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HEXITOL DERIVATIVES CONTAINING A 1,4-OXATHIANE RING

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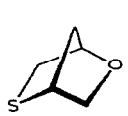
ABSTRACT

The synthesis of 2,5-anhydro-3-*O*-methylsulfonyl-6-thio-1,4-thioanhydro-D-galactitol (**4**; type *A* structure) and 2,5-anhydro-3,4-di-*O*-methylsulfonyl-1,6-thioanhydro-D-glucitol (**10**, type *B* structure), starting from 2,5-anhydro-1,6-dibromo-1,6-dideoxy-3,4-di-*O*-methylsulfonyl-D-glucitol (**1**) is described. The 4-*O*-methylsulfonyl group of **10** can be displaced by nucleophiles with retention of configuration. In this reaction, a cyclic sulfonium intermediate **21** is involved, which, depending on the nucleophilicity of the anion, leads to different ratios of type *A* and *B* compounds. Introduction of a three-membered ring into the 3,4-position of type *B* compounds yielded tricyclic derivatives of allitol.

INTRODUCTION

In a previous paper[1], we described the synthesis and investigation of bis-(thioanhydro)hexitol derivatives. During the structural determination of the corresponding disulfoxides by the n.m.r. method, the need arose for model compounds with known stereochemistry. Therefore, the synthesis of thioanhydrohexitols having rigid structures was attempted.

2,5-Anhydro-1,6-dibromo-1,6-dideoxy-3,4-di-*O*-methylsulfonyl-D-glucitol[2] (**1**), which was chosen as starting material, contains two different kinds of good leaving groups, namely bromine atoms at C-1 and C-6, and mesyloxy groups at C-3 and C-4. The bromine atoms could be selectively displaced by sulfur-containing nucleophiles and, according to the reaction conditions used, either type *A* or *B* compounds were obtained, containing in their skeleton the same 1,4-oxathiane ring but different bridged structures*.



A

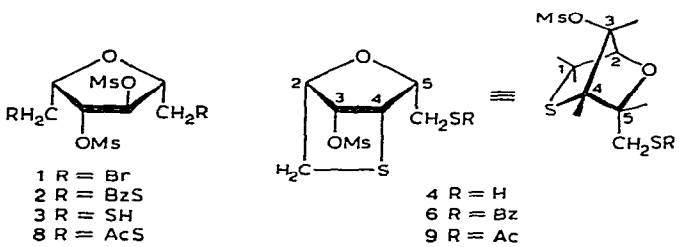
B

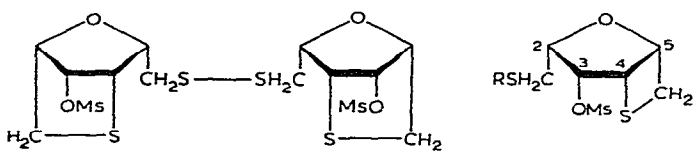
*According to the "Ring Index", type *A* is named 2-oxa-5-thiabicyclo[2.2.1]heptane and type *B* is 8-oxa-3-thiabicyclo[3.2.1]octane. In this paper, carbohydrate nomenclature is used, since it allows the stereochemistry to be conveniently designated.

Only one carbohydrate derivative with a similar, 1,3-oxathiane structure was previously known[3], but its substitution reactions had not been investigated.

DISCUSSION

Reaction of compound **1** with 2 equivalents of potassium thiolbenzoate afforded the crystalline di-*S*-benzoyl derivative **2**, which, on brief treatment with an excess of sodium methoxide, gave the corresponding 1,6-dithiol **3**. Prolonging the reaction time to 24 h gave the required 1,4-thioanhydro-D-galactitol derivative **4**, but a large proportion of the disulfide **5** was also obtained. Since **5** is formed preferentially under basic conditions, the amount of sodium methoxide was diminished to 1.02 equivalents, thereby avoiding oxidation of compound **4**. However, a new component appeared in the reaction mixture, which, after chromatographic separation, was shown to be the corresponding *S*-benzoyl derivative **6**. The same compound was obtained by treating the thiol **4** with benzoyl chloride.





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The presence of the 1,4-thioanhydro ring in these compounds was proved by n.m.r. spectroscopy, using tris(2,2,6,6-tetramethylheptane-3,5-dionato)europium(III) as shift reagent (Table I) and also spin decoupling. The data obtained excluded isomer **7**, which theoretically could also have been formed.

The 6-thiol **4** could also be prepared *via* the corresponding 1,6-di-*S*-acetyl derivative **8**, and subsequent acetylation gave a stable, crystalline thioester **9** which could be used advantageously for the otherwise difficult purification of **4**.

