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A New Approach to Some 1,6-Dideoxy 1,6-Epithio Sugars*

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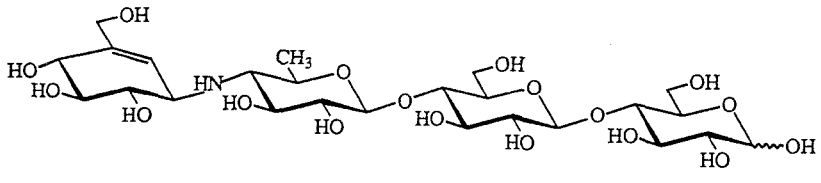
The treatment of hexopyranosyl bromides, also activated at C 6 (Br, OTs, OMs), with H_2S/$HCONMe_2$ under basic conditions gives rise to 1,6-dideoxy 1,6-epithio sugars. One such sugar has been further transformed into the synthetically useful 3,4-anhydro-1,6-dideoxy-1,6-epithio-β-D-galactose. The treatment of this epoxide with sodium azide and with cyclohexylamine is described. An analogous treatment of one doubly activated hexopyranosyl bromide with sodium hydrogen selenide has led to a novel 1,6-dideoxy 1,6-episeleno sugar which displayed interesting n.m.r. spectra. Finally, in an attempt to prepare 1,6-dideoxy 1,6-epidithio sugars, a tetraalkylammonium tetrathiomolybdate reagent was found to be the reagent of choice for converting doubly activated hexopyranosyl bromides into 1,6-dideoxy 1,6-epithio sugars.

A current synthetic target in our laboratory is 'β-acarbose' (1), a diastereoisomer of acarbose (2), a natural product isolated from an *Actinoplanes* sp. and shown to be a potent inhibitor of various enzymes which process molecules containing α-D-glucosidic linkages (e.g. amylose and sucrose).[1] It is our hope that β-acarbose will have significant inhibitory action against enzymes, namely cellulases and β-D-glucan hydrolases, which correspondingly process molecules containing β-D-glucosidic linkages.

One of our approaches to β-acarbose has been to prepare the carba disaccharide (3) which, with some manipulation, can act as a glycosyl donor for a cellobiose acceptor (4).[2] The precursor to a 1,6-anhydro sugar such as (3) was readily available from the treatment of the 1-epivalienamine (5)[3] with the well described epoxide (6).[4,5] However, it soon became apparent to us that considerable difficulties could arise in the chemical manipulation of (3), namely the activation of C 1 for its subsequent role as glycosyl donor and the selective deoxygenation at C 6. To avoid these pitfalls, we embarked upon a synthesis of the 1,6-dideoxy 1,6-epithio sugar (7), a molecule beautifully arranged for the introduction of nucleophiles (nitrogen in our



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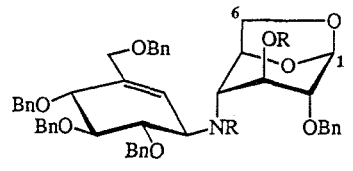

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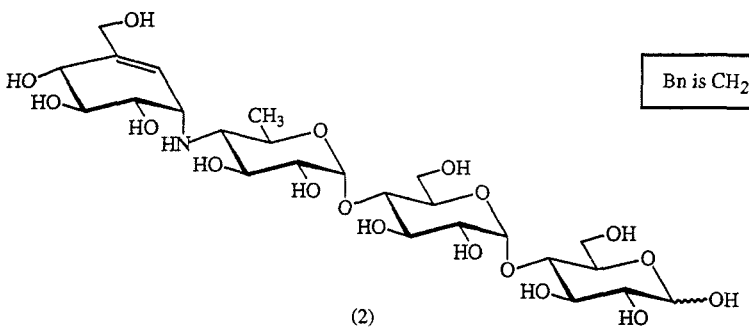
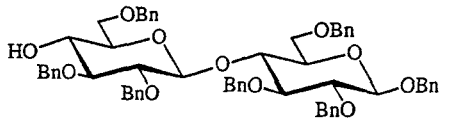


(2)

Bn is CH_2Ph



(4)

* Dedicated to Professor Stephen Angyal on the occasion of his 80th birthday.

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case) at C4, for anomeric activation (sulfur at C1) and for desulfurization at C6 (to provide the requisite methyl group found in β-acarbose).

The normal routes to 1,6-dideoxy 1,6-epithio sugars such as (8) and (9), both possible precursors of (7), involve the early introduction of sulfur either at the anomeric carbon[6,7] or at C6 of the appropriate monosaccharide.[8] Indeed, we prepared the thioacetate (10) in four steps from D-glucose, and, upon treatment with 'cysteamine' (2-aminoethanethiol) in the presence of 1,4-dithioerythritol,[9] the desired 1,6-dideoxy 1,6-epithio sugar (11) was formed in good yield.

It occurred to us, that, rather than inserting sulfur at an early stage of the synthesis, it might be better to form the 1,6-epithio bridge by treating an appropriately functionalized precursor with a source of sulfide ions. In an early experiment, we prepared the dibromide (12) (from D-galactose in four steps) and treated it with hydrogen sulfide/sodium hydride in *N*,*N*-dimethylformamide (dmf)—the desired 1,6-dideoxy 1,6-epithio sugar (13) was formed in good yield.

