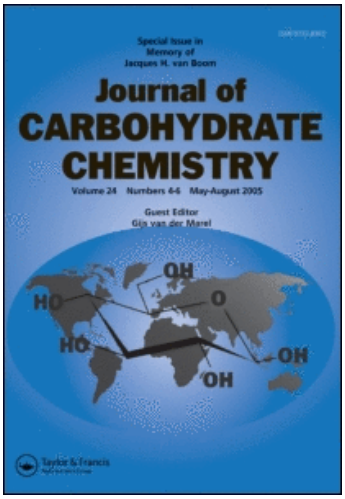

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Microsynthesis of Dianhydrohexitols

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MICROSYNTHESES OF DIANHYDROHEXITOLS

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ABSTRACT

Conditions have been established for the microsyntheses of dianhydrohexitols by reaction of 1,4-monoanhydro-D,L-galactitols and 1,5-monoanhydro-D-galactitol as well as of 1,4- and 1,5-monoanhydro-D-glucitols and -D-mannitols with tosyl chloride in pyridine followed by cyclization of the resulting 6-*O*-tosyl derivatives in methanolic solution of sodium methoxide. The dianhydrohexitols were formed by intramolecular nucleophilic substitution of the C-6 *O*-tosyl group with a properly stereochemically oriented hydroxyl group.

Components of the mixtures were separated by capillary gas chromatography using columns coated with SP-2340 and identified by GC-MS. The identities of the synthesized dianhydrohexitols were confirmed by comparison with the GC retention times and mass spectra of authentic samples.

INTRODUCTION

Alditols, anhydroalditols and their derivatives are known compounds of the family of carbohydrates.[1,2] Some of them occur in plants[3] as well as in cerebrospinal fluid in animals.[4-6] Others have found medicinal uses, e.g., D-mannitol is an effective brain antioedemic agent,[7] 1,2:5,6-dianhydro-D-galactitol (DAG) is a renowned anticancer agent,[8] and 1,4:3,6-

dianhydro-D-mannitol is a completely non-toxic diuretic.[9] In the cerebrospinal fluid these compounds are identified by a capillary column GC-MS method.[6] Some difficulties are usually experienced when assigning relative configurations to the detected mono- and di-anhydrohexitols, due to lack of significant differences in the mass spectra of their configurational isomers. The GC-MS determination of the configurational isomers is possible by comparison of the compounds with those of known standards .

Classical methods of the preparative syntheses of particular standards by dehydration of the hexitols in acidic medium,[10-12] reduction of 1-bromo-1-deoxy-per-*O*-acetylhexopyranoses with $LiAlH_4$,[13] reduction of sulfur-containing glycosides over Raney nickel[14] or cyclization of the mono-*O*-tosyl derivatives of 1,5-anhydrohexitols in methanolic solution of sodium methoxide[15,16] are time-consuming and often deceptive. Therefore, there is a need for the development of simple and rapid methods for synthesis of these compounds even without their separation. The compounds obtained in this way on the micro-scale, could be used as standards in gas chromatography.

Methods of the synthesis of dianhydrohexitols are reported herein.

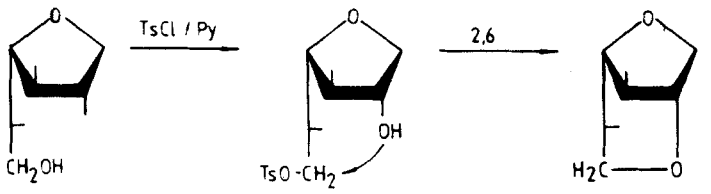
RESULTS AND DISCUSSION

Both the regioselectivity of *O*-tosylation of sugar derivatives and the results of cyclization of the pentitols via their *O*-tosyl derivatives[17] were utilised for the preparation of dianhydrohexitols. Heating of the corresponding monoanhydrohexitols with tosyl chloride in pyridine at 100 °C for 2 h gave intermediate 6-*O*-tosyl derivatives which underwent intramolecular nucleophilic substitution by properly stereochemically oriented hydroxyl groups (Scheme 1, 1a, FIG. 1 and reaction 1a, described in the Experimental section).

The dianhydrohexitols were identified by the GC-MS method and by comparison with standard retention times of known compounds. Two representative mass spectra, from a total of six recorded, (FIG. 2,3) permit unambiguous confirmation of the dianhydrohexitol structure of the compounds owing to common characteristic fragment-ions at *m/z* 230 (M), *m/z* 170 (M-AcOH) and m/z 110 (M- 2xAcOH).