When the dibromide **1** was treated in boiling methanol with sodium sulfide, a thioether link was established between C-1 and C-6, yielding the 2,5-anhydro-3,4-di-*O*-methylsulfonyl-1,6-thioanhydro-D-glucitol (**10**). The corresponding 4-bromide **11** and 2,5-anhydro-3,4-epithio-1,6-thioanhydroallitol (**29**) were obtained as by-products. The structure of **11** was established by comparing its n.m.r. spectrum with that of the di-*O*-mesyl derivative **10** (Table II). As shown in the projection formula, H-2 and H-3

TABLE I

CHEMICAL SHIFT DATA[a] (δ, p.p.m.) for compound 6

Mol. ratio of 6: complex	*H-1*	CH_3SO_2	*H-6*	*H-4*	*H-5*	*H-2*	*H-3*
1:0	3.0	3.15	3.58	3.80	4.5	4.5	5.30
3:1	3.21	3.21	4.24	4.02	5.35	5.08	5.65
3:2	3.43	3.40	4.95	4.30	6.25	5.60	6.00
1:1	3.53 3.80	3.50	5.45	4.45	6.92	5.95	6.25

[a]In the presence of tris(2,2,6,6-tetramethylheptane-3,5-dionato)europium(III).

are *cis*-related with a dihedral angle smaller than 30°, whereas H-4 and H-5 are *trans*-related with a dihedral angle of ~90°. In agreement with this steric arrangement, the signal for H-4 appears as a doublet ($J_{3,4}$ 3, $J_{4,5}$ ~0 Hz) and that for H-3 as a quartet ($J_{3,4}$ 3, $J_{2,3}$ 7 Hz). The corresponding 4-bromide **11** gave the same type of spectrum, differing only in the chemical shift of H-4. Consequently, the configuration at C-3 and C-4 must be the same in both derivatives. Thus, substitution of the 4-mesyloxy group in compound **10** by bromine occurred with retention of configuration.

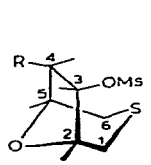
TABLE II

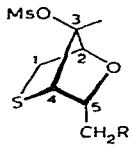
CHEMICAL SHIFT DATA[a] FOR THE 4-SUBSTITUTED 2,5-ANHYDRO-3-*O*-METHYLSULFONYL-1,6-THIOANHYDRO-D-GLUCITOLS

Compd.	*4-R*	*H-1,6* (*m*)	*H-1',6'* (*m*)	CH_3SO_2 (*s*)	*H-5* (*tr*)	*H-2* (*m*)	*H-3* (2×*d*)	*H-4* (*d*)	
10	MsO	140–165	175–190	3.32 3.34	4.60	280–300	5.33	5.67	
11	Br	130–155	180–210	3.23		270–290[b]	5.43	4.97	
13	N_3	130–155	180–210	3.20	4.60	270–290	5.10	4.77	
14	AcO	135–160	180–210	3.17	4.33	275–295	5.25	5.76	Ac, 2.15 s
15	BzO	130–170	180–210	3.17	4.48	275–300	5.42	5.98	Ph, 435–495 m
16	OH	125–155	180–205	3.22	4.30	275–295		290–310[b]	OH, 3.6 d
18	HCOO	130–160	180–210	3.16	4.38	275–295	5.25	5.88	HCO, 8.18 s
20	BzS	150–170	185–210	3.16	4.42	270–290	5.20	4.75	Ph, 440–485 m

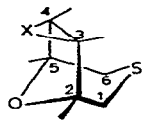
[a]m, multiplet (Hz); s, singlet (δ); d, doublet (δ); tr, triplet (δ). [b]Overlapping multiplets.

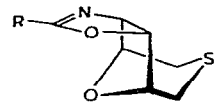
The ring closure of **1** with sodium sulfide gave unsatisfactory yields of **10**, and a new synthesis was worked out. Reaction of the dibromide **1** with 1 equivalent of potassium thiolbenzoate gave a syrupy mixture of the 1(6)-*S*-benzoyl-6(1)-bromo derivatives **12**, unchanged starting material, and the corresponding di-*S*-benzoyl ester **2**. It was unnecessary to separate these components because treatment of the crude mixture with sodium methoxide gave compound **10** in yields of over 50%.





25 R = BzO
26 R = N_3
27 R = AcO
28 R = Br





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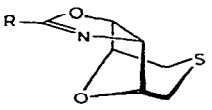
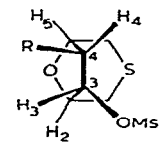
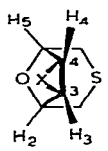


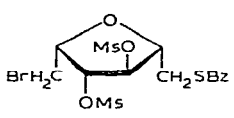
35 R = $C_6H_4NO_2$



10 R = MsO 16 R = OH
11 R = Br 17 R = I
13 R = N_3 18 R = HCOO
14 R = AcO 19 R = SNa
15 R = BzO 20 R = BzS



29 X = S
30 X = O
31 X = NH
33 X = N-Ms
34 X = N-$COC_6H_4NO_2$



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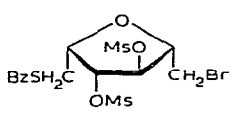