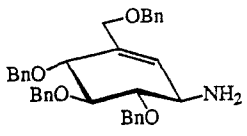
This result encouraged us to undertake a thorough study of our new method. Firstly, towards a synthesis of the D-*gluco* sugar (8) itself, the bromo tosylate (14) was again treated with hydrogen sulfide in dmf, but with *triethylamine* as the base—the 1,6-epithio sugar (11) was formed in high yield. A conventional deacetylation then gave the parent triol (8).[6] A similar treatment of the bromo tosylate (15) with H_2S/dmf/Et_3N gave the 1,6-epithio sugar (13) and hence the parent triol (9).[6]

We contemplated for just a while the conversion of (8) and (9) into the desired epoxide (7)—any selective functionalization of (8) necessary to form the precursor (16)[10] would inevitably suffer from some unwanted form of participation by the sulfur atom,[11] and the processing of the triol (9) to form the diol (17), ready for treatment with Viehe's salt to give the epoxide (7),[12] seemed unduly cumbersome.

In a direct approach to the epoxide (7), the diol (18) was converted into the dimesylate (19) (our attempts to form the ditosylate were not particularly successful) and thence the bromide (20). Treatment of (20) with H_2S/dmf/Et_3N gave the 1,6-epithio sugar (21) in high yield, and subsequent exposure to sodium methoxide in methanol formed the epoxide (22), also characterized as the acetate (7).

With our synthetic target (7) in hand, we decided to investigate some of the chemistry of these interesting molecules. Treatment of the epoxide (22) with sodium azide in dmf at 80° gave an acceptable yield of the azide (23)—the alternative approach to (23) by subjecting the epoxide to trimethylsilyl azide was not as successful. Treatment of the epoxide (22) with cyclohexylamine in butan-1-ol at 100° gave the amine (24), a nice model for the carba disaccharide (3).

Selenoglycosides are useful glycosyl donors.[13] In an attempt to extend the range of our new 1,6-epithio sugar synthesis, we treated the bromo tosylate (14) with sodium hydrogen selenide[14,15] in dmf—the 1,6-episeleno sugar (25) was formed in good yield. Deacetylation gave the parent triol (26). The ^1H n.m.r. spectrum of



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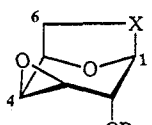
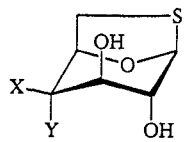
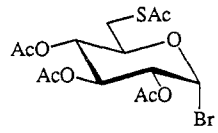


	X	R
(6)	O	Bn
(7)	S	Ac



	X	Y
(8)	H	OH
(9)	OH	H



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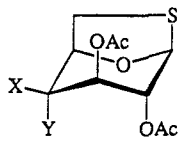
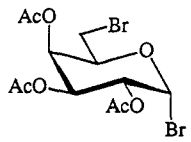


	X	Y
(11)	H	OAc
(13)	OAc	H



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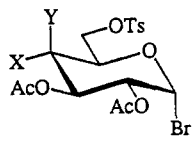
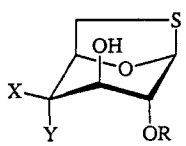
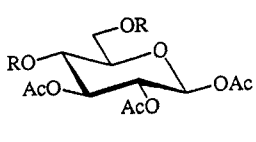


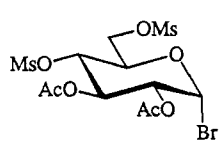
	X	Y
(14)	OAc	H
(15)	H	OAc



	X	Y	R
(16)	H	OTs	Ts
(17)	OH	H	Ac



(18) R = H
(19) R = Ms



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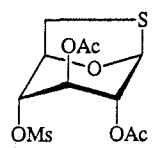

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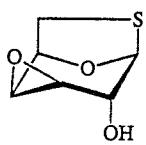

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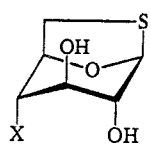
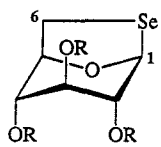
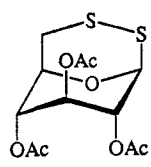


(23) X = N_3
(24) X = $C_6H_{11}NH$



(25) R = Ac
(26) R = H



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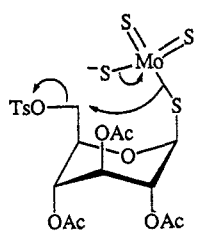

(28)

(25) was interesting in that the signals for H 1 and H 6 contained a coupling to ^{77}Se (7·6%, $I = \frac{1}{2}$)—the ^{77}Se n.m.r. spectrum of (25) naturally also showed these couplings and, as well, to virtually every hydrogen in the molecule! The ^{13}C n.m.r. spectrum likewise showed coupling to selenium for C 1 and C 6. Although similar effects were apparent in the ^{1}H and ^{13}C n.m.r. spectra of the triol (26), the values of the coupling constants were not obvious.

An attempt to prepare 1,6-epitelluro sugars by treating (14) with sodium hydrogen telluride[15] was unsuccessful. Likewise, treatment of (14) with benzyltriethylammonium tetrathiomolybdate did not give the expected disulfide (27) but rather the normal 1,6-epithio sugar (11)[16] in excellent yield—apparently the tetrathiomolybdate ion (MoS_4^{2-}) cannot bridge both C 1 and C 6 in (14) (a seven-membered ring is required), and the alternative and easier redox reaction occurs, possibly involving an intermediate such as (28). This treatment of doubly activated hexopyranosyl bromides, such as (14) and (20), with the tetrathiomolybdate ion now constitutes the most expeditious route to 1,6-dideoxy 1,6-epithio sugars.

