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Synthetically useful transformations of a branched-chain, deoxynitro-1-thio-D-glucitol, including a novel mode of 1-thioglycoside formation*†

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ABSTRACT

2-Deoxy-3,4;5,6-di-*O*-isopropylidene-2-*C*-(nitromethyl)-1-*S*-phenyl-1-thio-D-glucitol (**2**), obtainable from D-mannose in several steps with good overall yield, was converted into the corresponding sulfoxide, α-chlorosulfide, α-acetoxysulfide, and analogous 2-*C*-(acetamido)methyl derivatives. Mild hydrolysis of the 1-chloro derivative of **2** gave a 2-deoxy-2-*C*-methylene-*aldehydo* sugar 3,4;5,6-diacetal by concomitant elimination of nitrous acid, whereas a 2-deoxy-2-*C*-(nitromethyl)-D-glucitol 3,4;5,6-diacetal was obtained under reducing conditions. Pummerer rearrangement of the sulfoxide derived from **2** gave, depending on the reaction conditions, the corresponding α-acetoxysulfide or phenyl 2-deoxy-2-*C*-(nitromethyl)-1-thio-β-D-glucopyranoside 3,4,6-triacetate.

INTRODUCTION

In a preceding paper[1] it was suggested that the readily accessible carbohydrate nitrocyclopropane derivative[2] **1** constitutes, by virtue of its stereochemically defined center of chain branching (C-2), a potentially useful starting point for the synthesis of chiral isoalkyl structures. Thus, nucleophilic ring opening with sodium thiophenoxide gave the branched phenyl thioether **2** and the thiohydroximic ester **3**, both of which were converted, by reductive desulfurization with Raney nickel and subsequent *N*-acetylation, into 1-acetamido-1,2-dideoxy-3,4;5,6-di-*O*-isopropylidene-2-*C*-methyl-D-mannitol (**4**). Deblocking and oxidative degradation of the polyol chain in **4** furnished the biochemically important thymine catabolite, (*R*)-3-amino-2-methylpropanoic acid (**5**). The present article records further chemical transformations of the branched nitrothioalditol **2**, designed to provide enantiospecific access to (*S*)-2-(aminomethyl)-3-hydroxypropanoic acid (**6**), a skeletal isomer (as yet unknown) of the familiar amino acid L-threonine, and it discloses a novel mode of 1-thioglycoside formation.

* Dedicated to Professor Leslie Hough in the year of his 65th birthday.
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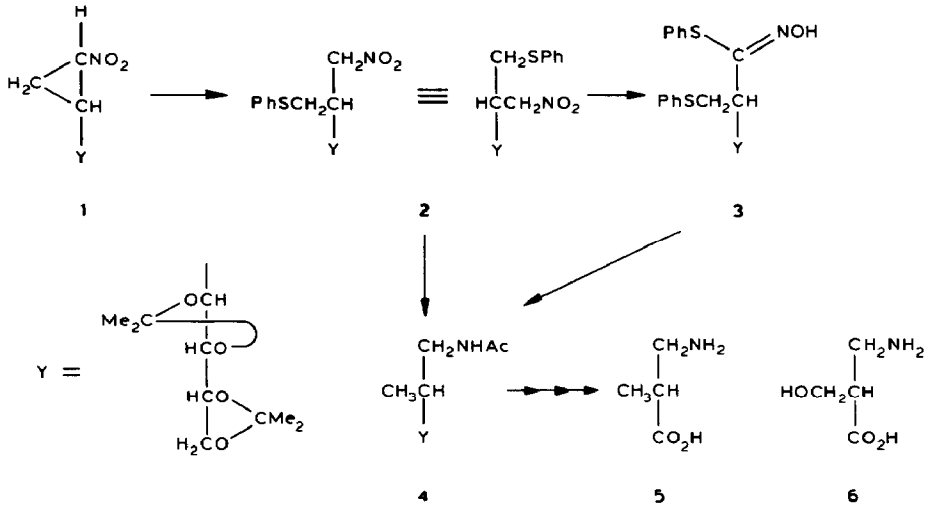

RESULTS AND DISCUSSION

The key compound **2**, now designated as 2-deoxy-3,4;5,6-di-*O*-isopropylidene-2-*C*-(nitromethyl)-1-*S*-phenyl-1-thio-D-glucitol*, had been found[1] to arise in the course of several h during the action of sodium thiophenoxide upon the nitrocyclopropane **1** in refluxing oxolane, and to be slowly converted into the thiohydroximate **3** as the reaction progressed. Interruption of the process after an optimal length of time had permitted the isolation of 30–40% of **2**, together with 10–24% of **3** and 20–40% of unreacted **1**; continuation of the process until **1** was completely consumed (24 h) gave **3** as the major product. At the outset of the present work it was therefore desirable to improve the preparation of **2**. This was accomplished by performance of the aforementioned ring opening in **1** in *N,N*-dimethylformamide solution during 2.5 h at 60–70°, which produced **2** in 93% yield, without evident transformation into **3**. Moreover, the compound, previously described as an (analytically pure) syrup, has now been obtained crystalline.

For enantiospecific approaches to such chiral isoalkyl structures as **6**, various ways to convert the (phenylthio)methyl group of **2** into a hydroxymethyl group were considered. It appeared that this might be achievable via an intermediate aldehyde or equivalent functionality, to be engendered perhaps by Pummerer reaction, or through an α-chlorosulfide according to Bakuzis[3], provided the nitro group present should prove compatible with such operations. Alternatively, similar manipulations might be tried after reduction of the nitro group to the amine stage, which had to be performed at any

* Compound **2** was originally[1] designated as 1,2-dideoxy-3,4;5,6-di-*O*-isopropylidene-1-nitro-2-*C*-(phenylthio)methyl-D-mannitol, which expressed more clearly its generic relationship to the D-*manno* compounds **1**, **3** and **4**. However, application of the sequence rule to the CH_2SPh and CH_2NO_2 groups attached to C-2 requires that the former be regarded as the C-1 terminal of the hexitol, which should therefore be named as a 1-thio-D-glucitol.

rate at some point on the route to **6**. Prior to discussing reactions involving the (phenylthio)methyl group we therefore record the reduction of **2**.