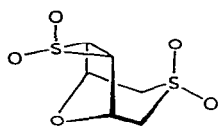

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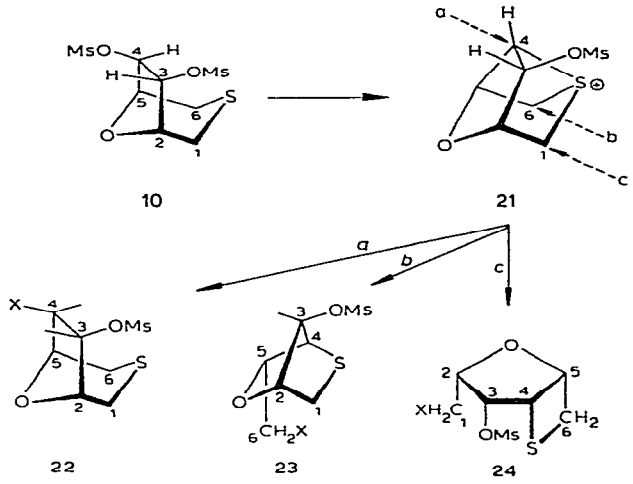
The substitution reaction of the 4-*O*-mesyl group was investigated by treating compound **10** in boiling *N*,*N*-dimethylformamide with sodium bromide, azide, acetate, and benzoate, when the 4-substituted derivatives **11**, **13**, **14**, and **15**, respectively, were obtained. The last two compounds could be deacetylated with sodium methoxide to give the 4-hydroxy derivative **16**, which gave **10** on mesylation. When substitution was attempted with potassium iodide, the 4-*O*-formyl ester **18** was obtained and not the 4-iodo derivative **17**. This was due to contamination of the solvent with ammonium formate; formate anion is a stronger nucleophile than iodide.

Formation of the epithio by-product **29** can be explained by substitution of the 4-mesyloxy group by sodium sulfide to give the intermediate **19**, followed by formation of the epithio ring by a *trans*-elimination reaction. This possibility was confirmed when treatment of compound **10** with potassium thiolbenzoate gave not only the predicted 4-*S*-benzoyl derivative **20** but also the isomeric 6-*S*-benzoyl derivative **6**. The unexpected formation of **6** may be explained as follows. The facile substitution at C-4, with retention of configuration, suggests a two-step mechanism, since direct replacement of *trans*-situated, secondary mesyloxy groups is an extremely hindered process[4]. The formation of an intermediate sulphonium cation **21** (Scheme 1) by a neighbouring-group reaction appears to be involved. In this cyclic cation, C-4 will be the most positive centre, and consequently nucleophilic attack should occur preferably at this position (route *a*), giving **22** with overall retention of configuration. Because of steric hindrance and electrostatic repulsion of the 3-mesyloxy group, an attack at C-1



SCHEME 1

(route *c*) is unfavoured. Thus, in addition to **22**, only the rearanged product **23** (route *b*) has to be considered as a possible reaction product. On repeating the substitution reactions mentioned above, it was found that the corresponding isomers **23** were always formed, but the ratio of the *a* and *b* routes depends very much on the nucleophilicity of the reactant. With potassium thiolbenzoate, the two isomers **20** and **6** were formed in the ratio 60:40, sodium benzoate gave **15** and **25** in the ratio of 90:10, and the two azides **13** and **26** were isolated in the ratio of 95:5. If the reaction was carried out with acetate or bromide ions, the corresponding isomers **27** and **28** could only be detected chromatographically.

Treatment of the 4-*S*-benzoyl derivative **20** with sodium methoxide gave the thiol **19**, which immediately formed the epithio compound **29**. The analogous hydroxy compound **16** was unaffected even by boiling, methanolic sodium methoxide. Formation of the epoxide **30** could be achieved only by potassium *tert*-butoxide at elevated temperature. The corresponding epimino derivative **31** was obtained directly from the azide **13** by reduction with lithium aluminium hydride. The structure of these tricyclic compounds was confirmed by n.m.r. data (Table III); H-3 and H-4 gave a singlet ($J_{2,3} = J_{4,5} \approx 0$), due to their equivalence and to the *trans*-position of the adjacent protons (H-2 and H-5).

TABLE III

CHEMICAL SHIFT DATA (δ, p.p.m.) OF THE TRICYCLIC ALLITOL DERIVATIVES

Compd.	*X*	*H-2,5*	*H-3,4*	*H-1',6'*	*H-1,6*
29	S	4.35	4.47	3.30	2.33
30	O	4.30	3.83	3.32	2.35
31	NH	4.20	2.62	3.28	2.30

The stability of the strained rings in these compounds is unusual; for example, the epithio derivative **29** cannot be converted into the trithiocarbonate by carbon disulfide and sodium hydroxide[5], the epoxide gives no blue colour with 4-*p*-nitrobenzylpyridine[6], and the epimino derivative **31** formed a stable hydrochloride which was recovered unchanged after treatment with boiling, conc. hydrochloric acid. This stability is probably due to the "crowded" structure of the molecules, which inhibits reactions involving a "rear-side attack" on the three-membered ring. However, the heteroatom reacts normally; thus the episulfide can be oxidized to its disulfone **32**, and the epimine gives the corresponding amides **33** and **34** with mesyl chloride and *p*-nitrobenzoyl chloride. The latter amide undergoes the oxazoline rearrangement[7] when treated with conc. sulfuric acid, yielding the racemic mixture **35**. However, the same reaction could not be carried out with potassium iodide. Treatment of the epimine with nitrous acid afforded the unsaturated compound **36**, and not the *N*-nitroso or the 3,4-dihydroxy derivative.