The standards were prepared both on the macro scale (1,4:3,6-dianhydro-D-glucitol[18] and -D-mannitol[16]), and on the micro scale (reaction 3). In the latter instance the standards were formed by cyclization of 6-*O*-

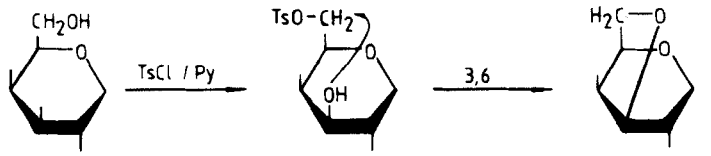
a /



1,4 - anhydro - -D - GALACTITOL

1,4 ; 2,6 - dianhydro - - D - GALACTITOL

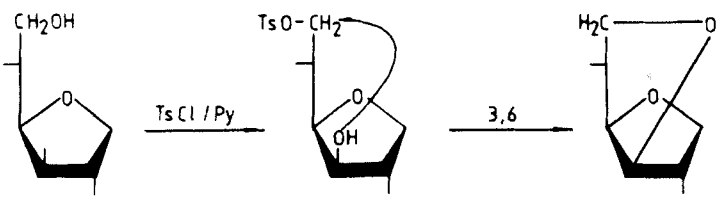
b /



1,5 -anhydro - - D - GALACTITOL

1,5 ;3,6 - dianhydro - -D - GALACTITOL

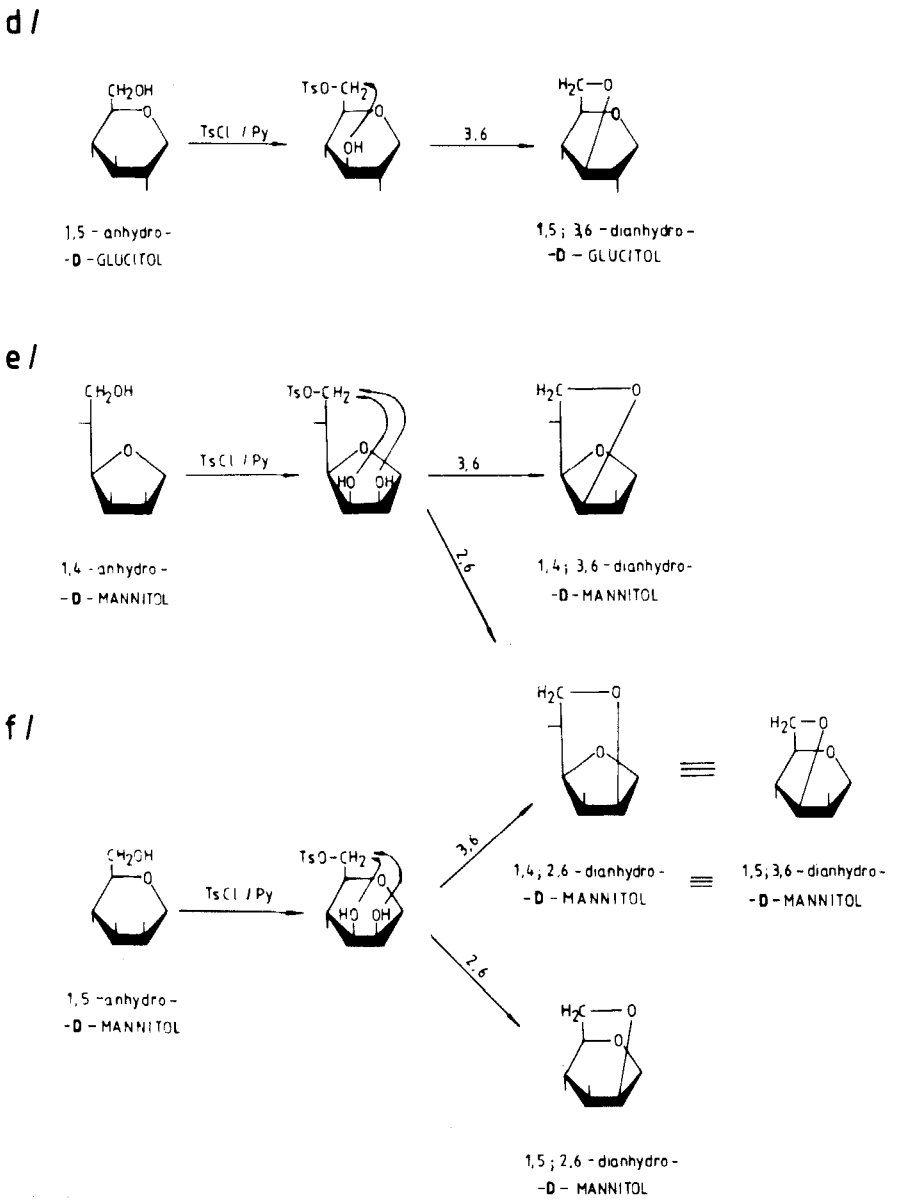
c /



1,4 - anhydro - -D - GLUCITOL

1,4 ; 3,6 - dianhydro - - D - GLUCITOL

SCHEME 1



SCHEME 1a

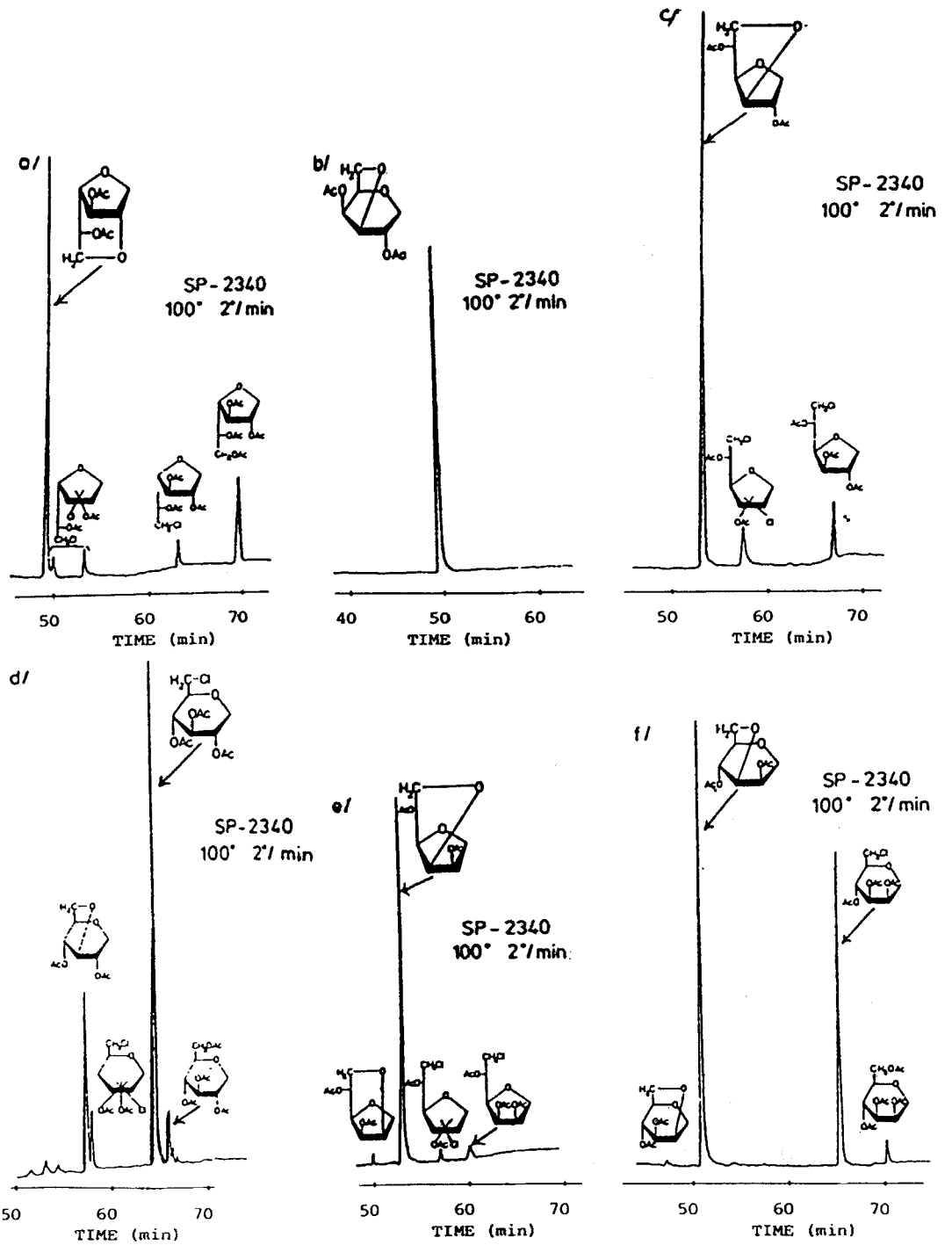