Treatment of **2** with lithium aluminium hydride in oxolane gave the amine **7** in 75% yield. Acetylation of **7** with acetic anhydride and pyridine at room temperature quantitatively furnished the *N*-acetyl derivative **8**, which was converted by boiling acetic anhydride (without any addition) into the *N,N*-diacetyl derivative **9** (87%).

Both the nitro sulfide **2** and the acetamido sulfide **8** were oxidized by 3-chloroperoxybenzoic acid to the corresponding sulfoxides **10** and **11**, obtained in high yields as mixtures of *S*-epimers. Whereas **11** could be partially resolved by chromatography to give a crystalline ($[\alpha]_D$ −58°) and a syrupy ($[\alpha]_D$ +88°) epimer, the components of **10** revealed by n.m.r. spectroscopy could not be separated. A similar mixture of epimeric sulfoxides **10** was formed when **2** was treated with 2 equiv. of *N*-bromoacetamide in acetone solution (10 min at −15°). On the other hand, treatment (6 h at +25°) of **2** with *N*-chlorosuccinimide in carbon tetrachloride[4] led to the α-chlorosulfide **12**, shown by its ^{1}H-n.m.r. spectrum to be a 3:2 mixture of 1-epimers. (Chromatographic evidence was obtained that **12** also arises by treatment[5] of the sulfoxide **10** with thionyl chloride). The highly unstable **12** could not be freed chromatographically from accompanying succini-