EXPERIMENTAL

General methods. — Melting points are uncorrected. T.l.c. was effected on Kieselgel G with carbon tetrachloride–ethyl acetate 1:1 (*A*), 2:1 (*B*), 3:1 (*C*), and 5:1 (*D*). 0.1M Potassium permanganate–M sulfuric acid (1:1), with heating at 105°, was used for detection. For column chromatography, silicic acid was used with carbon tetrachloride. N.m.r. spectra were recorded at 60 MHz, with a Varian A-60D spectrometer, for solutions in $CDCl_3$ with Me_4Si as internal standard. All evaporations were carried out in a rotary evaporator under diminished pressure, after drying of the organic solutions over sodium sulfate. Light petroleum had b.p. 60–80°. Optical rotations were determined in chloroform (*c* 1), if not otherwise stated.

*2,5-Anhydro-1,6-di-*S*-benzoyl-3,4-di-*O*-methylsulfonyl-1,6-dithio-*D*-glucitol* (**2**). — A solution of the dibromo compound[2] **1** (44.6 g) and potassium thiolbenzoate (44 g) in dry acetone (1 litre) was heated on a steam bath with stirring for 3 h. The cooled slurry was filtered and the salts were washed with acetone. The filtrate was evaporated and the solid residue was treated with water and chloroform. The organic layer was washed with 5% aqueous sodium hydrogen carbonate and water, dried, and evaporated. The residue was treated with methanol to give a crude product (50.5 g, 90%) which, on recrystallization from ethyl acetate–ether–light petroleum, yielded **2** (41.5 g, 74%), m.p. 103–105°, $[\alpha]_D^{20}$ +9.25°, R_F 0.5 (solvent *C*) (Found: C, 47.28; H, 4.24; S, 22.84. $C_{22}H_{24}O_9S_4$ calc.: C, 47.12; H, 4.32; S, 22.88%).

Treatment of compound **2** *with sodium methoxide.* — (*a*) A solution of **2** (5.6 g) in dry chloroform (40 ml) and dry methanol (10 ml) was treated at room temperature with 4M methanolic sodium methoxide (5 ml, 2 equiv.). After 10 min, the solution was acidified with M hydrochloric acid and the organic layer was washed with water. The dried solution was evaporated, and the residue was treated with ethyl acetate–light petroleum to give a crude product (3.2 g, 90.8%). Recrystallization from methanol (25 ml) gave 2,5-anhydro-3,4-di-*O*-methylsulfonyl-1,6-dithio-D-glucitol (**3**) (2.6 g,

74%), m.p. 78–80°, $[\alpha]_D^{20}$ +43.5°, R_F 0.35 (solvent *B*) (Found: C, 27.32; H, 4.72; S, 36.13, $C_8H_{16}O_7S_4$ calc.: C, 27.26; H, 4.58; S, 36.39%).

(*b*) A solution of **2** (5.6 g) as in (*a*) was treated with methanolic 4M sodium methoxide (3 ml, 1.2 equiv.) at room temperature for 24 h. The slurry was washed with water, dried, and evaporated. The residual syrup was chromatographed on silicic acid with solvent *B*. The fractions were monitored by t.l.c. and those containing components of R_F 0.45 and 0.25 were combined and evaporated to dryness. The former fraction (1.2 g, 46.8%), on recrystallization from ethyl acetate–light petroleum, gave 2,5-anhydro-3-*O*-methylsulfonyl-6-thio-1,4-thioanhydro-D-galactitol (**4**) (0.8 g, 31.2%), m.p. 111–112°, $[\alpha]_D^{20}$ −45° (Found: C, 32.92; H, 4.78; S, 37.46. $C_7H_{12}O_4S_3$ calc.: C, 32.79; H, 4.72; S, 37.53%). The latter fraction (0.6 g, 24.6%), on recrystallization from chloroform–ether, yielded bis(2,5-anhydro-6-deoxy-3-*O*-methylsulfonyl-1,4-thioanhydro-D-galactitol) 6,6′-disulfide (**5**) (0.3 g, 12.3%), m.p. 162–164°, $[\alpha]_D^{20}$ −27.9° (Found: C, 33.05; H, 4.52; S, 37.42. $C_{14}H_{22}O_8S_6$ calc.: C, 32.92; H, 4.34; S, 37.67%). Compound **5** (0.9 g, 82%) was also obtained by treating 6-thiol **4** (1.1 g) in methanol (15 ml) with a solution of iodine (0.5 g) in methanol (25 ml).

(*c*) When the deacylation of **2** was carried out with 4M sodium methoxide (2.55 ml, 1.02 equiv.), **5** was not formed; the products were the 6-thiol **4** (1.35 g, 52.8%) and a product of R_F 0.35 (0.42 g, 11.7%) which could be separated by column chromatography. Recrystallization from ethyl acetate–light petroleum afforded 2,5-anhydro-6-*S*-benzoyl-3-*O*-methylsulfonyl-6-thio-1,4-thioanhydro-D-galactitol (**6**) (0.37 g, 10.25%), m.p. 90–92°, $[\alpha]_D^{20}$ −41.7° (Found: C, 46.76; H, 4.62; S, 26.76. $C_{14}H_{16}O_5S_3$ calc.: C, 46.46; H, 4.47; S, 26.69%). Compound **6** (0.6 g, 71%) was also obtained by treating the 6-thiol **4** (0.6 g) in pyridine (3 ml) with benzoyl chloride (0.4 ml).

