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STRUCTURAL COMPARISON OF TREHALOSE ANOMERS; THE X-RAY CRYSTAL STRUCTURES OF αα-(2,3,4-TRI-O-METHYL-6-METHANESULPHONYL)GLUCOPYRANOSYL-1-O-(2',3',4'-TRI-O-METHYL-6'-METHANESULPHONYL)GLUCOPYRANOSE, AND ITS ββ-ISOMER.

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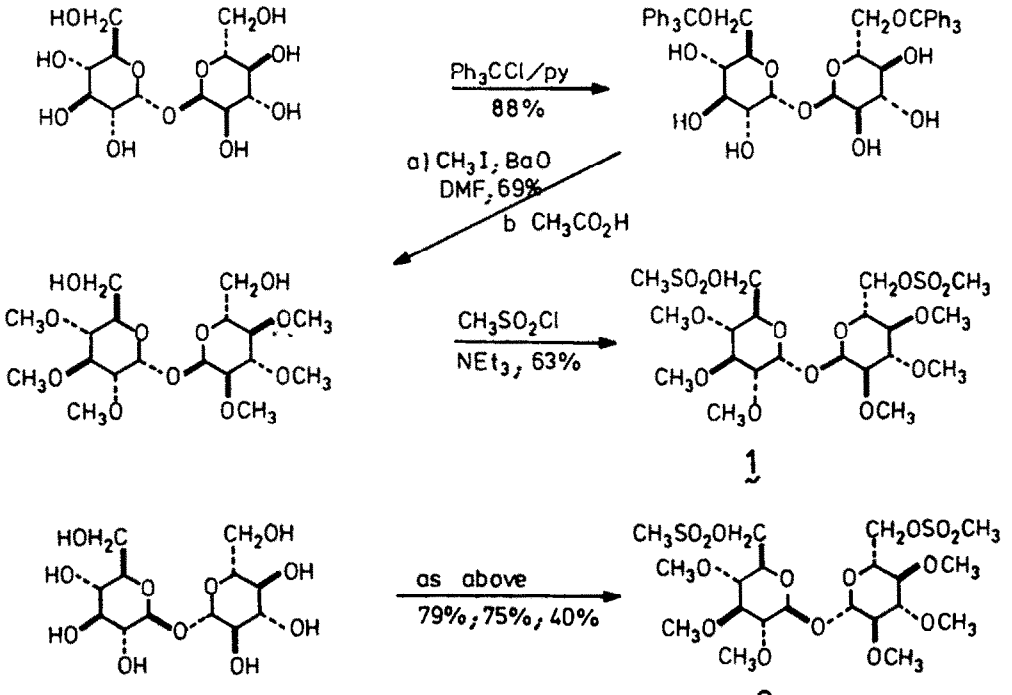
Summary: The structures of the title compounds have been determined by X-ray analysis. The αα-isomer was refined to a final R-factor of 0.073, and the ββ-isomer was refined to a final R-factor of 0.072. The anomeric geometry is compared with previously determined values, indicating a general tendency for (endo)O-C (exo)-O-C torsion angles in the 60°-90° region.

The αα-isomer of trehalose is widely occurring in nature, being particularly common in the spores and fruiting bodies of fungi and the eggs, larvae and pupae of insects.[1] There is a considerable amount of structural information available for the compound and its complexes and derivatives but not for the ββ-anomer. In the course of a project directed towards the synthesis of flexible trans-chelating ligands for organometallic catalysis,[2] we have developed an improved route to ββ-trehalose[3] via trichloroacetimidate coupling.[4] In the course of this work the methanesulphonates 1 and 2 were obtained in crystalline form and their X-ray structures obtained. The preparation followed straightforward routes outlined in Scheme 1.



Scheme 1

Structure determination

Single crystals of the αα-isomer 1 suitable for X-ray diffraction were obtained by the diffusion method, by permitting Et_2O vapour to transfer slowly to a CH_2Cl_2 solution of the dimethanesulphonate. A crystal of appropriate size was selected and mounted for Weissenberg camera. When the diffraction pattern was shown to be satisfactory, a full data collection was carried out using the Esraf-Nonius CAD 4 diffractometer of the Chemical Crystallography Department Oxford. The structure was solved by direct methods using the Multan 80 programs[5] together with the software package CRYSTALS.[6] Refinement proceeded smoothly to an R-factor of 0.073, at which point a random orientation of one of the two methanesulphonate positions was apparent and two independent positions (populations 0.67 and 0.33) were assigned. Full details are incorporated in Table 1.