FIG. 1. Gas chromatograms of the products obtained in reaction 1a from: a/ 1,4-anhydro-D,L-galactitol, b/ 1,5-anhydro-D-galactitol, c/ 1,4-anhydro-D-glucitol, d/ 1,5-anhydro-D-glucitol, e/ 1,4-anhydro-D-mannitol, f/ 1,5-anhydro-D-mannitol.

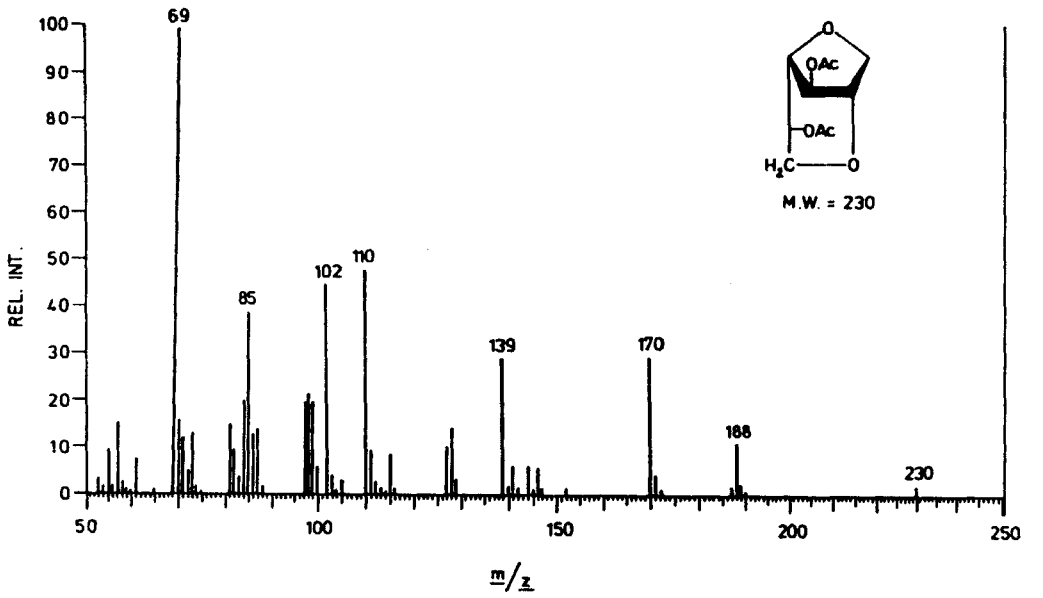


FIG. 2. The mass spectrum of per-O-acetyl-1,4 : 2,6-dianhydro-D-galactitol.