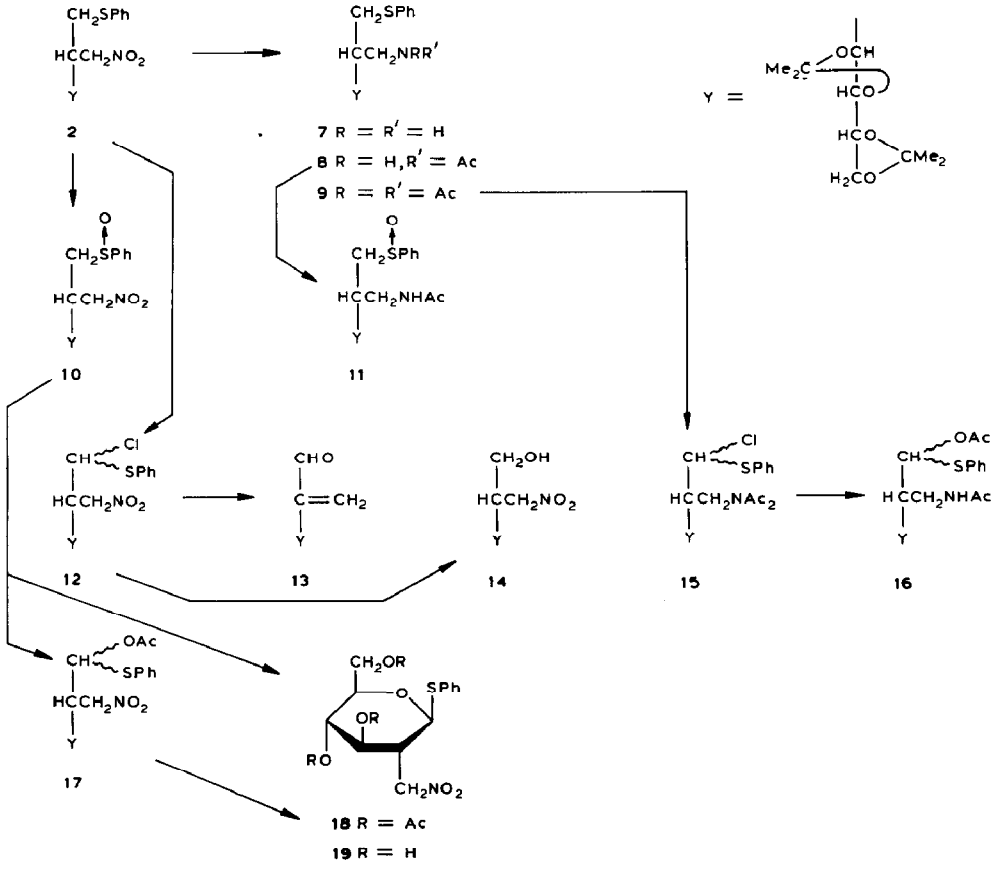

TABLE I

^{1}H-N.m.r. data at 300 MHz for compounds 7–19 in chloroform-*d* solution

Compound[a]	*Chemical shifts*[b] *(δ)*										
	H-1	*H-1'*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*	*H-7*[c]	*H-7'*	*Others*[d]
7[e]	——3.10[f] ——		1.90m	4.19dd	3.76dd	4.00dt	4.11dd	3.90dd	——2.92d(2 H)——		
8	3.10dd	2.98	2.13m	4.24dd	3.71t	3.98dt	4.11dd	3.89dd	3.74m	3.30dt	6.09br(NH), 1.92s (Ac)
9	3.02dd	2.93dd	2.26m	4.29dd	3.77dd	4.00dt	4.12dd	3.85dd	3.99dd	3.77dd	2.34s(6 H, NAc_2)
10[g]	——3.23–2.88m(3 H)——		[h]	4.26dd	3.64dd	4.00dt	[h]	[i]	——4.81d(2 H)——		
				3.59dd	[i]	[h]	[i]	4.66dd	4.52dd		
11[j]	——2.94[f] ——2.45m			[k]	3.59dd	4.07dt	[k]	[k]	[k]	3.33ddd	6.53br(NH), 1.99s(Ac)
11[l]	3.03dd	2.86dd	2.55m	4.13dd	3.74dd	4.00dt	4.14dd	3.91dd	3.61ddd	3.23ddd	6.80br(NH), 1.97s(Ac)
12[m]	5.71d		3.50m	4.35dd	3.71dd	——4.14–3.88m(3 H)——			——4.83–4.69m(2 H)——		
	5.67d		3.41m	4.31dd	3.64dd						
13	9.59s			4.66dd	3.96dd	4.18dt	4.11dd	3.85dd	6.58d	6.21s	
14	3.86ddd[n]	3.71sp[n]	2.63cm	4.20dd	3.81dd	4.01dt	4.08 ~ t	3.95dd	——4.65m(2 H)——		2.57dd(OH)
15[o]	5.49d		2.95m	——4.4–3.7m(7 H)——							2.42s(3.4 H, NAc_2)
	5.75d										2.46s(2.6 H, NAc_2)
16[o]	6.28d			4.51dd	3.68t					3.11dt	2.05s,186s(2 Ac)
			2.40cm			4.11m	——4.0–3.85m(3 H)——				
	6.32d			4.20dd	3.81t					3.33dt	2.07s,192s(2 Ac)
17[o]	6.27d		3.27m	4.43dd	3.56 ~ t		4.11dd		——4.50m(2 H)——		2.02s(Ac)
	6.44dd		3.33 ~ o	4.21dd	3.76dd	[p]	4.14dd	[p]	——4.68[f](2 H)——		2.00s(Ac)
18	4.80d		2.58tdd	5.25dd	4.94dd	3.72ddd	4.25dd	4.16dd	4.67dd	4.59dd	2.08, 2.00, 1.98 (Ac)
19[q]	4.93d		2.47tt	3.58dd	3.43dt	——3.86,375–3.66,3.38)[r]——			——4.83d(2 H)——		4.64d(OH-3),4.44d(OH-4)

TABLE I continued

	Coupling constants (Hz)												
	$J_{1,2}$	$J_{1',2}$	$J_{1,1'}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	$J_{2,7}$	$J_{2,7'}$	$J_{7,7'}$	*Others*
7	6.3	7.5	13	4.6	7.0	8.1	6.0	5.5	8.2	4.9	4.9		
8	7.3	6.7	13.6	3.5	7.7	~8	5.9	5.3	8.3		4.2	14.7	4.2 ($J_{NH,7'}$)
9	7.7	5.3	13.5	3.9	7.4	~8	6.1	6.1	8.3	9.0	4.8	14.9	
10				5	7	8.7	6.1	6.1		4.8	4.8		
					6.5	8.6				6.0	5.3	13.8	
11[j]	4.3	7.4	13.9		6.3	~8	3.3	~8			4.5	14.3	7 ($J_{NH,7'}$)
11[l]	5.3	6.6	13.9	4.4	~7	8.5	6.1	5.5	8.5	4.2	4.7	14.1	6.4 ($J_{NH,7}$), 8($J_{NH,7'}$)
12	4.3			5.4	7.4	8.5							
	3.5			6	7.5	8.5							
13					8.1		6.3	6.2	8.2				0.8 ($J_{3,7}$)
14	3.7	3.8	12.4	5.6	8.2	8.8	~6	5.2	~8				5.4 ($J_{1,OH}$), 8.5 ($J_{1',OH}$)
15	2.5												
	2.0												
16	9.7			4.3	8.0	8					~2.5	14.5	4 ($J_{NH,7'}$)
	6.6			1.7	8.4	8.4					4.5	14.5	4.5 ($J_{NH,7'}$)
17	7.8			2.2	7.8	8.4	5.9		8.4	5	~5		
	4.9			5.8	6.9	8.4	5.9		8.3	5.8	5.8		
18	10.7			10.8	9.1	10.1	5.1	2.4	12.3	3.6	5.2	14.1	
19	10.8			10.6	8.2	9.5				4.8	4.8		5.4 ($J_{3,OH}$),4.6 ($J_{4,OH}$)

[a] For mixtures of epimers, the upper line refers to the major, and the lower line, to the minor component. Values that could not be specifically attributed to either epimer are centered between the two lines. [b] With reference to the $CHCl_3$ signal at 7.24 p.p.m. [c] H-7 and H-7′ refer to the $-CH_2N$ moiety at C-2. [d] All isopropylidene acetals showed four 3-proton singlets in the range δ 1.35 ± 0.01. Phenyl proton multiplets occurred at δ 7.35–7.10 in **7–9**, 7.50–7.30 in **12** and **15–19**, and 7.66–7.50 in **10** and **11**. [e] After D_2O exchange. [f] Center of two AB-quartets. [g] Mixture (~1:1) of *S*-epimers. [h] Part of unresolved multiplets (1.5 H) at δ 4.16–4.08. [i] Part of unresolved multiplets at δ 3.95–3.83. [j] Crystalline epimer. [k] Part of unresolved multiplets (4 H) at δ 3.88–3.77. [l] Syrupy epimer. [m] Mixture (~2:1) of 1-epimers. [n] Collapsing to dd upon D_2O exchange; sp denotes apparent septet. [o] Mixture (~4:3) of 1-epimers. [p] Part of multiplet (2 H) at δ 4.03–3.90. [q] In acetone-d_6, with reference to the acetone signal at 2.04 p.p.m. [r] Multiplets (1 H, 2 H, and 1 H, respectively) containing the OH-6 signal at δ ~3.7.

mide as it decomposed on the silica gel column. When the crude product was dissolved at room temperature in aqueous acetone, it underwent hydrolysis at C-1 and β-elimination of nitrous acid, to give the α,β-unsaturated aldehyde **13**, isolated in 33% yield* after chromatography and well characterized by spectroscopic data. (Its structure was corroborated by the ^{1}H-n.m.r. spectrum of the allylic acetate obtained from it by borohydride reduction and acetylation.) However, when crude **12** was treated with aqueous acetonitrile in the presence of sodium cyanoborohydride, part of it was reconverted into **2** (55% recovery) by hydride displacement of the chlorine atom, and part incurred hydrolysis at C-1 whereby the aldehyde engendered was reduced *in situ* to the primary alcohol **14**, isolated in 26% yield based on the starting **2** (or 58%, taking into account the **2** recovered).