For the ββ-isomer 2, suitable crystals were grown by diffusing 30-40 petroleum ether into an Et_2O solution. Data collection and refinement were carried out as above. In similar manner, it was necessary to assume two equivalent orientations for one of the mesylate groups, which permitted refinement down to R = 0.072.

TABLE 1 Crystallographic data

	αα-Isomer 1	ββ-Isomer 2
Molecular Formula	$C_{20}H_{38}S_2O_{15}$	$C_{20}H_{38}S_2O_{15}$
Molecular Weight	582.62	582.62
Crystal size, mm.	0.8 x 0.1 x 0.1	1.0 x 0.1 x 0.1
Cell constants, a, Å:	24.057(1)	13.235(1)
b, Å:	11.047(1)	8.154(4)
c, Å:	10.872(1)	13.555(2)
β°	-	99.78(1)
Cell volume Å	2889.3	1441.6
Space Group	$P2_12_12$	$P2_1$
Z	4	2
D_{calc} g cm^{-3}	1.34	1.34
F(000)	1240	620
Absorption coefficient mm^{-1}	2.21	2.21
Data collection range		
(λ = 1.5418 Å) 2θ	4-130°	4-130°
Scan angle w°	1.0 + 0.14 tan θ	1.0 + 0.14 tan θ
Scan speed range (deg m^{-1})	0.7 - 6.7	0.7 - 6.7
Total unique data	2794	2578
Significant date [I > 36(I)]	2168	2198
Least squares weights[7,8]	103.8, 105.6	530.0, 703.6, 177.9
Final R (R_w)	0.073(0.103)	0.072(0.100)

The atomic coordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation.

The derived structures are shown in Figure 1, viewed perpendicular to the C-O-C unit of the anomeric bridge. Bond lengths and bond angles are unexceptional and the orientation of $-OCH_3$ side-chains appears to be dictated by non-bonded interactions. The pyranose rings adopt a slightly flattened $^4C_1$ conformation similar to other carbohydrates[9] the average ring torsion angles in compound 1 are ± 57.6° and ± 55.2°, whilst they are ± 55.4° and ± 58.6° for compound 2. The torsion angles around the anomeric carbon are remarkably similar, given the difference in configuration between the two mesylates. Thus for compound 1, torsion angle O1-C1-O8-C11 = 91.4° and C1-O8-C11-O11 = 80.0°; for compound 2 they are respectively -90.5 and -83.4°.