2,5-Anhydro-3-O-methylsulfonyl-6-thio-1,4-thioanhydro-D-galactitol (**4**). — A solution of compound **3** (3.5 g) or its di-*S*-acetyl derivative **8** (4.4 g) in dry chloroform (50 ml) and dry methanol (10 ml) was boiled on a steam bath with 4M methanolic sodium methoxide (2.5 ml) for 30 min. The cooled slurry was washed with water, dried, and evaporated. The semi-solid residue was dissolved in ethyl acetate and purified by column chromatography (solvent *B*). The fractions showing the component having R_F 0.45 (t.l.c.) were combined and evaporated. Recrystallization of the residue from ethyl acetate–light petroleum gave compound **4** (1.3 g, 46%), identical with that prepared from the di-*S*-benzoyl derivative **2**. Purification by column chromatography could not be avoided, as attempts to remove contaminants by recrystallization failed.

1,6-Di-S-acetyl-2,5-anhydro-3,4-di-O-methylsulfonyl-1,6-dithio-D-glucitol (**8**). — A solution of compound **3** (0.3 g) in pyridine (1 ml) and acetic anhydride (0.5 ml) was kept overnight at room temperature to give, after the usual work-up, **8** as a colorless syrup (0.4 g, 91.7%), $[\alpha]_D^{20}$ +6.9° (Found: C, 32.82; H, 4.40; S, 29.09. $C_{12}H_{20}O_9S_4$ calc.: C, 33.01; H, 4.62; S, 29.38%).

6-S-Acetyl-2,5-anhydro-3-O-methylsulfonyl-1,4-thioanhydro-6-thio-D-galactitol (**9**). — A solution of the 6-thiol **4** (1.1 g) in pyridine (3 ml) and acetic anhydride (1.5 ml) was kept overnight at room temperature. The crude compound, obtained

after the usual work-up, was recrystallized from chloroform–ether to give **9** (0.6 g, 46.8%), m.p. 153–154°, $[\alpha]_D^{20}$ −31.7°, R_F 0.50 (solvent *B*) (Found: C, 36.27; H, 4.82; S, 32.27. $C_9H_{14}O_5S_3$ calc.: C, 36.22; H, 4.73; S, 32.24%).

2,5-Anhydro-3,4-di-O-methylsulfonyl-1,6-thioanhydro-D-glucitol (**10**). — (*a*) *From dibromide* **1**. A stream of dry hydrogen sulfide was passed into 2M methanolic sodium methoxide (15 ml) at 0°. After saturation, further 2M sodium methoxide (15 ml) was added, followed by **1** (4.5 g). The reaction mixture was stirred on a steam bath for 4 h. The residue, obtained after evaporation, was partitioned between chloroform and water, and the organic layer was washed with water until neutral, dried, and evaporated. The residue was extracted with hot carbon tetrachloride (2 × 10 ml), and the insoluble material was recrystallized from benzene (30 ml) to yield compound **10** (1.5 g, 47%), m.p. 139–140°, $[\alpha]_D^{20}$ −10°, R_F 0.40 (solvent *B*) (Found: C, 30.32; H, 4.67; O, 34.85; S, 30.12. $C_8H_{14}O_3S_7$ calc.: C, 30.18; H, 4.43; O, 35.18; S, 30.21%). The yield was markedly less on repeating the reaction on a larger scale.

The carbon tetrachloride extracts of 10 experiments were combined, evaporated, and separated into components by column chromatography (solvent *D*). The fractions containing the components of R_F 0.75 and 0.55 were evaporated. The crude material (1.7 g) obtained from the former fractions was recrystallized from carbon tetrachloride–light petroleum to give 2,5-anhydro-3,4-epithio-1,6-thioanhydroallitol (**29**) (1.3 g), m.p. 96–98° (Found: C, 45.12; H, 5.20; S, 39.78. $C_6H_8OS_2$ calc.: C, 44.97; H, 5.03; S, 40.02%).

Evaporation of the fractions containing the slower-moving component gave 0.6 g of material which, on recrystallization from carbon tetrachloride–light petroleum, afforded 2,5-anhydro-4-bromo-4-deoxy-3-*O*-methylsulfonyl-1,6-thioanhydro-D-glucitol (**11**) (0.4 g), m.p. 125–126°, $[\alpha]_D^{20}$ −24.6° (Found: C, 27.82; H, 3.68; Br, 26.27; S, 21.34. $C_7H_{11}BrO_4S_2$ calc.: C, 27.73; H, 3.66; Br. 26.36; S, 21.15%).

(*b*) *From compound* **12**. A solution of crude **12** (50 g) in dry chloroform (1 litre) and methanol (100 ml) was treated with 4M methanolic sodium methoxide (27 ml). The resulting slurry was kept at room temperature for 30 min, then extracted with water (3 × 100 ml), dried, and evaporated. The residue was recrystallized from benzene to give compound **10** (17.5 g, 55%), identical with that obtained *via* route (*a*).

The combined, aqueous extracts were stirred with acetic anhydride (20 ml) overnight. The mixture was then extracted with chloroform, washed with 5% aqueous sodium hydrogen carbonate, and water, dried, and evaporated. The resulting, syrupy di-*S*-acetyl compound **8** (9.4 g, 21.5%) was deacylated with sodium methoxide, as described for compound **2** (route *a*), to yield the 1,6-dithiol **3** (6.5 g, 18.3%).

