in poor yield (besides the mono-*O*-methyl compound **2f** and some unreacted starting-material). The yield of **2e** could be substantially increased when the Hakamori process was applied, *i.e.*, using sodium hydride–methyl iodide in dimethyl sulfoxide solution.



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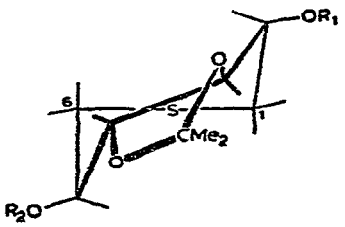
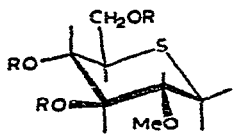
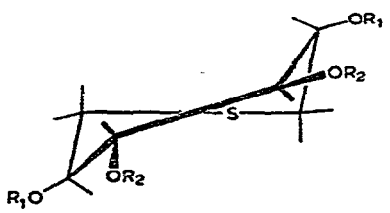
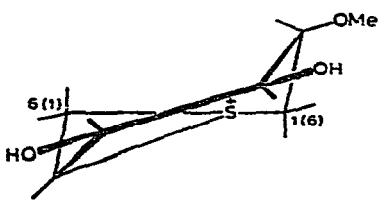


2a $R_1 = R_2 = H$
2b $R_1 = R_2 = Ac$
2c $R_1 = Ac, R_2 = H$
2d $R_1 = R_2 = Ms$
2e $R_1 = R_2 = Me$
2f $R_1 = Me, R_2 = H$



4a R = H
4b R = Ac





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3a $R_1 = R_2 = H$
3b $R_1 = Me, R_2 = H$
3c $R_1 = Me, R_2 = Ac$
3d $R_1 = Me, R_2 = Ms$

The isopropylidene group of **2a** (as well as that of **2e**) was removed by hydrolysis in aqueous trifluoroacetic acid, yielding 1,6-anhydro-1(6)-thio-L-iditol (**3a**), and its 2,5-di-*O*-methyl derivative **3b**, respectively. Nevertheless, in the latter reaction, 1,5-anhydro-2-*O*-methyl-5-thio-D-glucitol (**4a**) was formed as a side-product, too. This rearrangement can be explained by a neighboring-group participation, as

follows. One of the methoxyl groups of **3b** is protonated, polarizing the ring-carbon atom being attached to. This atom is then attacked by the sulfur atom, leading to the elimination of methanol, and formation of a bicyclic, sulfonium cation **5** with inversion of configuration at C-2 (C-5). A similar mechanism could be proved for the substitution of the mesyloxy group at C-4, with retention of configuration, in 1,6:2,5-dianhydro-3,4-di-*O*-(methylsulfonyl)-1(6)-thio-D-glucitol[2]. The sulfonium cation **5** could be opened either at C-1 (C-6) or at C-2 (C-5), but the attack of water occurs at the (less-hindered) methylene group. Because of the symmetrical structure of iditol, elimination of either methoxyl group leads to the same product (**4a**). The presence of the primary hydroxyl group was proved by converting **4a** into the triacetate **4b**, the structure of which was established by n.m.r. and i.r. spectroscopy. The acetyl groups gave signals at δ 2.05 and 2.10 with an intensity of 9 H, compared to the 3 H intensity of the methoxyl group at δ 3.45. The corresponding i.r. bands appear at 1745, 1715 (C=O), 1245, 1225, 1090, and 1030 cm^{-1} (C–O ester), respectively. One of these acetoxyl groups is attached to a primary carbon atom, as the multiplets appearing downfield of δ 4—belonging to the protons geminal to the acetoxyl groups—represent four protons. One of these multiplets consists of eight lines (four intense and four weak lines), corresponding to the AB part of an ABX spin system with J_{AB} 13 Hz, proving the presence of a methylene group carrying an acetoxyl substituent. Both H-3 and H-4 give triplets, at δ 5.20 and 4.90, respectively, both split by 9 Hz; this indicates that $J_{2,3} \approx J_{3,4} \approx J_{4,5} \approx 9$ Hz, proving an all-*trans*-axial arrangement of H-2–5. In $CDCl_3$, these two triplets partly overlap, giving by coincidence an equi-spaced quintet, but, in dimethyl sulfoxide-d_6, no overlapping occurs. The upfield shift of the H-4 signal, compared to that of H-3, is due to the anisotropy of the acetoxyl group on C-6.