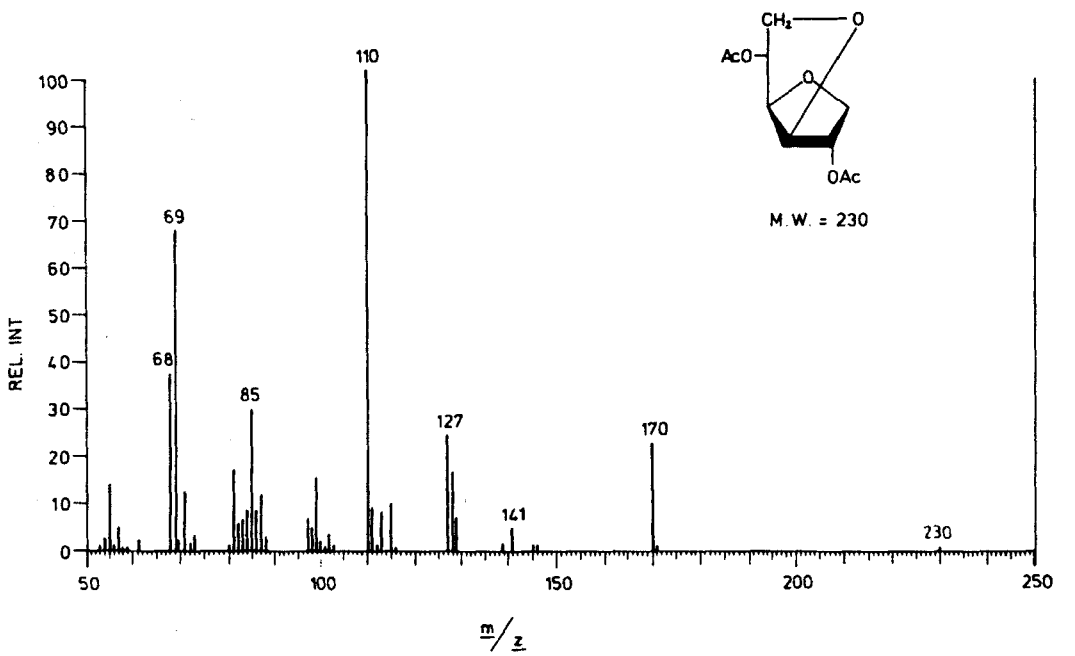


FIG. 3. The mass spectrum of per-O-acetyl-1,4 : 3,6-dianhydro-D-glucitol.

tosyl-2,3,4-tri-*O*-benzoyl-1,5-anhydro-D-galactitol,[15] -D-glucitol[16] and -D-mannitol[16] in a solution of sodium methoxide in methanol with retention of the configuration of all asymmetric carbon atoms (reaction 3).

Along with the expected dianhydrohexitols, monochloro derivatives of 1,4- and 1,5-anhydrohexitols, accompanied by small amounts of dichloro derivatives appeared in almost all of the derivatives (with the exception of the products derived from 1,5-anhydro-D-galactitol; FIG. 1b).

The structures of the 6-chloro-6-deoxy-1,4- and 1,5-anhydrohexitols were established on the basis of their mass spectra and fragmentation patterns, which gave *inter alia* the following diagnostic fragment-ions; *m/z* 273 (M-Cl), *m/z* 146/148 (M- 2xAcOH - CH_2CO) and *m/z* 187 (M-$ClCH_2CHOAc$), (Table 1/I-IV).

The structures of dichlorodideoxy monoanhydrohexitols were established on the basis of GC retention times[17] and mass spectra. Hence the ions at *m/z*193/195 (M-CH_2Cl - CH_2CO), *m/z* 163/165 (M-$ClCH_2CHOAc$), (Table 1/V), *m/z* 235/237 (M- CH_2Cl), *m/z* 163/165 (M-$ClCH_2CHOAc$), (Table 1/VI), as well as the missing ion of *m/z* 187 in both spectra (Table 1/V-VI) and the GC retention times revealed the presence of two chlorine atoms in the molecule, one at C-6 and the other at one of the carbon atoms in the monoanhydrohexitol ring.

The monochloro- and dichloro-derivatives of 1,4- and 1,5-anhydrohexitols resulted from the nucleophilic attack of the chloride anion, released during tosylation, on the carbon atoms attached to the *O*-tosyl groups.[17]

The conditions described in reaction 1a for cyclization of monoanhydrohexitols were unsatisfactory in certain cases (e.g., cyclization of 1,5-anhydro-D-glucitol; FIG. 1d). However, the use of a solution of sodium methoxide in methanol (reaction 1b) may cyclize the undesired 6-chloro-6-deoxy-1,5-anhydro-D-glucitol, to afford the expected 1,5:3,6-dianhydro-D-glucitol in a satisfactory yield (FIG. 4a).

Recently we developed better conditions for the selective synthesis of dianhydrohexitols. Tosylation of the monoanhydrohexitols using TsCl at room temperature (1:1.1 molar ratio of the reactants) and directly cyclizing the post-reaction mixture with a solution of sodium methoxide in methanol (1:1 molar ratio, reaction 2) ensured the formation of the expected dianhydro-compounds free of any side products (FIG. 4b).

The dianhydrohexitols obtained in this way, after acetylation, can be directly used as standards for GC analysis. .