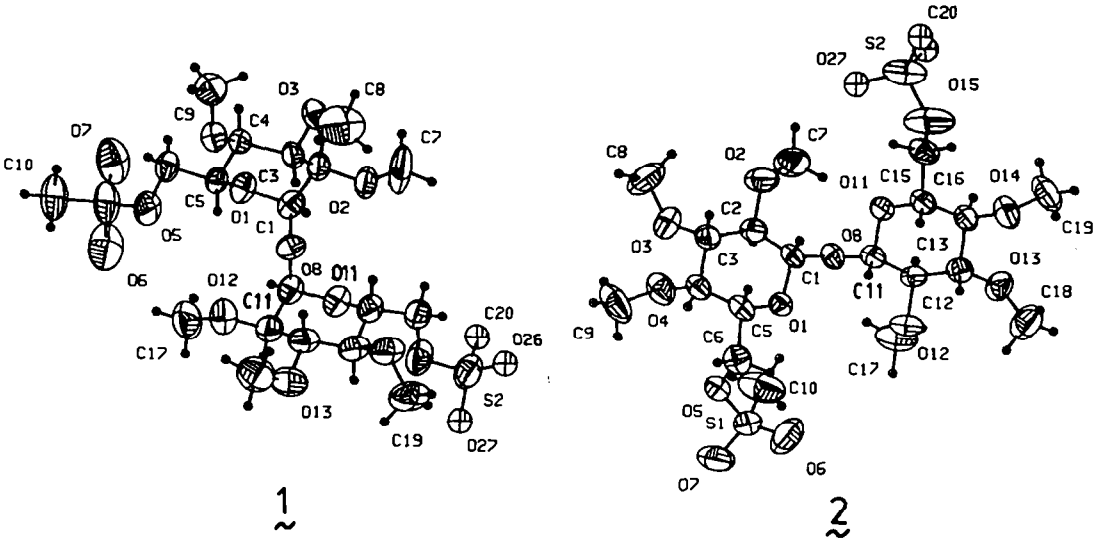


Figure 1 X-ray crystal structures of 2,3,4-tri-O-methyl 6-O-methanesulphonyl-α-D-glucopyranosyl-2',3',4'-tri-O-methyl-6'-O-methanesulphonyl-α-D-glucopyrano side (1) and of 2,3,4-tri-O-methyl-6-O-methanesulphonyl-β-D-glucopyranosyl-3',4'-tri-O-methyl-6'-O-methanesulphonyl -β-D-glucopyranoside (2). Principal bond lengths around the anomeric linkage for (1) : O1-C1 1.427(8), C1-O8 1.410(8), O8-C11 1.414(8), C11-O11 1.40(8); for (2) : O1-C1 1.414(7) C1-O8 1.403(7), O8-C11 1.402(7), C11-O11 1.412(7).

It has previously been recognised that the structure of αα-trehalose and its derivatives exhibit common conformational features. In general the C-C-O-C-C unit which contains the anomeric linkage has an extended W-conformation with torsion-angles in that unit of 180° and consequently torsion-angles in the O-C-O-C-O unit close to 60°. With access to the CSSR data file, the analysis may be extended to all known structures containing an acetal linkage between two pyran rings, including loganin and its derivatives.

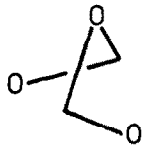
Results are collected in Table 2.

In four other cases where crystal structures have been determined namely 14,[24] 15,[25] 16[26] and 17[27] the data is unavailable, but inspection of published diagrams indicates that the extended 'W'-arrangement of the C-C-O-C-C ring linkage atoms is operative, with perhaps up to 30° distortion in the appropriate torsion angles.

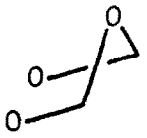
It can be seen that a substantial number of related compounds posess very similar geometry about the anomeric site, with just one exception.[22] This is not a consequence of intermolecular hydrogen-bonding since it is impossible in several of the examples and does not exist in at least one case where it could occur.[15] The preference results from a combination of two factors. Firstly, the exo-anomeric effect strives to maintain antiperiplanarity between lone-pairs on the interannular oxygen and the corresponding endocyclic C-O bond, giving torsion-angles of 60° in the preferred conformation.[28,29] Secondly, this is the diamond- lattice conformation which posesses least interannular non-bonded interactions, and the torsion angles vary from this ideal arrangement (usually towards 90°) to minimise repulsion further Force-field calculations which incorporate the exo-anomeric effect reproduce the conformation of αα-trehalose.[30] For the ββ-isomer these calculations predict the 'W'-arrangement of the C-C-O_β-C-C array.[31] For methanesulphonates 1 and 2, this results in the side-chains being placed well apart. Subsequent work will demonstrate the flexibility of the anomeric linkage through the formation of chelate complexes.

TABLE 2 Inter-ring torsional angles in dipyranosyl acetals

Compound	O_R-C-O_R-C[a]	C-O_R-C-OY	Reference
Methanesulphonate (1)	91.4	80	This work
Methanesulphonate (2)	90.5	83.4	This work
αα-Trehalose, 2 H_2O (3a)	61.7	74.8	10, 11
αα-Trehalose; $CaBr_2$,H_2O (3b)	b	b	12
αα-allo Trehalose; $CaBr_2$ (4)	45.1	57.1	13
6,6'-Dibromo-6,6'-dideoxy-αα-trehalose hexaacetate (3c)	76.5°	77.0°	14
O,O-Dimethylipecoside (5)	63	85	15
Dentapicrin A (6)	69.6	35.5	16
Loganin (7)	61.3	87.5	17
Mannoglucose derivative (8)	85.9	62.8	18
Olgose (9)	64.5	69.6	19
Avileurekanose C pentaacetate (10)	77	74.8	20
Iridoid V	67.4	41.2	21
Dimer ex costatolide (12)	73.5	-83.0	22
Seco Loganin bis epoxide (13)	68.0	102.0	23



60°,60°



-60°,60°

a First angle normalised to read positive.
b Quoted to be within 2-6° of the values for (3a).
c Mean of two independent molecules.