We will report in due course on our studies of (7) and (25) as glycosyl donors and as assistants in the synthesis of β-acarbose.

Experimental

General experimental methods have been given previously.[17]

Diphenyl diselenide (δ 460) was employed as an external standard for the ^{77}Se n.m.r. spectrum.

*2,3,4-Tri-*O*-acetyl-6-bromo-6-deoxy-α-*D*-galactosyl Bromide (12)*

(i) To a chilled solution of 1,2:3,4-di-*O*-isopropylidene-α-D-galactose (2·0 g, 7·7 mmol) in pyridine (50 ml) were added triphenylphosphine (3·5 g, 13 mmol) and carbon tetrabromide (5·0 g, 15 mmol). The dark reaction mixture was then stirred for 12 h at 60°C and methanol (5 ml) was added. The pyridine was removed by repeated co-evaporation with toluene, and the residue was dissolved in CH_2Cl_2 (50 ml). Silica gel (6 g) was added, the solvent removed by evaporation and the residual powder applied to the top of a silica gel pad (30 g). The fraction which eluted with $CHCl_3$/MeOH (19 : 1) was then subjected to flash chromatography (20% EtOAc, petrol) to yield 6-bromo-6-deoxy-1,2 : 3,4-di-*O*-isopropylidene-α-D-galactose as a clear syrup (2·3 g, 92%), $[\alpha]_D^{24}$ −44° (lit.[18,19] −51°, −58·9°). ^{13}C n.m.r. (75·5 MHz) δ 24·41, 24·83, 25·88, 25·97, 4C, Me; 29·62, C 6; 68·35, 70·45, 70·85, 70·95, C 2,3,4,5; 96·51, C 1.

(ii) To a solution of the impure bromo deoxy sugar above in methanol (80 ml) was added methanolic sulfuric acid (80 ml of 1%) and then water (160 ml). The solution was stirred at 100°C for 3 h. The cooled solution was neutralized (10 M KOH), evaporated to dryness and the residue treated with pyridine/acetic anhydride (100 ml of 2 : 1). After 12 h the mixture was evaporated, co-evaporated with toluene and the residue subjected to normal workup (CH_2Cl_2). Flash chromatography of the residue (25% EtOAc, petrol) afforded the expected 1,2,3,4-tetra-*O*-acetyl-6-bromo-6-deoxy-D-galactose (2·0 g, 74% for the two steps from the di-*O*-isopropylidene-D-galactose).

(iii) The above anomeric mixture of acetates (635 mg) was dissolved in dry dichloromethane (20 ml), cooled (0°C) and hydrogen bromide in acetic acid (3 ml of 30%) added. After 2 h, workup (CH_2Cl_2) gave the bromide (12) (620 mg). This compound was unstable and was used directly and immediately in the next step.[20]

*2,3,4-Tri-*O*-acetyl-1,6-dideoxy-1,6-epithio-β-*D*-galactose (13)*

(i) To a solution of the above bromide (12) (620 mg) in dmf (5 ml) was added a solution of sodium sulfide in dmf [prepared from sodium hydride (240 mg of 60%, 6 mmol) suspended in dmf (3 ml) and saturating with hydrogen sulfide gas]. After 2 h, workup (Et_2O) gave an oil which was subjected to flash chromatography (25% EtOAc, petrol) to yield the D-*galacto* triacetate (13) (280 mg, 60% for the two steps from the bromo tetraacetate).

(ii) 2,3,4-Tri-*O*-acetyl-6-*O*-(*p*-tolylsulfonyl)-α-D-galactosyl bromide (15)[6] (190 mg) was dissolved in anhydrous dmf (2 ml), and anhydrous triethylamine (1 ml) added. H_2S was bubbled through the mixture for 10 min and the solution stirred for 2 days. The solution was subjected to a normal workup (EtOAc) to give a clear oil (100 mg) which was purified by flash chromatography (35% EtOAc, petrol) to give the D-*galacto* triacetate (13) as an oil which rapidly crystallized (56 mg, 52%). This was recrystallized to give white plates, m.p. 130–131°C (anhydrous EtOH; lit.[6] 126–127°C), $[\alpha]_D^{23}$ +28·6° (lit.[6] +34·0°). ^{1}H n.m.r. (300 MHz) δ 2·03, 2·09, 2·10, 3s, 9H, Me; 3·04, dd, $J_{5,6}$ 7·2, $J_{6,6}$ 10 Hz, H 6; 3·34, dd, $J_{5,6}$ 0·8 Hz, H 6; 4·73–4·77, m, H 5; 4·82, t, $J_{1,2} \approx J_{2,3}$ 1·6 Hz, H 2; 5·11, dq, $J_{3,4}$ 5·1, $J_{1,3} \approx J_{2,3} \approx J_{3,5}$ 1·4 Hz, H 3; 5·15, t, $J_{3,4} \approx J_{4,5}$ 4·9 Hz, H 4; 5·44, t, $J_{1,3} \approx J_{2,3}$ 1·4 Hz, H 1. ^{13}C n.m.r. (75·5 MHz) δ 20·39, 20·63, 3C, Me; 30·50, C 6; 65·36, 67·09, 73·34, 75·77, 80·74, C 1,2,3,4,5; 169·03, 169·12, 169·40, 3C, C=O.