The dihydroxy compound **3b** could be readily converted into its diacetate **3c** and dimesylate **3d**, but the latter proved to be unstable, and it decomposed on storage at room temperature, methanesulfonic acid being liberated. As the corresponding D-glucitol isomer[1] is a stable compound, this lability of **3d** must be due to the different configuration at C-5, as a consequence of which, these diastereoisomers may exist in different conformations.

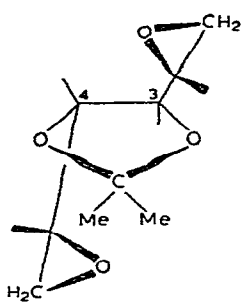
According to the n.m.r. spectra, the 3,4-*O*-isopropylidene derivatives **2a,b,d,e** have C_2 symmetry (H-1,6, H-1′,6′, and H-2,5, as well as the H-3,4 proton-pairs, have identical signals); consequently, they may exist in a twist-chair ($_{4,5}TC^{2,3}$) or twist-boat ($^{4,5}TB_{2,3}$) conformation. The latter is not likely to take part in the conformational equilibrium, as the substituents at C-2 and C-5 would both be *axial*. The four methyne protons (H-2–5) give an AA′XX′ multiplet, the A and X parts of which consists of six–six lines only, in consequence of the fact[5] that $J_{XX'} \equiv J_{2,5} = 0$. From the H-3,4 signal, *i.e.*, the A part*, the following coupling-constants could be determined: $J_{3,4} \approx J_{2,3} \equiv J_{4,5} = 9$ Hz, indicating the *trans* arrangement of these protons,

*In the *X* part, a further triplet splitting of the six lines exists, due to the couplings between H-1,2 (H-5,6) and H-1′,2 (H-5,6′) and the spacings correspond to the mean value of the coupling constants (ABX spin system!).

with a dihedral angle of ~180°. Removal of the 3,4-*O*-isopropylidene group does not significantly influence the conformation of the seven-membered ring, as the derivatives of type **3** gave similar spectra (*e.g.*, for **3c**, $J_{3,4} = 8$ Hz). The instability of **3d** may be due to the dominant $_{4,5}TC^{2,3}$ conformation of the molecule, in which all substituents are "*equatorial*"; consequently, the ring-sulfur atom can readily attack either C-3 or C-4, forming a cyclic sulfonium cation *via* elimination of a mesyloxy anion.

Because of the discrepancy between the stability of 1,6-anhydro-2,5-di-*O*-methyl-3,4-di-*O*-(methylsulfonyl)-1(6)-thio-D-glucitol and of the L-iditol analog **3d**, we decided to synthesize the corresponding D-mannitol isomer **12c**, differing from **3d** in the steric arrangement of both methoxyl groups.

When diepoxide **6** was treated with sodium sulfide under the conditions described for the iditol isomer **1**, the corresponding 1,6-anhydro-1(6)-thio derivative **7a**—which could be separated as its diacetate **7b**—was obtained in poor yield (as polymerization became the predominant process). The yield of **7b** could not be increased by using the 1,6-dibromo compound **8** as starting material, as polymerization took place to the same extent in this case too. The ready formation of the iditol derivative **2b**, compared to the mannitol isomer **7b**, can be explained by their different configurations.



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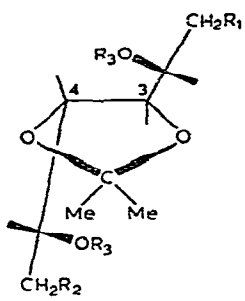
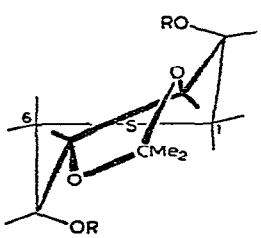
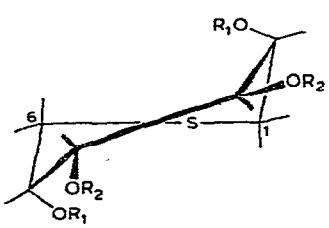