Acknowledgements

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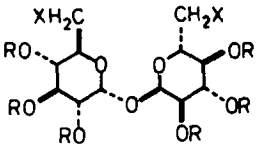
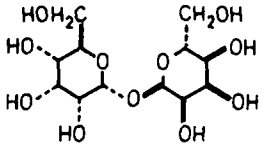
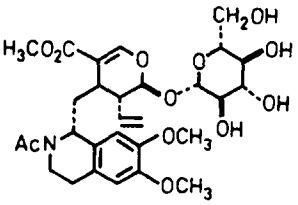


3a X=OH R=H
3b " " " ", $CaBr_2$
3c X=Br R=Ac



4 ; $CaBr_2$



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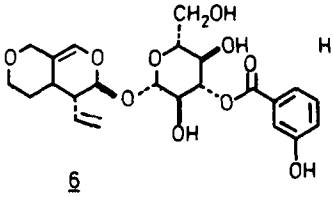

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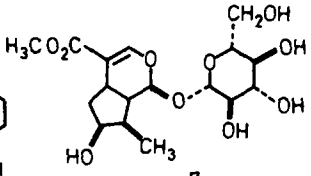

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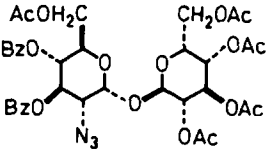

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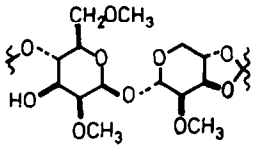

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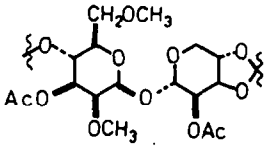

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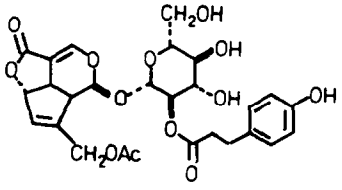

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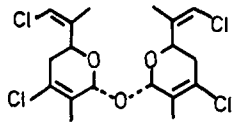

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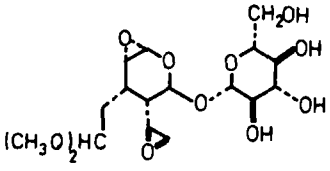

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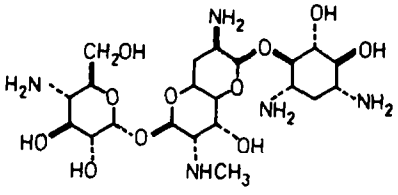

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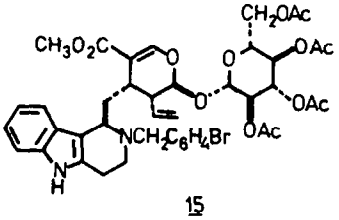

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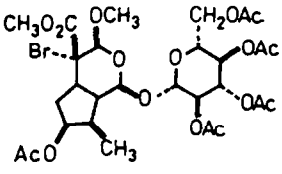

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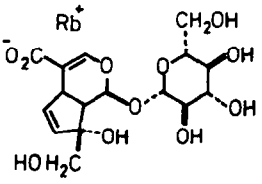

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EXPERIMENTAL

2,3,4-Tri-O-methyl-6-O-(triphenylmethyl)-α-D-glucopyranosyl-2'3'4'-tri-O-methyl-6'-O-(triphenylmethyl)-α-D-glucopyranoside.