*2,3,4-Tri-*O*-acetyl-1,6-dideoxy-1,6-epithio-β-*D*-glucose (11)*

(i) To an ice-cold solution of 1,2,3,4-tetra-*O*-acetyl-6-*S*-acetyl-6-thio-β-D-glucose[6,8] (230 mg, 0·56 mmol) in CH_2Cl_2 (5 ml) was added HBr/AcOH (1 ml of 30%). The mixture was stirred for 2 h at 0°C and then diluted with CH_2Cl_2. Normal workup gave the bromide (10) as an oil (230 mg), homogeneous by t.l.c. ^{1}H n.m.r. (300 MHz) δ 1·95, 2·01, 2·03, 2·30, 12H, Me; 3·06, m, 2H, H 6; 4·20, br q, $J_{5,6} \approx J_{5,6}$ 5·0, $J_{4,5}$ 10·0 Hz, H 5; 4·73, dd, $J_{1,2}$ 4·0, $J_{2,3}$ 10·0 Hz, H 2; 4·98, t, $J_{3,4}$ 10·0 Hz, H 3; 5·42, t, H 4; 6·47, d, H 1. ^{13}C n.m.r. (75·5 MHz) δ 20·41, 20·51, 28·96, 4C, Me; 30·18, C 6; 69·09, 69·99, 70·46, 72·85, C 2,3,4,5; 86·19, C 1; 169·71; 169·76, 176·45, 4C, CO. F.a.b. mass spectrum (positive, 3-$O_2NC_6H_4CH_2OH$ matrix+KCl) *m/z* 427 $(M+H)^+$; 465 $(M+K)^+$. The bromide (10) (130 mg) was dissolved in hexamethylphosphoramide (5 ml), then dithioerythritol (80 mg) and cysteamine (40 mg) were added. After 24 h at room temperature, the reaction mixture was poured into ice-cold water, the precipitate was filtered, dissolved in CH_2Cl_2, and purified by flash chromatography (20% EtOAc, petrol) to give the triacetate (11) as an oil (102 mg, 60%), $[\alpha]_D^{24}$ −53°. ^{1}H n.m.r. (300 MHz) δ 1·95, 2·08, 2·10, 3s, 9H, Me; 3·02, dd, $J_{5,6}$ 6·5, $J_{6,6}$ 10·0 Hz, H 6; 3·13, dd, $J_{5,6}$ 1·0 Hz, H 6; 4·55, dd, $J_{3,4}$ 4·7, $J_{4,5}$ 2·0 Hz, H 4; 4·64, dd, $J_{1,2}$ 0·9, $J_{2,3}$ 3·5 Hz, H 2; 4·69, m, H 5; 4·90, dd, H 3; 5·37, br s, H 1. ^{13}C n.m.r. (75·5 MHz) δ 20·82, 3C, Me; 34·44, C 6; 69·07, C 3; 72·12, C 4; 74·26, C 2; 79·57, C 5; 81·73, C 1; 169·32, 169·85, 170·13, 3C, C=O.

(ii) Anhydrous triethylamine (1 ml) was dissolved in anhydrous dmf (5 ml), and H_2S was bubbled through the solution for 10 min. The α-D-glucosyl bromide (14)[21] (510 mg, 0·95 mmol) was dissolved in anhydrous dmf (5·5 ml), and added dropwise to the H_2S solution at 0°C. The solution was allowed to warm to room temperature and stirred for 3 days. Normal workup

(EtOAc) gave an oil which was purified by flash chromatography (35% EtOAc, petrol) to give the triacetate (11) as a clear oil (213 mg, 74%) which crystallized as white plates, m.p. 79–81°C (EtOH; lit.[22,8,6] 86–88°C, 93–94°C, 79–81°C), $[\alpha]_D^{24}$ −51·6° (lit.[8,6] −25·2°, −55·0°). I.r. (film) ν_{max} 1738 (C=O); 1434 cm^{-1} (CH_2S). E.i. *m/z* 304 (M).

(iii) The α-D-glucosyl bromide (14) (857 mg, 1·59 mmol) was taken up in anhydrous $CHCl_3$ (15 ml), and benzyltriethylammonium tetrathiomolybdate[16] (1·85 g, 3·19 mmol) added. The solution was stirred at room temperature under argon for 20 h, then filtered through a plug of silica. The solvent was evaporated and the residue purified by flash chromatography (30% EtOAc, petrol) to give an oil (425 mg, 88%). The ^1H n.m.r. (80 MHz), i.r. (thin film) and mass spectra of this compound were identical to those of the triacetate (11) above.