2,5-Anhydro-4-bromo-4-deoxy-3-O-methylsulfonyl-1,6-thioanhydro-D-glucitol (**11**). — A solution of compound **10** (0.32 g) and sodium bromide (0.3 g) in *N,N*-dimethylformamide (5 ml) was boiled for 1 h and then evaporated. The residue was treated with water, and the insoluble material (0.3 g, 99%) was recrystallized from carbon tetrachloride–light petroleum to yield **11** (0.2 g, 66%), identical with that obtained as a by-product from compound **1** *via* route (*a*).

2,5-Anhydro-1(6)-S-benzoyl-6(1)-bromo-6(1)-deoxy-3,4-di-O-methylsulfonyl-1(6)-thio-D-glucitol (**12**). — A solution of compound **1** (44.6 g) and potassium thiolbenzoate (21 g) in dry acetone (2 l) was heated on a steam bath for 3 h. The yellow solution became a white slurry, and was worked up as described for compound **2** to yield a syrup (50 g). Purification of the syrup (5 g) by column chromatography (solvent *C*) gave **12** (4.2 g, 83.8%) as a colorless syrup, R_F 0.50 (solvent *C*), $[\alpha]_D^{20}$ +27.4° (Found: C, 36.08; H, 3.96; Br, 16.14; S, 18.97. $C_{15}H_{19}BrO_8S_3$ calc.: C, 35.79; H, 3.80; Br, 15.87; S, 19.13%).

2,5-Anhydro-4-azido-4-deoxy-3-O-methylsulfonyl-1,6-thioanhydro-D-glucitol (**13**) *and 2,5-anhydro-6-azido-6-deoxy-3-O-methylsulfonyl-1,4-thioanhydro-D-galactitol* (**26**). — A solution of compound **10** (15.9 g) and sodium azide (6.9 g) in *N,N*-dimethylformamide (250 ml) and water (25 ml) was boiled for 30 min. The residue obtained by evaporation of the reaction mixture was partitioned between chloroform and water, and the organic layer was washed with water, dried, and evaporated. The solid residue was boiled with methanol (25 ml), cooled, filtered off, and washed with methanol to give azide **13** (11.1 g, 83.8%), m.p. 107–108° (unchanged after recrystallization from methanol), $[\alpha]_D^{20}$ +12.4°, R_F 0.65 (solvent *B*) (Found: C, 31.81; H, 4.20; N, 16.02; S, 23.92. $C_7H_{11}N_3O_4S_2$ calc.: C, 31.69; H, 4.18; N, 15.84; S, 24.17%).

Evaporation of the methanolic filtrate afforded a syrupy mixture of two components which were separated by column chromatography (solvent *B*). The fraction containing the faster-moving component (R_F 0.65) gave, on evaporation, a further crop of **13** (0.4 g, 3%), while the other fraction (R_F 0.55) yielded the 6-azide **26** (0.7 g, 5.3%) as a colorless syrup, $[\alpha]_D^{20}$ −22.4° (Found: C, 31.57; H, 4.33; N, 15.72; S, 23.88%).

4-O-Acetyl-2,5-anhydro-3-O-methylsulfonyl-1,6-thioanhydro-D-glucitol (**14**). — A stirred solution of compound **10** (3.2 g) and sodium acetate (3.2 g) in *N,N*-dimethylformamide (30 ml) was boiled for 30 min. The cooled slurry was diluted with chloroform, filtered, and washed with chloroform. The filtrate was evaporated and the residue was partitioned between chloroform and water. The organic layer was washed with water, dried, and evaporated. The solid residue was dissolved in hot chloroform (25 ml), filtered through charcoal, and diluted with methanol (25 ml) to give **14** (1.5 g, 53.2%), m.p. 190–192°, $[\alpha]_D^{20}$ +36.6°, R_F 0.55 (solvent *B*) (Found: C, 38.16; H, 4.97; S, 22.83. $C_9H_{14}O_6S_2$ calc.: C, 38.28; H, 4.96; S, 22.71%).

2,5-Anhydro-4-O-benzoyl-3-O-methylsulfonyl-1,6-thioanhydro-D-glucitol (**15**) *and 2,5-anhydro-6-O-benzoyl-3-O-methylsulfonyl-1,4-thioanhydro-D-galactitol* (**25**). — A solution of compound **10** (15.9 g) and sodium benzoate (14.4 g) in *N,N*-dimethylformamide (250 ml) was boiled with stirring for 30 min, and was worked up as described for compound **14**. The residue from the evaporated chloroform solution was boiled with methanol (20 ml), cooled, filtered off, and washed with methanol to yield **15** (12.5 g, 72.5%), m.p. 121–123° [unchanged after recrystallization from methanol (25 vol.)], $[\alpha]_D^{20}$ −67.4°, R_F 0.65 (solvent *B*) (Found: C, 49.03; H, 4.88; S, 18.50. $C_{14}H_{16}O_6S_2$ calc.: C, 48.82; N, 4.68; S, 18.62%).