Anhydrous barium oxide (93.5 g, 0.61 mol) and iodomethane (95 ml, 1.525 mol) were added to a vigorously stirred solution of 6-O-(triphenylmethyl)-α-D-glucopyranosyl-6'-O-(triphenylmethyl)-α-D-glucopyranoside (40.55 g, 49.0 mmol) in dry dimethylformamide (400 ml). Stirring was continued at 40° for 24h, then further barium oxide (95 g, 620 mmol) and iodomethane (95 ml, 1525 mmol) were carefully added, with stirring, over 15m. After a further 48h excess iodomethane was removed in vacuo and the red/brown residue was extracted with dichloromethane (3 x 500 ml) and water (10 x 500 ml). The dark red organic layer was washed with sodium thiosulphate solution (to remove iodine), dried (anhydrous magnesium sulphate) and the solvent removed in vacuo. Addition of a little methanol gave a pale yellow solid which was filtered off, washed (methanol) and dried in vacuo to give 2,3,4,-tri-O-methyl-6-O-(triphenylmethyl)-α-D-glucopyranosyl-2',3',4'-tri-O-methyl-6'-O-(triphenylmethyl-α-D-glucopyranoside as a white solid (30.55 g, 68.4%), which could be recrystallized from dichloromethane methanol; m.p. 147-8°; $[\alpha]_D^{\circ}$ + 109° (c = 1.03, CH_2Cl_2); found C, 73.47; H, 6.81; $C_{56}H_{62}O_{11}$ requires: C, 73.77; H, 6.81%; ^{1}H-NMR δ (300 MHz, $CDCl_3$) 3.1 (2H, dd, J_{6aS} 4.5 Hz, J_{6aS6b} 10 Hz, H_{6a}), 3.25 (2H, dd, J_{21} 4 Hz, J_{23} 10 Hz, H_2), 3.3 (6H, s, OMe), 3.35 (2H, m, H_5), 3.4 (6H, s, OMe), 3.45 (2H, m, H_{6b}), 3.5 (2H, t J 9 Hz, H_4), 3.6 (6H, s, OMe), 4.0 (2H, m, H_3), 5.4 (2H, d, J 4Hz, H), 7.2-7.55 (30H, m, Ph); m/z (field desorption) 910 (M^+).

2,3,4-Tri-O-methyl-α-D-glucopyranosyl-2',3',4'-tri-O-methyl-α-D-glucopyranoside.

Water (60 ml) was added to a solution of 2,3,4-tri-O-methyl-6-O-(triphenylmethyl)-α-D-glucopyranosyl-2',3',4'-tri-O-methyl-6'-O-(triphenylmethyl)-α-D-glucopyranoside (14.0 g, 15.4 mmol) in hot ethanoic acid (300 ml). The solution was heated under reflux for 30m., water (600 ml) was added, the cold solution was filtered, the solids washed with water, and the solvent removed in vacuo. A little methanol was added, then water to precipitate the remaining solid, the solution was filtered and the solvent removed in vacuo to give 2,3,4-tri-O-methyl-α-D-glucopyranosyl-2',3',4'-tri-O-methyl-α-D-glucopyranoside (6.55 g, 15.4 mmol, 100%) as an orange oil; $[\alpha]_D^{\circ}$ + 74.4° (c = 0.75, CH_3OH); ^{1}H-NMR δ (300 MHz, $CDCl_3$) 3.1 (4H, m, H_6), 3.4 (6H, s, OMe), 3.5 (6H, s, OMe), 3.6 (6H, s, OMe), 3.45-3.75 (6H, m, H_2, H_3, H_4), 3.85 (2H, m, H_5), 5.1 (2H, d, J 3.5 Hz, H_1); m/z (direct chemical ionisation) 429 (M^+).

2,3,4-Tri-O-methyl-6-O-methanesulphonyl-α-D-glucopyranosyl-2',3',4'-tri-O-methyl-6'-O-methanesulphonyl-α-D-glucopyranoside.

Methanesulphonyl chloride (2.0 ml, 25.7 mmol) was added dropwise to a stirred solution of 2,3,4-tri-O-methyl-α-D-glucopyranosyl-2',3',4'-tri-O-methyl-α-D-glucopyranoside (4.6 g, 10.8 mmol) and triethylamine (6.0 ml, 43 mmol) in dichloromethane (120 ml) at 0°. Stirring was continued at 0° for 1h, then the solution was washed with water (5 x 100 ml), dried over magnesium sulphate and the solvent removed in vacuo. Flash chromatography (eluant 90% ether/10% dichloromethane) gave 2,3,4-tri-O-methyl-6-O-methanesulphonyl-α-D-glucopyranosyl-2',3',4-tri-O-methyl-6'-O-methanesulphonyl-α-D-glucopyranoside 1 (3.95 g, 6.79 mmol, 62.8%) as a colourless plates. Recrystallization from dichloromethane/ether gave crystals suitable for X-ray crystallography. m.p. 136-7°; $[\alpha]_D^{\circ}$ + 152-3° (c = 0.681, CH_2Cl_2); found: C, 41.26; H, 6.52; $C_{26}H_{50}O_{15}S_2$ requires C, 41.24; H, 6.53%; ^{1}H-NMR δ (300 MHz, $CDCl_3$) 3.05 (6H, s, OMs), 3.1 (2H, m, H_4), 3.15 (2H, m, H_2), 3.45 (6H, s, OMe), 3.5 (2H, m, H_3), 3.6 (6H, s, OMe), 3.65 (6H, s, OMe), 4.1 (2H, m, H_5),m 4.4 (4H, m, H_6), 5.15 (2H, d, J 3.5 Hz, H_1); m/z (direct chemical ionisation) 582 (M^+).