8 $R_1 = R_2 = Br$, $R_3 = H$
9 $R_1 = R_2 = TsO$, $R_3 = Ac$
10 $R_1 = BzS$, $R_2 = TsO$, $R_3 = Ac$
11 $R_1 = R_2 = BzS$, $R_3 = Ac$





7a R = H
7b R = Ac
7c R = Me

12a $R_1 = R_2 = H$
12b $R_1 = Me$, $R_2 = H$
12c $R_1 = Me$, $R_2 = Ms$

The n.m.r. spectra of the 3,4-*O*-isopropylidene derivatives **7a–c** prove clearly the C_2 symmetry of these compounds: consequently, they may exist, like the iditol derivatives, in the ${}_{4,5}TC^{2,3}$ or ${}^{4,5}TB_{2,3}$ conformation. From the H-3,4 signal (A part of the AA'XX' multiplet of H-2–5), the coupling constants $J_{2,3} \equiv J_{4,5} = 3.5$ Hz and $J_{3,4} = 8$ Hz could be determined, suggesting a dihedral angle of $\sim 60°$ and $\sim 180°$, respectively. It should be noted, however, that, whereas the ${}_{4,5}TC^{2,3}$ conformation was unambiguously favored in the iditol series because of the "*all-equatorial*" arrangement of the substituents, the same conformation becomes destabilized for the mannitol derivatives in consequence of the two "*axial*" substituents at C-2,5, each representing[6] a strain energy of ~ 12.5 kJ.mole^{-1} (~ 3 kcal.mole^{-1}). On the other hand, the ${}^{4,5}TB_{2,3}$ conformation is still unfavored, because of the strong "*diaxial*" interactions prevailing between H-1 and H-4, as well as between H-2 and H-6. In consequence of these destabilizing effects, the cyclic compound is energetically disfavored and, therefore, polymerization becomes the main process in the case of **7b**. The existence of this steric restriction could be proved by using an independent, synthetic route for **7b**. The 1,6-di-*O*-tosyl derivative **9** was treated with one equivalent of potassium thiobenzoate (PhCOSK) and the mono- and di-*S*-benzoates (**10** and **11**) formed were separed by column chromatography. Compound **7b** was obtained from **10** on treatment with sodium methoxide and subsequent acetylation, in about the same yield as *via* the two other methods already described.

The diacetate **7b** was deacetylated with sodium methoxide, to give crystalline **7a** which, on hydrolysis with aqueous trifluoroacetic acid, afforded the (known) 1,6-anhydro-1(6)-thio-D-mannitol[7] (**12a**). Methylation of **7a** with sodium hydride–methyl iodide afforded the di-*O*-methyl derivative **7c**. Hydrolysis of **7c** in aqueous trifluoroacetic acid yielded **12b** as the only product, and, in contrast to the iditol derivative **2e**, no rearrangement leading to a 1,5-anhydro derivative (corresponding to **4a**) took place. The absence of this reaction can be explained by the different configuration of **2e** and **7c**, as the two methoxyl groups are "*axial*" in the latter; and, consequently, a rear-side attack of the sulfur atom at C-2 or C-5 is sterically disfavored.

No change in conformation occurs on removing the 3,4-*O*-isopropylidene group of **7c**, as the derivatives of type **12** obtained give very similar n.m.r. spectra, proving both the C_2 symmetry and the dihedral angle of $\sim 180°$ for H-3,4 and $\sim 60°$ for H-2,3 and H-4,5, respectively.

Mesylation of **12b** yielded the di-*O*-mesyl derivative **12c**, which was unstable at room temperature, like the iditol analog **3d**. Neither of these two dimesyl derivatives showed any significant ulcerostatic activity; this may be due to their instability.

EXPERIMENTAL

General methods. — Melting points are uncorrected. T.l.c. was effected on Kieselgel G with ethyl acetate (*A*), and with ethyl acetate–carbon tetrachloride 1:1 (*B*), 1:3 (*C*), and 1:5 (*D*), and with 5:1 ethyl acetate–ethanol (*E*). For detection, 1:1

0.1M potassium permanganate–M sulfuric acid was used at 105°. Column chromatography was performed on Kieselgel 40 (63–200 μm). P.m.r. spectra (60 MHz) were recorded at room temperature with a JEOL 60-HL spectrometer for solutions in chloroform-*d*, with tetramethylsilane as the internal standard (see Table I). I.r. spectra were recorded, for KBr pellets, with a Perkin–Elmer 577 spectrometer. Mass spectra were recorded with a Varian MAT SM-1 instrument.