Reaction of the *N,N*-diacetyl derivative **9** with *N*-chlorosuccinimide gave an unstable α-chlorosulfide (**15**) as a 3:4 mixture of 1-epimers, characterized by ^{1}H-n.m.r. and mass-spectral data, which on treatment with aqueous acetone underwent hydrolysis involving displacement of the chlorine atom and acetyl migration, to furnish the α-acetoxysulfide **16** as an inseparable mixture of 1-epimers in 46% yield. On the assumption that **16** might also be obtainable by Pummerer rearrangement of the acetamido sulfoxide **11**, an experiment using the conditions proposed by Tanikaga *et al.*[7] (see later) was performed but yielded a complex mixture of products that were not identified.

More rewarding was the study of Pummerer reactions of the nitro sulfoxide **10**. Treatment[7] of **10**, at room temperature, with a mixture of acetic anhydride and trifluoroacetic anhydride, followed by 2,6-dimethylpyridine, gave a 47% yield of the α-acetoxysulfides **17** as a mixture of 1-epimers. An interesting observation was made when the rearrangement was performed under different conditions, namely, with acetic anhydride, acetic acid, and a catalytic amount of *p*-toluenesulfonic acid in refluxing dichloromethane: from the mixture of products formed, a 36% yield of phenyl 2-deoxy-2-*C*-(nitromethyl)-1-thio-β-D-glucopyranoside 3,4,6-triacetate (**18**) was isolated by chromatography, together with a similar proportion of unidentified material which possibly contained the α-anomer or furanosidic isomers. Zemplén deacetylation of **18** gave the unprotected thioglycoside **19**, and the same product resulted from acid-catalyzed deisopropylidenation of **17** with trifluoroacetic acid in toluene. Evidently, the composition of the reagent and the reaction conditions employed in the transformation **10**→**18** allowed for solvolytic deprotection of the polyol chain, ring closure by OH-5, and acetylation of the remaining hydroxyl groups to occur concomitantly with the Pummerer rearrangement.

The ^{1}H- and ^{13}C-n.m.r. data of new compounds (see Tables I and II) are in accord with the assigned structures.

* Addition of cupric chloride and cupric oxide to the hydrolytic medium (to oxidize the liberated thiophenol[6]) might have improved the yield[3]. The matter was not pursued since **13**, having lost the crucial chirality at C-2, was of no immediate interest for the present project. However, as an acrolein bearing a chiral substituent it may conceivably be valuable for other synthetic designs.

TABLE II

^{13}C-N.m.r. data at 75.43 MHz in chloroform-*d* solution

Compound	*Chemical shifts*[a] *(p.p.m.)*							
	C-1	*C-2*	*C-3, C-4, C-5*	*C-6*	*C-7*	O_2CMe_2	CMe_2	$COCH_3$
7	33.7	42.5	81.3, 79.4, 77.3	67.8	41.0	109.6, 109.1	27.4, 27.1, 26.6, 25.4	
8	34.9	38.7	81,4, 78.8, 77.2	67.9	39.3	109.7, 109.2	27.3, 26.9, 26.6, 25.3	169.8; 23.5
9	34.6	39.1	80.5, 78.9, 77.2	67.9	45.0	109.7, 109.3	27.1, 26.9, 26.6, 26.4	173.3; 25.3
10[b]	56.3	36.1	80.31, 80.1, 76.9	68.1	74.8	110.0, 109.95	27.1–25.1 (8 peaks)	
	55.5	35.7	80.27, 79.5, 76.8	67.9	74.3			
11[c]	57.9	36.1	82.0, 79.7, 76.9	67.9	39.1	109.8, 109.6	27.3, 27.2, 26.5, 26.2	170.4; 23.4
11[d]	58.8	36.8	81.9, 79.1, 77.0	67.9	40.0	109.9, 109.4	27.3, 27.1, 26.6, 25.3	170.2; 23.4
14	60.8	43.6	79.7, 79.4, 77.5	68.2	73.9	110.2, 109.9	27.0, 26.9, 26.2, 25.2	
16[b]	80.1	41.6	79.4 79.1, 78.3	67.75	35.8	109.7, 109.2	27.2–25.3 (8 peaks)	169.7–169.3; 23.3, 21.1
	80.4	43.5	79.5,	67.8	37.2	109.9, 109.2		
17[b]		43.0	81.0–76.9 (8 peaks)[e]	67.8	73.1	110.1–109.9	27.5–25.2 (8 peaks)	169.0; 20.9
		44.8		67.9	72.6			
18		43.5	(75.6, 73.5, 72.4, 68.9)[e]	62.0	84.4			170.7, 170.3, 169.8; 20.5, 20,4, 20.2
19[f]		46.6	(86.1, 81.5, 75.0, 72.4)[e]	62.7	75.0			

[a] All compounds except **14** gave signals for Ph in the expected region. The quaternary carbon atom (C-1) resonated at ~136–134 p.p.m. in **7–9**, **18**, and **19**, but at ~143 p.p.m. in **10** and **11**, and the *o*, *m*, and *p* carbon atoms, at ~132–124 p.p.m. In **16** and **17**, the C-1 signal was at ~131 p.p.m., intermediate between those of the other Ph signals at ~134 and ~128 p.p.m. [b] Mixture of two epimers; some values in the upper and lower lines may have to be interchanged. [c] Crystalline epimer. [d] Syrupy epimer. [e] Includes C-1. [f] In acetone-d_6.