6-O-(Triphenylmethyl)-β-D-glucopyranosyl-6'-O-(triphenylmethyl-β-D-glucopyranoside.

ββ-Trehalose (3.21 g, 9.38 mmol) and triphenylmethyl chloride (5.28 g, 18.9 mmol) were reacted together in pyridine (40 ml) to give 6-O-(triphenylmethyl-β-D-glucopyranosyl-6'-O-(triphenylmethyl)-β-D-glucopyranoside (6.14 g, 7.43 mmol, 79.2%) as a white solid; m.p. 146.5-8°; $[\alpha]_D^{\circ}$ - 35° (c = 0.571, pyridine); found: C, 72.27; H, 6.03; $C_{56}H_{56}O_{11}$ requires: C, 72.62; H, 6.10%; ^{1}H-NMR δ (300 MHz, $CDCl_3$) 3.0-3.5 (12H, m, H_2, H_3, H_4, H_5, H_6), 4.95 (2H, d, J 6 Hz, OH), 5.0 (2H, d, J 7.5 Hz, H_1), 5.1 (2H, d, J 5 Hz, OH), 5.3 (2H, d, J 5 Hz, OH), 7.2-7.55 (30H, m, Ph); m/z (field desorption) 826 (M^+).

2,3,4-Tri-O-methyl-6-O-(triphenylmethyl)-β-D-glucopyranosyl-2',3',4',-tri-O-methyl-6'-O-(triphenylmethyl-β-D-glucopyranoside

6-O-(Triphenylmethyl)-β-D-glucopyranosyl-6'-O-(triphenylmethyl)-β-D-glucopyranoside (85) (5.95 g, 7.20 mmol) was dissolved in dimethylformamide (60 ml) and iodomethane (15 ml, 23.6 mmol) and barium oxide (12.0 g, 7.8 mmol) were added with stirring. The solution was heated under reflux and further iodomethane (25 ml, 9.3 mmol) and barium oxide (18 g, 11.7 mmol) were added in three portions at intervals over 30h. After a total of 72h excess iodomethane was removed in vacuo and the red/brown residue was extracted with dichloromethane (3 x 400 ml) and water (8 x 300 ml). The red organic layer was washed with sodium thiosulphate solution, dried (anhydrous magnesium sulphate) and the solvent removed in vacuo. Crystallization of the residue from methanol/water gave methyl-6'-2,3,4-tri-O-methyl-6-O-(triphenylmethyl-β-D-glucopyranosyl-2',3',4'-tri-O-methyl6'-O-(triphenylmethyl)-β-D-glucopyranoside as a white solid (4.88 g, 5.36 mmol, 74.5%); m.p. 157-60°; $[\alpha]_D^{\circ}$ + 27.5° (c = 0.751, CH_2Cl_2); found: C, 73.70; H, 6.91; $C_{56}H_{62}O_{11}$ requires: C, 73.80; H, 6.81%; ^{1}H-NMR δ (300 MHz, $CDCl_3$) 3.05 (2H, dd, J_{6aS} 4 Hz, J_{6aS6b} 10 Hz, H_{6a}), 3.35 (6H, s, OMe), 3.25-3.5 (10H, m, H_2, H_3, H_4, H_5, H_{6b}), 3.7 (6H, s, OMe), 3.75 (6H, s, OMe), 4.85 (2H, d, J 7.5 Hz, H_1), 7.25-7.55 (30H, m, Ph); m/z (field desorption) 910 (M^+).

2,3,4-Tri-O-methyl-β-D-glucopyranosyl-2',3',4'-tri-O-methyl-β-D-glucopyranoside (87).