TABLE I

P.M.R. DATA[a] FOR COMPOUNDS 2a–f, 3a–d, 4a,d, 7a–c, 10, 11, AND 12b,c

Compound	*H-1*	*H-6*	*H-2,5*	*H-3,4*	*CMe_2*	*Acetyl*	*Mesyl*	*Methoxyl*	*Other protons*
2a	2.58[b] 2.83[b]		3.85*m*		1.35*s*	—	—	—	OH 5.15*d*(2)
2b	2.70[a] 2.90[b]		5.10*m*	4.15*m*	1.40*s*	2.10*s*	—	—	
2c	140–190[c]		5.05*m* 4.25*m*	215–245[c]	1.45*s*	2.10*s*	—	—	
2d	2.95*d*(5)		4.75*m*	4.20*m*	1.45*s*	—	3.10*s*	—	
2e	2.75*d*(5)		190–220[d]	4.00*m*	1.45*s*	—	—	3.48*s*	
2f	140–190[c]		200–260[c]		1.40*s*	—	—	3.40*s*	
3a[e]	2.54[b] 2.73[b]		190–230[c]		—	—	—	—	OH 4.85, broad
3b	155–170[c]		190–210[d]	210–230[c]	—	—	—	3.45*s*	
3c	155–175[c]		4.95*m*	3.55*m*	—	2.00*s*	—	3.35*s*	
3d	150–190[c]		4.75*m*	210–230[c]	—	—	3.15*s*	3.45*s*	
4a[e]	2.47[b] 2.95[b]	3.73[b] 3.90[b]		185–215[c]	—	—	—	3.45*s*	OH 4.40*t*(6), 4.80*d*(4), 4.85*d*(4)
4b	2.57[b] 2.95[b]	4.14[b] 4.26[b]	180–230[c]	4.90*t*(9) 5.20*t*(9)	— —	2.05*s* 2.10*s*	—	3.45*s*	
7a	2.40[f] 2.80[f]		240–260[c]		1.40*s*	—	—	—	
7b	2.70[f] 2.85[f]		5.55*t*(5)	4.60*s*	1.40*s*	2.10*s*			
7c	2.55[f] 2.85[f]		3.85*sx*	4.50*sx*	1.45*s*	—	—	3.50*s*	
10	3.15[b] 3.57[b]	4.10*m*	5.05*m*	4.45*m*	1.30*s* 1.37*s*	1.97*s* 2.00*s*	—	—	tosyl-CH_3 2.33*s*
11[e]	3.24[b] 3.63[b]		5.15*m*	4.20*m*	1.45*s*	2.05*s*	—	—	
12b	2.65*d*(5)		215–245[c]		—	—	—	3.47*s*	
12c	155–175[c]		5.05*s*	4.00*t*	—	—	3.10*s*	3.45*s*	

[a] δ scale, $CDCl_3$ solution; coupling constants in Hz are given in parentheses. [b] AB part of an ABX multiplet (J_{AB} = 13 Hz). [c] *m* in Hz. [d] Overlapped by the MeO signal. [e] In Me_2SO-d_6 solution. [f] AB part of an ABX multiplet (J_{AB} = 15 Hz).

All evaporations were performed in a rotary evaporator under diminished pressure, after the organic solutions had been dried with sodium sulfate. Light petroleum refers to the fraction having b.p. 60–80°. Optical rotations were determined

in chloroform (*c* 1) if not stated otherwise. Reaction mixtures containing sodium methoxide were made neutral with carbon dioxide.

1,6-Anhydro-3,4-O-isopropylidene-1(6)-thio-L-iditol (**2a**). — A solution of the diacetate **2b** (30.4 g) in dry chloroform (60 ml) and methanol (60 ml) was treated with 4M methanolic sodium methoxide (0.5 ml) and kept overnight at room temperature. The precipitated dihydroxy compound **2a** (16 g) was filtered off, and washed with chloroform. The filtrate was made neutral, and evaporated. The solid residue was recrystallized from ethyl acetate, to yield a second crop of **2a** (5.5 g; total yield 93.5%), m.p. 186–188°, $[\alpha]_D^{20}$ +83.4° (methanol); R_F 0.30 (*B*).