1,2,3-Tri-O-acetyl-β-D-glucopyranose (18)

(i) α-D-Glucopyranose (5·0 g, 28 mmol) and camphor-10-sulfonic acid (25 mg) were suspended in anhydrous dmf (50 ml). Benzaldehyde dimethyl acetal (5·0 ml, 33 mmol) was added dropwise to the stirred solution at 50°C while nitrogen was bubbled through the mixture. After 90 min, more benzaldehyde dimethyl acetal (2·5 ml) and camphor-10-sulfonic acid (35 mg) were added. An hour later more camphor-10-sulfonic acid (20 mg) was added and, after another 2 h, more benzaldehyde dimethyl acetal (2·5 ml). The solution was stirred for a further 3 h. The reaction was quenched with pyridine (10 ml), and allowed to cool to room temperature. Acetic anhydride (20 ml) and 4-(dimethylamino)pyridine (20 mg) were added and the solution was stirred for 15 h. The solvent was removed under reduced pressure to give a crystalline residue. Normal workup (EtOAc) gave an orange oil which was crystallized to give 1,2,3-tri-*O*-acetyl-4,6-*O*-benzylidene-β-D-glucose as white plates (4·84 g, 39%), m.p. 201–202°C (EtOH; lit.[23] 201°C), $[\alpha]_D^{23}$ −45·0° (lit.[23] −51·7°). ^1H n.m.r. (80 MHz) δ 2·06, 2·13, 2s, 9H, Me; 3·56–3·94, 4·22–4·50, 5·00–5·38, 3m, 6H, H2,3,4,5,6; 5·50, s, CHPh; 5·80, d, $J_{1,2}$ 7·8 Hz, H1; 7·22–7·53, m, Ph.

(ii) 1,2,3-Tri-*O*-acetyl-4,6-*O*-benzylidene-β-D-glucose (4·18 g) was heated at 100°C in aqueous AcOH (50% v/v, 15 ml) for 1 h. The solvents were evaporated via addition of EtOH and toluene, and the residue was dried at 60°C under vacuum to give the diol (18) as a pale yellow oil (3·94 g), contaminated by benzaldehyde and acetic acid. ^1H n.m.r. (300 MHz) δ 1·98, 2·06, 2·13, 3s, 9H, Me; 3·06, 3·16, br 2s, 2H, OH; 3·45–3·95, m, 4H, H4,5,6; 4·98, t, $J_{1,2} \approx J_{2,3}$ 9·3 Hz, H2; 5·09, t, $J_{3,4} \approx J_{4,5}$ 9·3 Hz, H3; 5·67, d, H1. ^{13}C n.m.r. (75·5 MHz) δ 20·41, 20·49, 20·69, 3C, Me; 61·03, C6; 68·30, 69·32, 72·32, 75·29, C2,3,4,5; 89·30, C1; 169·39, 170·05, 171·19, 3C, C=O.

1,2,3-Tri-O-acetyl-4,6-di-O-(p-tolylsulfonyl)-β-D-glucose

1,2,3-Tri-*O*-acetyl-β-D-glucopyranose (18) (687 mg, 2·25 mmol) and tosyl chloride (1·28 g, 6·70 mmol) in anhydrous pyridine (5 ml) were allowed to react at room temperature for 24 h. Water (1 ml) was added and the solution stirred for 5 min. Normal workup (EtOAc) gave an oil which was taken up in EtOH and allowed to crystallize (115 mg, 8%). A small portion was recrystallized to give *1,2,3-tri-O-acetyl-4,6-di-O-(p-tolylsulfonyl)-β-D-glucose* as fine white needles, m.p. 158–159°C (EtOH), $[\alpha]_D^{23}$ +2·0° (Found: C, 50·7; H, 5·2. $C_{26}H_{30}O_{13}S_2$ requires C, 50·8; H, 4·9%). ^1H n.m.r. (300 MHz) δ 1·94, 1·97, 2·08, 3s, 9H, Ac; 2·46, s, 6H, ArMe; 3·72, ddd, $J_{4,5}$ 9·9, $J_{5,6}$ 2·1, 5·1 Hz, H5; 3·97, dd, $J_{6,6}$ 11 Hz, H6; 4·28, dd, H6; 4·71, dd, $J_{3,4}$ 9·3 Hz, H4; 4·98, dd, $J_{1,2}$ 8·3, $J_{2,3}$ 9·3 Hz, H2; 5·25, dd, H3; 5·59, d, H1; 7·32–7·40, 7·70–7·80, 2m, 8H, Ar. ^{13}C n.m.r. (75·5 MHz) δ 20·50, 20·70, 3C, COMe; 21·71, 2C, ArMe; 66·60, C6; 70·08, 71·63, 72·30, 73·49, C2,3,4,5; 91·19, C1; 127·85–145·70, Ar; 168·57, 169·14, 169·94, 3C, C=O.

1,2,3-Tri-O-acetyl-4,6-di-O-(methylsulfonyl)-β-D-glucose (19)