Water (4 ml) was added to a solution of 2,3,4-tri-O-methyl-6-O-(triphenylmethyl)-β-D-glucopyranosyl-2',3',4'-tri-O-methyl-6'-O-(triphenylmethyl)-β-D-glucopyranoside (86) (0.969 g, 1.06 mmol) in hot ethanoic acid (20 ml). The solution was heated under reflux for 40m, water (40 ml)

was added, the cold solution was filtered, the solids washed with water and the solvent removed in vacuo. A little methanol was added, then water to precipitate the remaining solid, the solution was filtered and the solvent removed in vacuo to give 2,3,4-tri-O-methyl-β-D-glucopyranosyl-2',3',4'-tri-O-methyl-β-D-glucopyranoside (0.427 g, 1.00 mmol, 93.9%) as an orange oil; $[\alpha]_D^{\circ}$ -16.5° (c = 0.81, CH_2Cl_2); ^{1}H-NMR δ (300 MHz, $CDCl_3$) 3.05-3.25 (8H, m, H_2, H_3, H_4, H_5), 3.55 (6H, s, OMe), 3.6 (6H, s, OMe), 3.65 (6H, OMe), 3.7 (2H, dd, J_{6a5} 4.5 Hz, J_{6a6b} 12.5 Hz, H_{6a}), 3.85 (2H, dd, J_{6b5} 2.5 Hz, J_{6b6a} 12.5 Hz, H_{6b}), 4.7 (2H, d, J 7 Hz, H_1); m/z (direct chemical ionisation) 426 (M^+).

2,3,4-Tri-O-methyl-6-O-methanesulphonyl-β-D-glucopyranosyl-2',3',4'-tri-O-methyl-6'-O-methanesulphonyl-β-D-glucopyranoside.

Methanesulphonyl chloride (0.50 ml, 6.42 mmol) was added dropwise to a stirred solution of 2,3,4-tri-O-methyl-β-D-glucopyranosyl-2',3',4'-tri-O-methyl-β-D-glucopyranoside (1.01 g, 2.37 mmol) and triethylamine (2.0 ml, 14.3 mmol) in dichloromethane (20 ml)/ether (25 ml) at 0°. Stirring was continued at 0° for 1h, then the solid was filtered off and washed with water (3 x 50 ml), dried (magnesium sulphate), and the solvent removed in vacuo. Flash chromatography [ether/dichloromethane (9:1) eluant] gave 2,3,4-tri-O-methyl-6-O-methanesulphonyl-β-D-glucopyranosyl-2',3',4'-tri-O-methyl-6'-methanesulphonyl-β-D-glucopyranoside 2(0.575 g, 0.988 mmol, 41:7%) after recrystallization from ether/petroleum ether. Colourless needles suitable for X-ray crystallography were obtained; m.p. 125-6°; $[\alpha]_D^{\circ}$ - 24.5° (c = 0.44, CH_2Cl_2); found: C, 41.63; H, 6.47; $C_{20}H_{38}O_{15}S_2$ requires C, 41.24; H, 6.53%; ^{1}H-NMR δ (300 MHz, $CDCl_3$) 3.05 (6H, s, OMs), 3.0-3.25 (6H, m, H_2, H_3, H_4), 3.45 (2H, m, H_5), 3.54 (6H, s, OMe), 3.57 (6H, s, OMe), 3.63 (6H, s, OMe), 4.4 (2H, dd, J_{6b5} 2 Hz, J_{6b6a} 11.5 Hz, H_{6b}), 4.5 (2H, dd, J_{6a5} 4.5 Hz, J_{6a6b} 11.5 Hz, H_{6a}), 4.65 (2H, d, J 7.5 Hz, H_1); m/z (direct chemical ionisation) 582 (M^+).

X-ray analysis

Data were measured with graphite-monochromated Cu-K_α radiation on an Enraf- Nonius Cad-4 diffractometer operating in the ω-2θ scan mode. Three standard reflections measured every hour showed no appreciable variation with time. Lorentz and polarization corrections were applied but no correction was made for absorption.

Both structures were solved by direct methods,[5] the refinements were carried out by least squares routines.[6] During the course of the refinement it was observed that in both 1 and 2 one of the methanesulphonyl groups exhibited disorder and two orientations of this group were refined whilst applying restraints.[7,8] Site occupation factors (constrained to add up to 1) were refined for the two orientations and these converged to 0.67(1) and 0.33(1). Anisotropic temperature factors were used for the sulphur atoms and for the non disordered non hydrogen atoms, the disordered atoms were assigned a common isotropic temperature factor. Hydrogen atoms were located, but were placed in calculated positions (C-H = 1.00A) 'riding' on their respective carbon atoms. Refinement was terminated when all shifts were <0.1σ. Scattering factors were taken from International Tables for crystallography.[9,10] Details of crystals and experimental parameters are in Table 1.

Computations were carried out on a Vax 11/750 computer.

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