Anal. Calc. for $C_9H_{16}O_4S$: C, 49.07; H, 7.32; S, 14.56. Found: C, 49.39; H, 7.43; S, 14.33.

Mesylation of **2a** (4.4 g) in pyridine (20 ml) with methanesulfonyl chloride (5 ml) afforded the di-*O*-mesyl derivative **2d** (6.7 g, 89%) which, after recrystallization from acetone–light petroleum, had m.p. 161–163°, $[\alpha]_D^{20}$ +77.7°; R_F 0.75 (*B*).

Anal. Calc. for $C_{11}H_{20}O_8S_3$: C, 35.10; H, 5.36; S, 25.55. Found: C, 35.11; H, 5.45; S, 25.42.

2,5-Di-O-acetyl-1,6-anhydro-3,4-O-isopropylidene-1(6)-thio-L-iditol (**2b**). — Sodium sulfide nonahydrate (14 g) was added to a solution of[8] **1** (10.2 g) in ethanol (120 ml) and water (27 ml). The mixture was stirred for 1 h at room temperature, and was then evaporated without neutralization. Two portions of ethanol, and subsequently chloroform, were added to, and evaporated from, the residue, which was then dissolved in pyridine (60 ml) and treated with acetic anhydride (60 ml). The mixture was kept overnight at room temperature and then processed, to give crude **2b**, which was recrystallized from methanol–water (12.2 g, 73%), m.p. 175–177°, $[\alpha]_D^{20}$ +110°; R_F 0.55 (*C*).

Anal. Calc. for $C_{13}H_{20}O_6S$: C, 51.30; H, 6.62; S, 10.53. Found: C, 51.24; H, 6.58; S, 10.42.

2-O-Acetyl-1,6-anhydro-3,4-O-isopropylidene-1(6)-thio-L-iditol (**2c**). — The deacetylation process described for compound **2b** (10 g) was interrupted after 2 h by making the reaction mixture neutral. The residue obtained by evaporation was recrystallized from ethyl acetate, to yield **2a** (3.15 g, 43%). The filtrate was evaporated, and the residue was separated by column chromatography using solvent *B* for elution. Besides some starting material (0.35 g, 3.5%) and a further crop of **2a** (1.15 g, 16%), compound **2c** was obtained (2.8 g, 32%) which, after recrystallization from acetone–light petroleum, had m.p. 122–124°, $[\alpha]_D^{20}$ +100°; R_F 0.45 (*B*); ν_{max} 3480 (OH), 1710 (C=O), 1260, 1245, 1070, and 1030 cm^{-1} (C–O ester).

Anal. Calc. for $C_{11}H_{18}O_5S$: C, 50.37; H, 6.92; S, 12.22. Found: C, 50.21; H, 6.64; S, 12.16.

1,6-Anhydro-3,4-O-isopropylidene-2,5-di-O-methyl-1(6)-thio-L-iditol (**2e**). — Sodium hydride (55% suspension in oil, 15 g) was washed three times by decantation with light petroleum; then, dimethyl sulfoxide (200 ml) was added, and the mixture was stirred until foaming ceased. Subsequently, compound **2a** (22 g) was added, and, when the evolution of hydrogen stopped, the dark-lilac solution was chilled with ice.

Methyl iodide (15 ml) was added during 30 min, while the color of the slurry changed to light grey. The mixture was stirred for 30 min at room temperature, and was then diluted with water (100 ml). The mixture obtained was filtered from some undissolved, brown, fluffy material, and the filtrate was extracted with chloroform (5 × 200 ml). The extracts were combined, and washed successively with a small volume of aqueous sodium thiosulfate (to remove the yellow color) and a small volume of water, dried, and evaporated, and dimethyl sulfoxide was removed at 100°/1 Torr. The residue was treated with water, yielding pure **2e** (18.9 g, 79%), m.p. 62–64° (not raised by recrystallization from methanol–water), $[\alpha]_D^{20}$ +55°, R_F 0.50 (*C*), 0.75 (*B*).