1,2,3-Tri-*O*-acetyl-β-D-glucopyranose (18) (3·94 g, 13 mmol) was taken up in anhydrous dichloromethane (50 ml), anhydrous triethylamine was added (5·3 ml, 3·9 g, 38 mmol) and the mixture was cooled and maintained between −10 and 0°C. Mesyl chloride (2·9 ml, 4·3 g, 38 mmol) was added dropwise to the stirred solution under argon and stirring continued for a further 45 min. T.l.c. indicated complete conversion into a product of lower polarity. Water (1 ml) was added and the mixture stirred for 5 min, then subjected to a normal workup (CH_2Cl_2) which gave an orange oil (6·38 g). A small sample was crystallized by slow evaporation from a mixture of EtOAc and Pr^i_2O, and then recrystallized to give the *dimesylate* (19) as fine white needles, m.p. 173–175°C (EtOAc/Pr^i_2O), $[\alpha]_D^{17}$ −6·5° (Found: C, 36·1; H, 5·1. $C_{14}H_{22}O_{13}S_2$ requires C, 36·4; H, 4·8%). ^1H n.m.r. (300 MHz) δ 2·05, 2·10, 2·13, 3s, 9H, Ac; 3·10, 3·11, 2s, 6H, Ms; 3·96, ddd, $J_{4,5}$ 9·9, $J_{5,6}$ 2·2, 4·0 Hz, H5; 4·39, dd, $J_{6,6}$ 11·6 Hz, H6; 4·50, dd, H6; 4·83, dd, $J_{3,4}$ 9·4 Hz, H4; 5·13, dd, $J_{1,2}$ 8·3, $J_{2,3}$ 9·6 Hz, H2; 5·36, t, H3; 5·73, d, H1. ^{13}C n.m.r. (75·5 MHz) δ 20·50, 20·72, 3C, COMe; 37·83, 38·79, 2C, Ms; 65·74, C6; 69·96, 71·73, 72·12, 72·54, C2,3,4,5; 91·45, C1; 168·87, 169·14, 170·12, 3C, C=O.

2,3-Di-O-acetyl-4,6-di-O-(methylsulfonyl)-α-D-glucosyl Bromide (20)

1,2,3-Tri-*O*-acetyl-4,6-di-*O*-(methylsulfonyl)-β-D-glucose (19) (6·38 g) in HBr/AcOH (30% w/w, 30 ml) was stirred overnight. Normal workup (EtOAc, without the 1 M HCl wash) gave the bromide (20) as a yellow oil (5·87 g) which crystallized overnight. ^1H n.m.r. (80 MHz) δ 2·12, 2·14, 2s, 6H, Ac; 3·09, s, 6H, Ms; 4·22–4·56, m, 4H, H4,5,6; 4·81, dd, $J_{1,2}$ 3·5, $J_{2,3}$ 9·5 Hz, H2; 5·65, t, $J_{2,3} \approx J_{3,4}$ 9·4 Hz, H3; 6·59, d, H1.

2,3-Di-O-acetyl-1,6-dideoxy-1,6-epithio-4-O-(methylsulfonyl)-β-D-glucose (21)

(i) 2,3-Di-*O*-acetyl-4,6-di-*O*-(methylsulfonyl)-α-D-glucosyl bromide (20) (5·87 g, 12 mmol) was taken up in anhydrous dmf (25 ml), and anhydrous triethylamine (8 ml) added. H_2S was bubbled through the solution for 10 min and the solution stirred at room temperature for 2 days. Normal workup (EtOAc) followed by flash chromatography (35% EtOAc, petrol) gave a light yellow oil (2·10 g, 51%) which crystallized on standing. A small portion was recrystallized to give the *mesylate* (21) as fantastic fine white needles, m.p. 139–140°C (EtOH), $[\alpha]_D^{23}$ −41·5° (Found: C, 38·7; H, 4·7. $C_{11}H_{16}O_8S_2$ requires C, 38·8; H, 4·7%). ^1H n.m.r. (500 MHz) δ 2·12, 2·13, 2s, 6H, Ac; 3·08, dd, $J_{5,6}$ 2·2, $J_{6,6}$ 7·8 Hz, H6; 3·13, s, Ms; 3·14, d, H6; 4·52, dd, $J_{3,4}$ 5·2, $J_{4,5}$ 1·9 Hz, H4; 4·76, br d, $J_{2,3}$ 3·6 Hz, H2; 4·88–5·16, m, H5; 5·07, dd, H3; 5·46, br s, H1. ^{13}C n.m.r. (125·8 MHz) δ 20·87, 20·89, 2C, COMe; 34·55, C6; 38·51, Ms; 60·17, 74·47, 77·08, 80·10, 81·76, C1,2,3,4,5; 169·51, 170·02, 2C, C=O.

(ii) 2,3-Di-*O*-acetyl-4,6-di-*O*-(methylsulfonyl)-α-D-glucosyl bromide (20) (2·43 g, 5·03 mmol) was taken up in anhydrous $CHCl_3$ (20 ml), and benzyltriethylammonium tetrathiomolybdate (3·06 g, 5·03 mmol) added. The solution was stirred at room temperature under argon for 18 h, then filtered through a plug of silica. The solvent was evaporated and the residue purified by flash chromatography (35% EtOAc, petrol) to give an oil (1·29 g, 75%). The ^1H n.m.r. (80 MHz) spectrum of this compound was identical to that of the mesylate (21).