The methanolic filtrate was evaporated and chromatographed on a column

(solvent *B*). The first fraction (R_F 0.65) contained a further crop of compound **15** (1 g, 5.8%), and the second (R_F 0.55) the corresponding 6-*O*-benzoyl derivative **25** (1.3 g, 7.5%). After recrystallization from carbon tetrachloride, **25** (1.1 g, 6.4%) had m.p. 117–118°, $[\alpha]_D^{20}$ −4.3°. (Found: C, 48.80; H, 4.71; S, 18.66%).

*2,5-Anhydro-3-*O*-methylsulfonyl-1,6-thioanhydro-*D*-glucitol* (**16**). — A solution of the acetate **14** (2.8 g) or benzoate **15** (3.4 g) in chloroform (35 ml) and methanol (5 ml) was treated with 4M methanolic sodium methoxide (0.5 ml) overnight at room temperature. The reaction mixture was neutralized with carbon dioxide and evaporated. The residue was dissolved in ethyl acetate, treated with ether until turbid, filtered through charcoal, and evaporated. Recrystallization of the residue from ethyl acetate–light petroleum afforded **16** (2.0 g, 83.2%), m.p. 98–100°, $[\alpha]_D^{20}$ +17.5°, R_F 0.1 (solvent *B*), 0.35 (solvent *A*) (Found: C, 35.13; H, 5.05; S, 26.46. $C_7H_{12}O_5S_2$ calc.: C, 34.99; H, 5.03; S, 26.69%).

Conventional mesylation of **16** gave the dimesyl derivative **10** (73%), identical with the product prepared from compound **1**.

*2,5-Anhydro-4-*O*-formyl-3-*O*-methylsulfonyl-1,6-thioanhydro-*D*-glucitol* (**18**). — (*a*) A solution of compound **10** (0.64 g) and potassium methanesulphonate (0.6 g) in *N,N*-dimethylformamide (10 ml) and water (1 ml) was boiled for 1 h and worked up as described for compound **14**. Recrystallization of the product (0.3 g, 56%) from methanol or ethyl acetate–light petroleum gave **18** (0.2 g, 37%), m.p. 127–129°, $[\alpha]_D^{20}$ −27.5° (*c* 0.5, chloroform), R_F 0.55 (solvent *B*) (Found: C, 35.60; H, 4.41; S, 23.76. $C_8H_{12}S_2O_6$ calc.: C, 35.81; H, 4.48; S, 23.90%).

(*b*) A solution of compound **10** (3.2 g) and potassium iodide (3 g) in *N,N*-dimethylformamide (50 ml) was boiled for 30 min. The cooled, dark-brown solution was stirred with zinc dust until it became colorless, and was then filtered and evaporated. The residue was treated with water, and the insoluble material (0.5 g) was recrystallized to yield **18** (0.3 g, 11.2%), identical with that described in (*a*).

*2,5-Anhydro-4-*S*-benzoyl-3-*O*-methylsulfonyl-1,6-thioanhydro-*D*-glucitol* (**20**) *and 2,5-anhydro-6-*S*-benzoyl-3-*O*-methylsulfonyl-1,4-thioanhydro-*D*-galactitol* (**6**). — A solution of compound **10** (0.32 g) and potassium thiobenzoate (0.2 g) in *N,N*-dimethylformamide (10 ml) was treated as described for compound **14**. The crude product was chromatographed (solvent *C*), and the fraction (0.18 g, 50%) having R_F 0.60 was recrystallized from methanol to give **20** (0.12 g, 33%), m.p. 119–120°, $[\alpha]_D^{20}$ −33.4° (Found: C, 46.71; H, 4.61; S, 26.65. $C_{14}H_{16}O_5S_3$ calc.: C, 46.64; H, 4.47; S, 26.69%).

The fraction containing the slower-moving component (R_F 0.35) gave, on evaporation and recrystallization of the residue from methanol, compound **6** (0.1 g, 27.8%) which was identical with the 6-*S*-benzoyl derivative obtained from **2** *via* route (*c*).

2,5-Anhydro-3,4-epithio-1,6-thioanhydroallitol (**29**). — A solution of **20** (0.7 g) in dry chloroform (10 ml) and dry methanol (2 ml) was treated with 4M methanolic sodium methoxide (1 ml) overnight at room temperature, and then neutralized with carbon dioxide and evaporated. A solution of the residue in chloroform was washed with water, dried, and chromatographed on a column (solvent *D*). Evaporation of the

fractions containing the component of R_F 0.75 gave the crude **29** (0.25 g, 77.5%) which, on recrystallization from methanol, had m.p. 96–98°, and was identical with **29** prepared from **10** *via* route (*a*).

2,5:3,4-Dianhydro-1,6-thioanhydroallitol (**30**). — A solution of compound **16** (4.8 g) in *tert*-butyl alcohol (200 ml) and M potassium *tert*-butoxide (22 ml) was boiled on a steam bath for 1 h. The cooled slurry was diluted with chloroform, neutralized with carbon dioxide, filtered, and evaporated. The residue was partitioned between chloroform and water, and the organic layer was washed with water, dried, and evaporated. Recrystallization of the residue from carbon tetrachloride–light petroleum afforded the epoxide **30** (2.4 g, 83.2%), m.p. 105–106° (unchanged after recrystallization from water), R_F 0.80 (solvent *A*), 0.60 (solvent *B*) (Found: C, 50.05; H, 5.60; S, 22.21. $C_6H_8O_2S$ calc.: C, 49.98; H, 5.59; S, 22.24%).