In summary, this investigation has provided several branched-chain carbohydrate derivatives potentially useful as precursors for the enantiospecific synthesis of **6** and similar, chiral molecules having an isoalkyl skeleton. Furthermore, a novel mode of 1-thioglycoside formation has been discovered. It has been demonstrated that 1-*S*-phenyl-1-thioalditols can be converted into reactive α-chlorosulfides and aldose monothiohemiacetal acetates. A separate paper[8] deals with applications of these types of reaction to the synthesis of L-gulose and L-galactose, and their acetylated *aldehydo* forms, from D-glucose and D-galactose, respectively.

EXPERIMENTAL

General methods. — Column chromatography was performed on silica gel Merck 7734 (100–200 mesh) or equivalent material. Unless otherwise stated, the following solvent combinations (v/v) were used for column and thin-layer chromatography: (*A*) 3:7 acetone–hexane; (*B*) 1:2, (*C*) 1:1, (*D*) 2:1, and (*E*) 5:1 ether–hexane; (*F*) 1:10 MeOH–ether, and (*G*) 1:4 EtOAc–hexane. Optical rotations were determined at ~25° with a Perkin–Elmer 241 polarimeter, with solutions in chloroform unless otherwise specified. I.r. data (υ_{max}) were recorded from Nujol mulls for solids and from thin films for syrups; only bands of particular constitutional significance are listed. Mass-spectral data (*m/z*) were obtained by the chemical-ionization mode, using ether as the ionizing gas.

*Improved preparation of 2-deoxy-3,4;5,6-di-*O*-isopropylidene-2-*C*-nitromethyl-1-*S*-phenyl-1-thio-*D*-glucitol** (**2**). — To a mixture of NaOMe (2.8 g) and *N,N*-dimethylformamide (DMF; 5 mL) was added at 0° a chilled solution of thiophenol (6 mL) in DMF (20 mL), followed after 5 min by a solution of nitrocyclopropane[2] **1** (5.18 g) in DMF (25 mL). The mixture was stirred for 2.5 h at 60–70°, after which time a single spot (**2**, R_F 0.7) was revealed by t.l.c. (solvent *A*). The mixture was diluted with toluene (200 mL), washed with water (6 x 100 mL), dried ($MgSO_4$), concentrated, and chromatographed on SiO_2 (110 g) with hexane (300 mL) followed by 1:19 acetone–hexane as eluants. The syrupy **2** obtained (6.70 g, 93.5%) was identical ($[\alpha]_D$, i.r., ^{1}H-n.m.r.) with **2** previously described[1], and crystallized on seeding, and trituration with a little EtOH. (Seed crystals were obtained from a previous sample that had solidified during storage at 0° for 4 months.) Recrystallized from EtOH, **2** had m.p. 94–96° and its ^{1}H-n.m.r. spectrum was unchanged.

*2-*C*-Aminomethyl-2-deoxy-3,4;5,6-di-*O*-isopropylidene-1-*S*-phenyl-1-thio-*D*-glucitol* (**7**). — A solution of **2** (1.20 g) and $LiAlH_4$ (0.75 g) in oxolane (50 mL) was stirred and boiled under reflux for 3.5 h. After cooling, water (25 mL) and 20% aq. Na_2CO_3 (20 mL) were cautiously added, the precipitate was removed and washed well with EtOAc (4 x 50 mL), and the filtrate was evaporated to give a crude product that was chromatographed on a column by use of solvent *C* (250 mL) followed by solvent *F*. The ninhydrin-positive

* Previously designated[1] as 1,2-dideoxy-3,4;5,6-di-*O*-isopropylidene-1-nitro-2-*C*-(phenylthio)methyl-D-mannitol.

fractions gave syrupy **7** (0.83 g, 75%), $[\alpha]_D$ +3.5° and $[\alpha]_{436}$ +5.2° (*c* 2); υ_{max} 3500–3200 (broad), 1585 (sharp) cm^{-1}; *m/z* 368 (100%, $M^+ + 1$).

Anal. Calc. for $C_{19}H_{29}NO_4S$ (367.5): C, 62.09; H, 7.95; N, 3.81; S, 8.72. Found: C, 61.92; H, 7.87; N, 3.60; S, 8.81.

2-C-Acetamidomethyl-2-deoxy-3,4;5,6-di-O-isopropylidene-1-S-phenyl-1-thio-D-glucitol (**8**). — The amine **7** (320 mg) was treated with acetic anhydride (3 mL) and pyridine (0.5 mL) for 3 h at room temperature. The reagents were removed by coevaporation with MeOH (2 x 25 mL) followed by PhMe (2 x 25 mL), and the residue was chromatographed (20 g of SiO_2, solvent *E*) to give syrupy **8** (350 mg, 98%), $[\alpha]_D$ +19° and $[\alpha]_{436}$ +34° (*c* 2); υ_{max} 3300, 1650, and 1550 cm^{-1}; *m/z* 410 (100%, $M^+ + 1$), 352 (44%, $M^+ + 1 - NHAc$ or Me_2CO).

Anal. Calc. for $C_{21}H_{31}NO_5S$ (409.6): C, 61.59; H, 7.63; N, 3.42; S, 7.83. Found: C, 61.52; H, 7.67; N, 3.57; S, 7.66.