Anal. Calc. for $C_{11}H_{20}O_4S$: C, 53.20; H, 8.12; S, 12.91. Found: C, 53.27; H, 8.04; S, 12.79.

*1,6-Anhydro-3,4-*O*-isopropylidene-2-*O*-methyl-1(6)-thio-*L*-iditol* (**2f**). — To a stirred slurry of compound **2a** (1.7 g) in water (5 ml) were simultaneously added a solution of sodium hydroxide (4.25 g) in water (5 ml) and dimethyl sulfate (4.25 ml) during 30 min, the temperature of the mixture being kept below 20° by cooling with ice. Stirring was continued for 2 h at room temperature, and the reaction products were extracted with chloroform. The residue from evaporation of the extract was separated by column chromatography using solvent *B*. Besides the dimethyl derivative **2e** (0.64 g, 33.4%) and some starting-material **2a** (0.28 g, 16.5%), pure **2f** was obtained (0.30 g, 16.6%), m.p. 57–60°, $[\alpha]_D^{20}$ +58°, R_F 0.50 (*B*), ν_{max} 3450 (OH), 2820, and 1060 cm^{-1} (methoxyl).

Anal. Calc. for $C_{10}H_{18}O_4S$: C, 51.26; H, 7.74; S, 13.68. Found: C, 51.33; H, 7.81; S, 13.72.

*1,6-Anhydro-1(6)-thio-*L*-iditol* (**3a**). — A slurry of compound **2a** (1.1 g) in 0.1M aqueous trifluoroacetic acid (11 ml) was hydrolyzed on a steam bath for 2 h, and evaporated. Water and ethanol were successively added to, and evaporated from, the residue, which was then recrystallized from acetonitrile (8 ml), to give **3a** as needles (0.6 g, 66.6%), m.p. 110–112°, $[\alpha]_D^{20}$ +89° (water); R_F 0.50 (*E*).

Anal. Calc. for $C_6H_{12}O_4S$: C, 39.98; H, 6.71; S, 17.79. Found: C, 40.08; H, 6.47; S, 17.68.

*1,6-Anhydro-2,5-di-*O*-methyl-1(6)-thio-*L*-iditol* (**3b**) *and 1,5-anhydro-2-*O*-methyl-5-thio-*D*-glucitol* (**4a**). — A slurry of **2e** (24.8 g) in 0.1M aqueous trifluoroacetic acid (250 ml) was boiled for 2 h under reflux, and then evaporated. Water, ethanol (twice), and chloroform were successively added to, and evaporated from, the residue, which was then treated with ether. The solid mixture of **3b** and **4a** was filtered off, and washed with ether (15 g). The filtrate was evaporated, and the residue was resubmitted to hydrolysis as just described, to give a second crop of **3b** and **4a** (3 g). The combined solid material was dissolved in chloroform (35 ml), and the solution treated with light petroleum (35 ml). On slow cooling, compound **4a** crystallized in fine needles which were filtered off, and washed with ether. After recrystallization from ethyl acetate, pure **4a** was obtained (1.6 g, 8.23%), m.p. 124–125°, $[\alpha]_D^{20}$ +39°; R_F 0.30 (*A*); mass-spectral data: peaks at *m/e* 194 ([M^+], 100%), 162 (31), 145 (30), 144 (40), 74 (28), 59 (55), and 57 (26).

Anal. Calc. for $C_7H_{14}O_4S$: C, 43.28; H, 7.27; S, 16.51. Found: C, 43.12; H, 7.32; S, 16.50.

The filtrates were combined, and evaporated, and the residue was washed with ether, and recrystallized from ethyl acetate, to give a mixture of **3b** (1.8 g, 8.6%) and **4a** (0.7 g, 3.6%) which was separated by column chromatography, using solvent *A* for elution. Evaporation of the ethyl acetate filtrate afforded, after treatment with ether, pure **3b** (13.65 g, 65.5%), m.p. 74–76°, $[\alpha]_D^{20}$ +110°; R_F 0.40 (*A*).

Anal. Calc. for $C_8H_{16}O_4S$: C, 46.13; H, 7.74; S, 15.40. Found: C, 46.08; H, 7.69; S, 15.49.