3,4-Anhydro-1,6-dideoxy-1,6-epithio-β-D-galactose (22)

2,3-Di-*O*-acetyl-1,6-dideoxy-1,6-epithio-4-*O*-(methylsulfonyl)-β-D-glucose (21) (240 mg, 0·71 mmol) was suspended in anhydrous MeOH (3 ml) at −10°C, and sodium methoxide (0·65 ml of a 1·3 M solution in MeOH, 0·85 mmol) added. The mixture was allowed to warm to room temperature and stirred for 30 h. The solution was neutralized by the addition of cation-exchange resin (Amberlite IRC-50, H^+ form). The solution was filtered and the solvent evaporated under reduced pressure to give an oil (96 mg). A small portion of this was crystallized and recrystallized to give the *epoxy alcohol* (22) as fine white needles, m.p. 97–98°C ($CHCl_3$/petrol), $[\alpha]_D^{21}$ −54·0° (Found: C, 44·8; H, 5·3. $C_6H_8O_3S$ requires C, 45·0; H, 5·0%). ^{1}H n.m.r. (300 MHz) δ 2·36, br s, OH; 3·02, dd, $J_{5,6}$ 6·5, $J_{6,6}$ 8·8 Hz, H6; 3·15, d, H6; 3·19, br d, $J_{3,4}$ 4·5 Hz, H3; 3·57, t, $J_{3,4} \approx J_{4,5}$ 4·5 Hz, H4; 3·95, br s, H2; 5·09, dd, H5; 5·32, s, H1. ^{13}C n.m.r. ($CDCl_3$) δ 34·38, C6; 50·43, 53·62, C3,4; 68·00, 75·96, 82·05, C1,2,5.

2-O-Acetyl-3,4-anhydro-1,6-dideoxy-1,6-epithio-β-D-galactose (7)

3,4-Anhydro-1,6-dideoxy-1,6-epithio-β-D-galactose (22) (89 mg) was dissolved in anhydrous pyridine (2 ml), and acetic anhydride (1 ml) added. The solution was kept for 20 h, then water (1 ml) added and the mixture stirred for 10 min. Normal workup ($CHCl_3$) followed by flash chromatography (20% EtOAc, petrol) gave the *epoxy acetate* (7) as a clear oil (102 mg, 91%), $[\alpha]_D^{21}$ −21·1° (Found: C, 47·7; H, 4·9. $C_8H_{10}O_4S$ requires C, 47·5; H, 5·0%). ^{1}H n.m.r. (300 MHz) δ 2·14, s, Me; 3·01, dd, $J_{5,6}$ 6·4, $J_{6,6}$ 9·0 Hz, H6; 3·14, dd, $J_{1,3}$ 1·4, $J_{3,4}$ 4·0 Hz, H3; 3·15, d, H6; 3·59, dd, $J_{4,5}$ 4·0 Hz, H4; 4·98, s, H2; 5·12, dd, H5; 5·31, br s, H1. ^{13}C n.m.r. (75·5 MHz) δ 20·84, Me; 34·10, C6; 48·60, 53·45, C3,4; 69·08, 75·73, 79·42, C1,2,5; 169·81, C=O.

2,3-Di-O-acetyl-4-azido-1,4,6-trideoxy-1,6-epithio-β-D-glucose [Diacetate of (23)]

3,4-Anhydro-1,6-dideoxy-1,6-epithio-β-D-galactose (22) (127 mg, 0·79 mmol), sodium azide (410 mg, 6·3 mmol) and ammonium chloride (100 mg, 1·9 mmol) in anhydrous dmf (2 ml) were heated at 100°C under argon for 23 h. At this stage, t.l.c. indicated almost complete conversion of starting material into a compound of slightly higher polarity. The reaction mixture was allowed to cool to room temperature and pyridine (3 ml) and acetic anhydride (2 ml) were added. The mixture was stirred overnight at room temperature, then water (1 ml) was added. The solution was stirred for 5 min and then subjected to a normal workup (EtOAc) to give a brown oil (178 mg). This oil was purified by flash chromatography (25% EtOAc, petrol) to give the *diacetate* of azide (23) as a clear oil (108 mg, 47%), $[\alpha]_D^{21}$ −101° (Found: C, 42·0; H, 4·7. $C_{10}H_{13}N_3O_5S$ requires C, 41·8; H, 4·6%). I.r. (film) ν_{max} 2104 (N_3); 1745 cm^{-1} (C=O). ^{1}H n.m.r. (500 MHz) δ 2·05, 2·08, 2s, 6H, Me; 2·99, dd, $J_{5,6}$ 0·8, $J_{6,6}$ 9·9 Hz, H6; 3·12, dd, $J_{5,6}$ 6·7 Hz, H6; 3·26, br dd, $J_{3,4}$ 3·1, $J_{4,5}$ 2·0 Hz, H4; 4·69, br d, $J_{2,3}$ 3·1 Hz, H2; 4·80, br d, H5; 4·90, tt, $J_{2,3} \approx J_{3,4}$ 3·1, $J_{1,3} \approx J_{3,5}$ 1·0 Hz, H3; 5·42, t, $J_{1,2} \approx J_{1,3}$ 1·0 Hz, H1. ^{13}C n.m.r. (125·8 MHz) δ 20·81, 20·93, 2C, Me; 35·08, C6; 60·46, 69·76, 73·02, 79·11, 81·63, C1,2,3,4,5; 169·42, 169·85, 2C, C=O.