2,5-Anhydro-3,4-dideoxy-3,4-epimino-1,6-thioanhydroallitol (**31**). — A solution of the azide **13** (10.4 g) in tetrahydrofuran (100 ml) was added below 20° to a stirred and cooled slurry of lithium aluminium hydride (5 g) in tetrahydrofuran (100 ml). Stirring was continued for 1 h at room temperature, and the excess of hydride was destroyed by addition of a solution of potassium sodium tartrate (5 g) in water (10 ml). The salts were filtered off and washed with hot tetrahydrofuran (100 ml), and the filtrate was evaporated to yield crude **31** (5.3 g, 94.5%), m.p. 53–55°, R_F 0.50 (ethyl acetate–ethanol, 1:1), which could not be recrystallized.

The crude epimine **31** was dissolved in ethanol and treated with ethanol (20 ml) containing 10% hydrochloric acid. The resulting slurry was evaporated to a volume of 10 ml, filtered, and washed to give the hydrochloride (5.5 g, 82.5%), m.p. 169–171° (Found: C, 40.17; H, 5.86; Cl, 19.76; N, 7.73; S, 17.63. $C_6H_{10}ClNOS$ calc.: C, 40.11; H, 5.61; Cl, 19.73; N, 7.80; S, 17.85%).

Conventional mesylation of crude **31** (1.4 g) with methylsulfonyl chloride (1.1 ml) in pyridine (10 ml) gave, after recrystallization from chloroform–light petroleum, the *N*-mesyl derivative **33** (1.15 g, 51.6%), m.p. 193–194°, R_F 0.35 (solvent *B*) (Found: C, 38.08; H, 5.08; N, 6.41; S, 29.14. $C_7H_{11}NO_3S_2$ calc.: C, 37.99; H, 5.01; N, 6.33; S, 28.98%).

2,5-Anhydro-3,4-dideoxy-3,4-(p-*nitrobenzoylepimino*)*-1,6-thioanhydroallitol* (**34**). — A solution of crude **31** (4.7 g) in dry chloroform (100 ml) and triethylamine (5 ml) was treated below 10° with a solution of *p*-nitrobenzoyl chloride (6.4 g) in dry chloroform (50 ml). The reaction mixture was kept overnight at room temperature and the solid residue, obtained after evaporation, was washed with 5% aqueous sodium hydrogen carbonate, water, and methanol to yield crude **34** (7.1 g, 81%). Recrystallization from ethyl acetate–chloroform (1:1, 700 ml) gave, on evaporation to 300 ml, amide **34** (5.7 g, 65%), m.p. 204–205°, R_F 0.60 (solvent *B*) (Found: C, 53.56; H, 4.19; N, 9.78; S, 10.88. $C_{13}H_{12}N_2O_4S$ calc.: C, 53.41; H, 4.14; N, 9.58; S, 10.97%).

Oxazoline rearrangement. — A solution of **34** (0.7 g) in conc. sulfuric acid (10 ml) was kept overnight at room temperature and then poured on to ice. The solution was made alkaline with 50% aqueous potassium hydroxide, and the precipitate was filtered off and washed with water; yield, 0.7 g (100%). Recrystallization

from ethyl acetate–light petroleum afforded the racemate **35** (0.5 g, 71.5%) as yellow platelets, m.p. 192–193°, R_F 0.60 (solvent *B*) (Found C, 53.20; H, 4.35; N, 9.68; S, 11.0. $C_{13}H_{12}N_2O_4$ calc.: C, 53.41; H, 4.14; N, 9.58; S, 10.97%).

2,5-Anhydro-3,4-epithio-1,6-thioanhydroallitol disulfone (**32**). — The epithio derivative **29** (0.6 g) was dissolved in warm (30°) acetic acid (10 ml), and 33% aqueous hydrogen peroxide (2 ml) was added. The temperature of the reaction mixture rose to 50°. After 20 h at room temperature, it was evaporated and the residue was recrystallized from water (3 ml) to give **32** (0.4 g, 83.8%), m.p. 172–175°, R_F 0.35 (ethanol) (Found: C, 31.98; H, 3.63; S, 28.42. $C_6H_8O_5S_2$ calc.: C, 32.13; H, 3.60; S, 28.60%).

8-Oxa-3-thia-bicyclo[3.2.1]octa-6-ene (**36**). — To a solution of the hydrochloride (1.8 g) of **31** in water (10 ml), a solution of sodium nitrite (1.4 g) in water (10 ml) was added during 30 min. The reaction mixture was kept at room temperature for 2 days and was then extracted with chloroform without removal of the crystalline material formed. The organic solution was dried and evaporated, and the residue was extracted with hot, light petroleum (3 × 10 ml). Evaporation of the extract gave crude **36** (0.6 g, 46.8%), m.p. 53–54° after recrystallization from light petroleum, R_F 0.70 (solvent *B*) (Found: C, 56.28; H, 6.33; S, 24.82. C_6H_8OS calc.: C, 56.22; H, 6.29; S, 25.01%).

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