2-C-(N,N-Diacetylamino)methyl-2-deoxy-3,4;5,6-di-O-isopropylidene-1-S-phenyl-1-thio-D-glucitol (**9**). — The acetamide **8** (470 mg) was boiled in Ac_2O (5 mL) for 26 h. The solution was evaporated with several additions of PhMe. Column chromatography (solvent *B*) of the residue furnished crystalline **9** (450 mg, 87%), m.p. 81–82°, $[\alpha]_D$ +38.2° (*c* 2); υ_{max} 1710 and 1680 cm^{-1} (CO–N–CO), with no bands in the 3500–3000 cm^{-1} region; *m/z* 452 (77%, $M^+ + 1$), 394 (100%, $M^+ + 1 - Me_2CO$), and 352 (72%, $M^+ + 1 - NAc_2$).

Anal. Calc. for $C_{23}H_{33}NO_6S$ (451.6): C, 61.17; H, 7.36; N, 3.10; S, 7.10. Found: C, 61.17; H, 7.32; N, 3.06; S, 7.02.

1, 2-Dideoxy-3,4;5,6-di-O-isopropylidene-2-C-nitromethyl-1-C-phenylsulfinyl-D-glucitol (**10**). — *Procedure A.* To a chilled (−10°) solution of **2** (510 mg) in CH_2Cl_2 (25 mL) was added 3-chloroperoxybenzoic acid (260 mg) in CH_2Cl_2 (25 mL), dropwise during 15 min. After a further 15 min at −10°, the mixture was diluted with chilled CH_2Cl_2 (25 mL), washed with ice-cold aq. $NaHCO_3$ (100 mL), dried ($MgSO_4$), concentrated, and passed through a column of SiO_2 with solvent *C*, to give colorless, syrupy **10** (520 mg, 98%) that showed a single spot in t.l.c. (various developing systems) but was revealed by its ^1H-n.m.r. spectrum to be a mixture of *S*-epimers, $[\alpha]_D$ −4° and $[\alpha]_{436}$ −16° (*c* 2); υ_{max} 1550 (NO_2) and 1040 (S→O) cm^{-1}; *m/z* 414 (100%, $M^+ + 1$), 398 (6%, $M^+ + 1 - O$), and 356 (26%, $M^+ + 1 - Me_2CO$).

Anal. Calc. for $C_{19}H_{27}NO_7S$ (413.5): C, 55.19; H, 6.58; H, 3.38; S, 7.75. Found: C, 55.30; H, 6.60; N, 3.31; S, 7.81.

Procedure B. Compound **2** (100 mg) in acetone (5 mL) was treated with *N*-bromoacetamide (70 mg, 2 equiv.) at −15°. After 10 min, t.l.c. (solvent *A*) showed a major product (R_F 0.4, u.v.-visible) together with two faster-moving, minor products. (The pattern was the same after 30 min, and after 1 h at 0°.) Aqueous $Na_2S_2O_3$ was added dropwise to the yellow solution until it turned colorless; it was then carefully neutralized with aq. $NaHCO_3$, and concentrated until most of the acetone was removed. The remaining, aqueous solution was extracted three times with $CHCl_3$, and the extract was washed once with water, dried ($MgSO_4$), and evaporated to give a colorless, partially crystallizing syrup. Chromatography of the material on a small column (2 g of SiO_2;

solvent *G*) gave fractions of the two unidentified, fast-moving by-products (3 and 10 mg) followed by **10** (80 mg, 77%), identical (i.r., ^{1}H-n.m.r.) with the product from procedure *A*.

2-C-Acetamidomethyl-1,2-dideoxy-3,4;5,6-di-O-isopropylidene-1-C-phenylsulfinyl-D-glucitol (**11**). — To a solution of **8** (530 mg) in CH_2Cl_2 (20 mL), stirred at −15°, was added 3-chloroperoxybenzoic acid (260 mg) in CH_2Cl_2 (20 mL), dropwise during 15 min. The mixture was kept for a further 30 min at −15° and then processed as described for **10** (procedure *A*), with EtOAc being used as the eluant in chromatographic purification. There was obtained **11** (520 mg, 94%) as a partially crystalline mixture of *S*-epimers, R_F 0.4 and 0.3 (t.l.c., double irrigation with EtOAc). A 100-mg sample was partially separated by column chromatography with ether as the eluant, furnishing pure epimer I (R_F 0.4; 34 mg) and epimer II (R_F 0.3; 26 mg), and a mixed fraction (30 mg).

Epimer I was crystalline, m.p. 181–182°, $[\alpha]_D$ −58°(*c* 2); ν_{max} 3280 (NH), 1660, 1550 (amide I and II), 1030 (S→O) cm^{-1}.

Anal. Calc. for $C_{21}H_{31}NO_6S$ (425.6): C, 59.27; H, 7.34; N, 3.29. Found: C, 59.30; H, 7.36; N, 3.16.

Epimer II was a syrup, $[\alpha]_D$ +88° (*c* 2); ν_{max} 3280 (broad), 1650, 1540, and 1035 cm^{-1}.