Acetylation of **3b** (2.1 g) in pyridine (10 ml) with acetic anhydride (7 ml) afforded **3c** (2.3 g, 78.6%) as a colorless syrup, $[\alpha]_D^{20}$ +113°; R_F 0.75 (*B*).

Anal. Calc. for $C_{12}H_{20}O_6S$: S, 32.86. Found: S, 32.63.

Mesylation of **3b** (2.1 g) in benzene (10 ml) with methanesulfonyl chloride (1.9 ml) in the presence of triethylamine (4 ml) afforded **3d** (3.5 g, 96%) as a chromatographically homogenous syrup, $[\alpha]_D^{20}$ +47°; R_F 0.60 (*B*), which could be stored, without decomposition, only below 0°.

Anal. Calc. for $C_{10}H_{20}O_8S_3$: S, 26.40; CH_3O, 17.03. Found: S, 26.18; CH_3O, 16.84.

Acetylation of **4a** (0.55 g) afforded, after the usual processing, **4b** (0.80 g, 88%), m.p. 100–101°, $[\alpha]_D^{20}$ +57°; R_F 0.70 (*B*); mass-spectral data: peaks at *m/e* 320 ($[M^+]$, 0.3% of base peak at *m/e* 228), 260 (18), 186 (76), 160 (24), 159 (70), 158 (21), and 43 (64).

Anal. Calc. for $C_{13}H_{20}O_7S$: C, 48.74; H, 6.29; S, 10.01. Found: C, 48.81; H, 6.32; S, 9.98.

*1,6-Anhydro-3,4-*O*-isopropylidene-1(6)-thio-*D*-mannitol* (**7a**). — A solution of **7b** (15.2 g) in dry chloroform (30 ml) and methanol (30 ml) was treated with 4M methanolic sodium methoxide (1 ml). After 2 h at room temperature, the mixture was made neutral, and evaporated. The residue was dissolved in acetone (50 ml), and the solution poured into ether (300 ml). The precipitate was filtered off (on charcoal), and the filtrate was evaporated. The residue was recrystallized from ether–light petroleum, to give pure **7a** (9.0 g, 82%), m.p. 93–95°, $[\alpha]_D^{20}$ −122°; R_F 0.50 (*B*).

Anal. Calc. for $C_9H_{16}O_4S$: C, 49.07; H, 7.32; S, 14.56. Found: C, 49.12; H, 7.22; S, 14.50.

Hydrolysis of **7a** (2.3 g) in aqueous trifluoroacetic acid, as described for **3a**, gave **12a** (1.1 g, 58.5%), m.p. 120–122°, $[\alpha]_D^{20}$ −119.4° (water); lit.[7] m.p. 121–122°, $[\alpha]_D^{20}$ −119.5° (*c* 1, water).

*2,5-Di-*O*-acetyl-1,6-anhydro-3,4-*O*-isopropylidene-1(6)-thio-*D*-mannitol* (**7b**). — *Method a.* The diepoxide[9] **6** (50 g) was treated with sodium sulfide nonahydrate as described for compound **2b**. After 2 h at room temperature, the mixture was made neutral with carbon dioxide, and the precipitated inorganic salts were filtered off, and washed with ethanol. The filtrate was evaporated; then, two portions of ethanol and, subsequently, chloroform were added to, and evaporated from, the residue, which was taken up in acetone (100 ml) and the solution poured into ether (1 liter). The clear

solution was decanted from the precipitated material, and was evaporated. The residue was dissolved in pyridine (200 ml) and treated with acetic anhydride (150 ml), to give, after the usual processing, a semi-solid material, which was dissolved in carbon tetrachloride and freed from acetylated polymeric material by passage through a short column, using solvent *C* for elution. On evaporation of the filtrate, and recrystallization of the residue from carbon tetrachloride–light petroleum, pure **7b** (22 g, 26.8%) was obtained, m.p. 143–144°, $[\alpha]_D^{20}$ −144°; R_F 0.50 (*C*).

Anal. Calc. for $C_{13}H_{20}O_6S$: C, 51.30; H, 6.62; S, 10.53. Found: C, 51.35; H, 6.58; S, 10.62.