4-(Cyclohexylamino)-1,6-epithio-1,4,6-trideoxy-β-D-glucose (24)

3,4-Anhydro-1,6-dideoxy-1,6-epithio-β-D-galactose (22) (110 mg, 0·69 mmol) was taken up in anhydrous butan-1-ol (1 ml), and cyclohexylamine (0·25 ml, 2·5 mmol) was added. The solution was heated at 100°C under argon for 20 h, then evaporated under reduced pressure via the addition of EtOH. The microcrystalline residue was purified by flash chromatography (10% EtOH, 1% Et_3N, EtOAc) to give a pale brown microcrystalline solid (81 mg, 45%). A small portion was recrystallized to give the *amine* (24) as fine white needles, m.p. 175–176°C (Pr^i_2O/CH_2Cl_2), $[\alpha]_D^{15}$ −23·8° (Found: C, 55·3; H, 8·1. $C_{12}H_{21}NO_3S$ requires C, 55·6; H, 8·2%). ^{1}H n.m.r. (300 MHz) δ 0·92–1·27, 1·58–2·00, 2m, 10H, CH_2; 2·54, tt, *J* 10, 3·8 Hz, NCH; 2·91, m, H4; 3·19, dd, $J_{5,6}$ 7·0, $J_{6,6}$ 10 Hz, H6; 3·25, dd, $J_{5,6}$ 1·3 Hz, H6; 3·65–3·69, m, H2,3; 4·72, br d, H5; 5·51, br s, H1. ^{13}C n.m.r. (75·5 MHz) δ 25·03, 25·09, 33·49, 33·98, 34·57, 6C, C2′,3′,4′,5′,6′,6; 53·81, C1′; 57·51, 70·38, 72·75, 79·99, 84·08, C1,2,3,4,5.

2,3,4-Tri-O-acetyl-1,6-dideoxy-1,6-episeleno-β-D-glucose (25)

2,3,4-Tri-*O*-acetyl-6-*O*-(*p*-tolylsulfonyl)-α-D-glucosyl bromide (14) (1·12 g, 2·08 mmol) in anhydrous dmf (10 ml) was added portionwise to a solution of sodium hydrogen selenide (NaHSe) generated previously from selenium (250 mg, 3·16 mmol) and sodium borohydride (150 mg, 3·97 mmol) in anhydrous EtOH (12 ml).[14] The solution was stirred overnight under argon. Normal workup (EtOAc) gave an orange oil (377 mg) which was purified by flash chromatography (35% EtOAc, petrol) to give a pale yellow oil (545 mg, 56%). This was recrystallized to give the *seleno sugar* (25) as beautiful white cubes, m.p. 74–75°C (MeOH), $[\alpha]_D^{21}$ −74·5° (Found: C, 41·2; H, 4·7. $C_{12}H_{16}O_7Se$ requires C, 41·0; H, 4·6%). I.r. (film) ν_{max} 1739 (C=O); 1433 cm^{-1} (CH_2Se). ^{1}H n.m.r. (300 MHz) δ 2·02, 2·06, 2s, 9H, Me; 3·08, dd, $J_{5,6}$ 6·3, $J_{6,6}$ 9·5 Hz, H6-*exo*; 3·38, dd, $J_{5,6}$ 0·5 Hz, H6-*endo*; 4·62, dd, $J_{3,4}$ 6·3, $J_{4,5}$ 2·2 Hz, H4; 4·79, br dd, H5; 4·82, dd, $J_{1,2}$ 0·5, $J_{2,3}$ 4·4 Hz, H2; 5·01, br dd, H3; 5·73, br s, H1. ^{13}C n.m.r. (75·5 MHz, CD_2Cl_2) δ 21·01, 21·04, 21·08, 3C, Me; 31·35, d, $J_{Se,C}$ 60·0 Hz, C6; 31·36, C6; 69·14, 73·19, 76·35, 81·85, C2,3,4,5; 77·56, C1; 77·56, d, $J_{Se,C}$ 69·4 Hz, C1; 169·78, 170·34, 170·54, 3C, C=O. ^{77}Se n.m.r. (95·41 MHz) δ 290·0, dddt, $J_{Se,H1}$ 20, $J_{Se,H6\text{-}exo}$ 18, $J_{Se,H6\text{-}endo}$ 9·0, $J_{Se,H2} \approx J_{Se,H5}$ 2·5–3·0 Hz.

1,6-Dideoxy-1,6-episeleno-β-D-glucopyranose (26)

2,3,4-Tri-*O*-acetyl-1,6-dideoxy-1,6-episeleno-β-D-glucose (25) (835 mg, 2·38 mmol) was stirred at 0°C in anhydrous MeOH (3 ml), and sodium methoxide (1 ml of a 1 M solution in MeOH, 1 mmol) added. The mixture was stirred for 2 h under argon, then acid resin (Dowex 50W, H^+ form) was added until the solution was neutral. The mixture was filtered and then evaporated under reduced pressure to give the seleno sugar (26) as an oil (507 mg, 95%) which crystallized on standing. Further purification by chromatography (EtOAc) gave an oil which also crystallized on standing, but all attempts at recrystallization failed, $[\alpha]_D^{21}$ −45·5° (*c*, 0·4 in H_2O). ^{1}H n.m.r. (300 MHz) δ 3·12, dd, $J_{5,6}$ 6·0, $J_{6,6}$ 9·6 Hz, H6; 3·25, br d, H6; 3·53, br dd, $J_{2,3}$ 4·5, $J_{3,4}$ 7·0 Hz, H3; 3·57, br dd, $J_{4,5}$ 2·3 Hz, H4; 3·80, br d, H2; 4·86, m, H5; 5·79, s, H1. ^{13}C n.m.r. (75·5 MHz) δ 31·53, C6; 73·12, 77·33, 80·12, 83·85, C1,2,3,4,5.

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