Formation of 1-chloro-2-deoxy-3,4;5,6-di-O-isopropylidene-2-C-nitromethyl-1-S-phenyl-1-thio-D-glucitol (**12**), *and its hydrolysis and reduction. — A. Acrolein* **13** *from* **2** via **12**. A mixture of **2** (200 mg), *N*-chlorosuccinimide (NCS; 75 mg) and CCl_4 (3 mL) was stirred for 6 h at room temperature. Although no significant change was observable in t.l.c. (various solvents), the ^{1}H-n.m.r. spectrum of the filtered mixture indicated a replacement of the H-1,1′ signals for **2** by two doublets (intensity, ~0.5 H each) near δ 5.7, assignable to H-1 of **12** (two 1-epimers). Since initial attempts to isolate **12** chromatographically and free it from residual NCS and (or) succinimide had been unsuccessful owing to its instability, the filtered solution was concentrated without delay at low temperature, and the residue was immediately dissolved in 50% aqueous acetone (10 mL). After storage of the solution for 16 h at 25°, the solvent was partially evaporated and replaced by water. Extraction with EtOAc (2 x 25 mL), and drying ($MgSO_4$) and concentration of the extract, gave a material which was chromatographed on a small column with solvent *B*, to furnish 35 mg (33%) of syrupy *2-deoxy-3,4;5,6-di-O-isopropylidene-2-C-methylene*-aldehydo-D-arabino-*hexose* (**13**), R_F 0.15 (t.l.c., solvent *A*); ν_{max} 1700 and 1630 cm^{-1} (CO and C=C, conjugated); *m/z* 257 (100%, $M^+ + 1$), 241 (44%), 199 (100%, $M^+ + 1 - Me_2CO$), 141 (98%, $M^+ + 1 - 2\,Me_2CO$). A sample was reduced with $NaBH_4$ in EtOH, and then acetylated with Ac_2O and pyridine. The ^{1}H-n.m.r. spectrum of the product in $CDCl_3$ accorded with the structure of the corresponding 2-deoxy-2-*C*-methylenehexitol 1-acetate: δ 5.40 and 5.28 (2 very narrow d or t, 1 H each, methylene protons), 4.67 (AB-q, 2 H, H-1,1′), 4.45 (d, $J_{3,4}$ 7.8 Hz, H-3), 4.1–3.8 (m, 4 H, H-4,5,6,6′), 2.07 (s, 3 H, OAc), 1.40, 1.385, 1.365, and 1.32 (4 s, 3 H each, 2 Me_2C).

B. Formation of 2-deoxy-3,4;5,6-di-O-isopropylidene-2-C-nitromethyl-D-glucitol (**14**) *from* **2** via **12**. A solution of **2** (1.0 g) in dry CCl_4 (10 mL) was stirred under N_2 with

molecular sieve 4Å for 30 min at room temperature, NCS (0.36 g) was then added, and stirring was continued for 5 h. The suspended solids were filtered off and washed with CCl_4, and the filtrate (whose ^{1}H-n.m.r. spectrum indicated conversion of **2** into **12**) was evaporated. A solution of the syrupy residue in MeCN (15 mL) and water (15 mL) was treated with $NaBH_3CN$ (420 mg) for 6 h at 60–65°, cooled, diluted with water (15 mL), and extracted with EtOAc (2 x 50 mL). Column chromatography (solvent *C*) of the dried (Na_2SO_4) and concentrated extract furnished regenerated **2** (R_F 0.7, visible under u.v.; 0.55 g, 55%), the alcohol **14** (R_F 0.5, invisible under u.v.; 0.20 g, 26%), and an unidentified by-product (R_F 0.4, visible under u.v., 45 mg).

Compound **14** showed $[\alpha]_D$ +12° (*c* 2), ν_{max} 3480 (broad, OH) and 1550 (NO_2) cm^{-1}; *m/z* 306 (43%, $M^+ + 1$), 290 (38%), 248 (100%, $M^+ + 1 - Me_2CO$), 230 (80%, $M^+ + 1 - H_2O - Me_2CO$), 190 (24%, $M^+ + 1 - 2\,Me_2CO$), and 172 (20%, $M^+ + 1 - H_2O - 2\,Me_2CO$).

Anal. Calc. for $C_{13}H_{23}NO_7$ (305.3): C, 51.14; H, 7.59; N, 4.58. Found: C, 51.30; H, 7.59; N, 4.43.

C. Chromatographic evidence for the formation of **12** *from sulfoxide* **10**. A sample of **10** in CH_2Cl_2 containing $SOCl_2$ was boiled for 5 h under reflux in an N_2 atmosphere, as described[5] for other thio sugar sulfoxides. The spot for **10** (R_F 0.7) was replaced by a spot (R_F 0.4) attributable to **12** (t.l.c. with solvent *A*). When the solution was diluted with CH_2Cl_2 and washed with aq. $NaHCO_3$, the spot for **12** was in turn replaced by one identical with that given by **13** (R_F 0.15).

*2-*C*-Acetamidomethyl-1-*O*-acetyl-2-deoxy-3, 4; 5, 6-di-*O*-isopropylidene-1-*S*-phenyl-1-thio-*D*-glucitol* (**16**) via *2-*C*-(*N*,*N*-diacetylamino)methyl-1-chloro-2-deoxy-3,4; 5,6-di-*O*-isopropylidene-1-*S*-phenyl-1-thio-*D*-glucitol* (**15**). — A solution of **9** (310 mg) in dry CCl_4 (10 mL) was stirred with NCS (100 mg) for 16 h at room temperature. The ^{1}H-n.m.r. spectrum of the filtered solution revealed the absence of **9** and presence of **15** [δ 5.75 and 5.49, doublets (intensity ratio 3:4) for H-1 of two epimers, $J_{1,2}$ 2.0 and 2.5 Hz; δ 2.46 and 2.42, singlets, 3 H each, NAc_2]. The solvent was evaporated to give syrupy **15** [*m/z*, 488, 486 (4.2 and 1.4%, $M^+ + 1$), 450 (66%, $M^+ - Cl$), 4.08, 4.09, and 410 (70, 19, and 21%)] which was hydrolyzed in 2:1 acetone–water (15 mL) during 2 h at room temperature. The mixture was diluted with water and extracted with $CHCl_3$ (2 x 25 mL). Column chromatography (solvent *D*) of the dried (Na_2SO_4) and concentrated extract gave **16** (150 mg, 46%) as an inseparable mixture of 1-epimers, R_F 0.2 (t.l.c., ether), $[\alpha]_D$ +15° (*c* 2); ν_{max} 3600–3300 (3 peaks), 1750, 1660, 1530 cm^{-1}; *m/z* 468 (4%, $M^+ + 1$), 408 (67%, $M^+ + 1 - AcOH$), 358 ($M^+ + 1 - PhSH$).