Method b. 1,6-Dibromo-1,6-dideoxy-3,4-*O*-isopropylidene-D-mannitol[10] (**8**, 85 g) was dissolved in boiling ethanol (850 ml), and sodium sulfide nonahydrate (64.5 g) dissolved in water (130 ml) was added to the hot solution during 10 min. The mixture was boiled for 30 min, and then evaporated. The residue was processed according to method *a*, yielding **7b** (20 g, 27%), identical with that already described.

Method c. A solution of **10** (6 g) in chloroform (100 ml) and methanol (10 ml) was treated with 4M methanolic sodium methoxide (4 ml). After 2 days at room temperature, the mixture was made neutral, and evaporated. The residue was processed according to method *a*, yielding **7b** (0.61 g, 20.3%), identical with that obtained *via* route *a*.

*1,6-Anhydro-3,4-*O*-isopropylidene-2,5-di-*O*-methyl-1(6)-thio-*D*-mannitol* (**7c**). — Compound **7a** (6.3 g) was methylated as described for **2e**, but a reaction time of 2 h (at room temperature) was necessary in order to complete the reaction. The residue obtained by evaporation of the solvents gave, on recrystallization from methanol–water, pure **7c** (3 g, 42%), m.p. 65–66°, $[\alpha]_D^{20}$ −109°; R_F 0.70 (*B*).

Anal. Calc. for $C_{11}H_{20}O_4S$: C, 53.20; H, 8.12; S, 12.91. Found: C, 53.58; H, 8.22; S, 12.66.

*2,5-Di-*O*-acetyl-1-*S*-benzoyl-3,4-*O*-isopropylidene-1-thio-6-*O*-p-tolylsulfonyl-*D*-mannitol* (**10**) *and 2,5-di-*O*-acetyl-1,6-di-*S*-benzoyl-3,4-*O*-isopropylidene-1,6-dithio-*D*-mannitol* (**11**). — A solution of compound[3] **9** (30.7 g) and potassium thiobenzoate (12 g) in dry acetone (300 ml) was kept for 2 days at room temperature, and then boiled for 1 h. The mixture was cooled and filtered, and the salts were washed with acetone. The filtrate was evaporated, and the residue was partitioned between chloroform and water. The organic layer was dried, and evaporated, and the residue was separated by column chromatography using solvent *D*. Evaporation of the fraction having R_F 0.60 gave, after recrystallization from methanol, the di-*S*-benzoate **11** (3.7 g, 13.5%), m.p. 112–114°, $[\alpha]_D^{20}$ +80°.

Anal. Calc. for $C_{27}H_{30}O_8S_2$: C, 59.31; H, 5.53; S, 11.73. Found: C, 59.39; H, 5.64; S, 11.70.

Evaporation of the fraction having R_F 0.40 afforded, after recrystallization from ether–light petroleum, the mono-*S*-benzoate **10** (6.9 g, 24%), m.p. 81–83°, $[\alpha]_D^{20}$ +50.7°.

Anal. Calc. for $C_{27}H_{32}O_{10}S_2$: C, 55.83; H, 5.55; S, 11.05. Found: C, 55.72; H, 5.65; S, 10.98.

1,6-Anhydro-2,5-di-O-methyl-1(6)-thio-D-mannitol (**12b**). — Compound **7c** (5 g) was hydrolyzed in 0.1M aqueous trifluoroacetic acid as described for the iditol isomer **3b**. The syrupy **12b** (4 g, 96%) obtained after evaporation gave a single spot in t.l.c., $[\alpha]_D^{20}$ −132°, R_F 0.50 (*A*).

Anal. Calc. for $C_8H_{16}O_4S$: S, 15.40; CH_3O, 29.80. Found: S, 15.52; CH_3O, 29.43.

Mesylation of **12b** (3.8 g) was conducted as described for **3d**, affording **12c** (5.8 g, 88%) as a chromatographically homogenous syrup, $[\alpha]_D^{20}$ −46°; R_F 0.75 (*B*), which could be stored, without decomposition, only below 0°.

Anal. Calc. for $C_{10}H_{20}O_8S_3$: S, 26.40; CH_3O, 17.03. Found: S, 26.29; CH_3O, 16.80.

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