Anal. Calc. for $C_{23}H_{33}NO_7S$ (467.6): C, 59.08; H, 7.11; N, 2.99; S, 6.86. Found: C, 58.98; H, 7.09; N, 2.95; S, 7.01.

*1-*O*-Acetyl-2-deoxy-3, 4; 5, 6-di-*O*-isopropylidene-2-*C*-nitromethyl-*D*-glucose-*S*-phenyl monothiohemiacetal* (**17**). — Compound **10** (1.30 g) was treated at room temperature with 2:1 Ac_2O–trifluoroacetic anhydride (5 mL, mixed 5 h prior to use). After 1 h, 2,6-dimethylpyridine (0.8 mL) was added at 0°, and the mixture was then kept for 3 h at room temperature, diluted with CH_2Cl_2 (150 mL), washed with 5% HCl (2 x 100 mL) and aq. $NaHCO_3$ (2 x 100 mL), dried (Na_2SO_4), concentrated to a syrup, and chroma-

tographed on a column (1:4 ether–hexane), to give syrupy **17** (0.68 g, 47.5%), $[\alpha]_D$ −41° (*c* 2); ν_{max} 1755 (OAc), 1560 (NO_2) cm^{-1}; *m/z* 396 ($M^+ + 1 - AcOH$), 338 ($M^+ + 1 - AcOH - Me_2CO$), and 280 ($M^+ + 1 - AcOH - 2\,Me_2CO$). The n.m.r. data (Tables I and II) showed that **17** was a mixture of 1-epimers.

Anal. Calc. for $C_{21}H_{29}NO_8S$ (455.5): C, 55.37; H, 6.41; S, 7.04. Found: C, 55.62; H, 6.44; S, 7.12.

*Phenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-*C*-nitromethyl-1-thio-β-*D*-glucopyranoside* (**18**). — A mixture of **10** (490 mg), Ac_2O (10 mL), AcOH (1 mL), *p*-toluenesulfonic acid (0.4 g), and CH_2Cl_2 (20 mL) was boiled under reflux for 16 h, then cooled, diluted with CH_2Cl_2 (50 mL), and washed with aq. $NaHCO_3$ (3 x 50 mL) followed by water (50 mL). The organic phase was dried ($MgSO_4$) and concentrated to a syrup that was subjected to column chromatography (solvent *C*), yielding a fast-moving fraction of an unidentified product (200 mg) followed by **18** (190 mg, 36.3%), R_F 0.2 and 0.8 (t.l.c. with solvent *C* and EtOAc, respectively), m.p. 88–89° (from ether–hexane), $[\alpha]_D$ +6° (*c* 1), ν_{max} 1750 (OAc) and 1560 (NO_2) cm^{-1}; *m/z* 331 (7%, $M^+ - PhSH$) and 272 (100%, $M^+ + 1 - PhSH - AcOH$).

Anal. Calc. for $C_{19}H_{23}NO_9S$ (441.4): C, 51.69; H, 5.25; N, 3.06; S, 7.26. Found: C, 51.60; H, 5.20; N, 3.06; S, 7.15.

*Phenyl 2-deoxy-2-*C*-nitromethyl-1-thio-β-*D*-glucopyranoside* (**19**). — *A. From* **17**. To a solution of **17** (140 mg) in PhMe (10 mL) was added 90% trifluoroacetic acid (1 mL). After 6 h at room temperature, the solution was concentrated with repeated additions of PhMe, and the product was chromatographed on a small column by use of ether (100 mL) followed by EtOAc as eluants, to give **19** (22 mg, 22%), m.p. 126–127° (from ether–hexane), $[\alpha]_D$ −37° (*c* 1, acetone); ν_{max}^{KBr} 3500–3150 (OH), 1554 (NO_2) cm^{-1}; *m/z* 314 (2.5%, $M^+ - 1$), 280 (21%, $M^+ + 1 - 2\,H_2O$), 251 (30%, $M^+ + 1 - H_2O - HNO_2$), and 206 (100%, $M^+ + 1 - PhSH$).

Anal. Calc. for $C_{13}H_{17}NO_6S$ (315.3): C, 49.51; H, 5.43; S, 10.17. Found: C, 49.60; H, 5.56; S, 10.09.

B. From **18**. Triacetate **18** (30 mg) was deacetylated at room temperature with MeOH (10 mL) containing a catalytic amount of NaOMe. After 30 min, complete replacement of **18** (R_F 0.8) by **19** (R_F 0.4) was indicated by t.l.c. (EtOAc), the solution was deionized (Amberlite IR-120[H^+]) and evaporated, and **19** (18 mg, 86%) crystallized from ether–hexane; m.p. 126–127°.

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REFERENCES

1 H. H. Baer, U. Williams, and B. Radatus, *Carbohydr. Res.*, 174 (1988) 291–303.
2 B. Radatus, U. Williams, and H. H. Baer, *Carbohydr. Res.*, 157 (1986) 242–250.
3 P. Bakuzis, M. L. F. Bakuzis, C. C. Fortes, and R. Santos, *J. Org. Chem.*, 41 (1976) 2769–2770.
4 D. L. Tuleen and T. B. Stephens, *J. Org. Chem.*, 34 (1969) 31–35.
5 F. Santoyo González, P. Garcia Mendoza, and F. J. López Aparicio, *Carbohydr. Res.*, 183 (1988) 227–240.
6 K. Narasaka, T. Sakashita, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 45 (1972) 3724.
7 R. Tanikaga, Y. Yabuki, N. Ono, and A. Kaji, *Tetrahedron Lett.*, (1976) 2258–2261.
8 F. Santoyo González and H. H. Baer, *Carbohydr. Res.*, 202 (1990) 33–47.