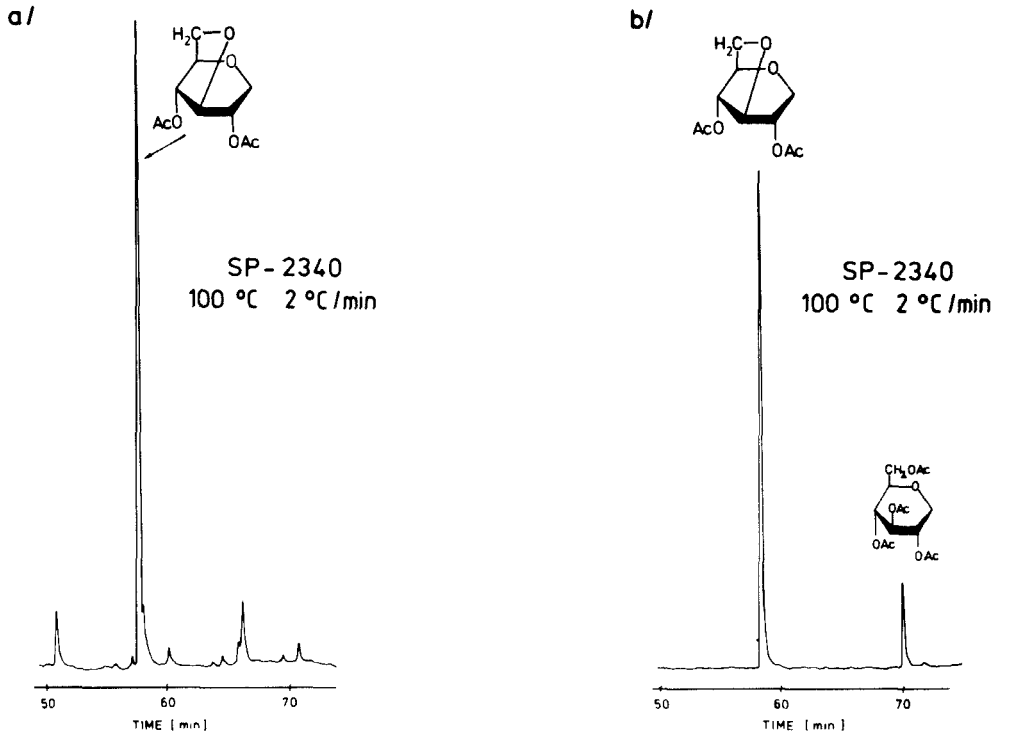


FIG. 4. Gas chromatograms of the products obtained in a/ reaction 1b , b / reaction 2.

TABLE 1. Electron-impact mass spectra (*inter alia*) of per-O-acetylated derivatives of 6-chloro-6-deoxy-1,5-anhydro-D-glucitol (I), -1,5-anhydro-D-mannitol (II), -1,4-anhydro-D-glucitol (III), -1,4-anhydro-D-mannitol (IV), dichloro-dideoxy-1,4-anhydrohexitol (V), -1,5-anhydrohexitol (VI).

	Relative intensities (%)					
m/z	I	II	III	IV	V	VI
308/310	2.5/1	1/0.3	-	-	-	-
273	48	100	1	3	-	-
259	8	11	15	8	-	-
235/237	-	-	-	-	-	6/2
206/208	12/4	18/6	-	-	-	-
193/195	-	-	-	-	27/9	-
187	34	27	78	96	-	-
163/165	-	-	6/2	6/2	100/32	55/30
146/148	80/32	63/22	15/5	12/4	9/3	9/3
139	100	33	13	9	-	11
127	55	32	36	28	41	5
115	29	16	100	100	-	100

EXPERIMENTAL

Reaction 1. (a) 4.92 mg ($3x10^{-5}$ mol) of each of the following anhydrohexitols: 1,4-anhydro-D,L-galactitol, -D-glucitol, -D-mannitol and 1,5-anhydro-D-galactitol, -D-glucitol,and -D-mannitol together with 11.46 mg ($6x10^{-5}$ mol) of *p*-toluenesulphonyl chloride (TsCl) were placed in screw-capped glass vials. To each vial, 0.3 mL of dry, freshly distilled pyridine was added and the mixtures were maintained at 100 °C for 2 h. After the mixtures were cooled, the pyridine was expelled in a nitrogen stream and the residue was acetylated with 0.3 mL of acetic anhydride in the presence of anhydrous sodium acetate at 100 °C for 1 h.

(b) After removal of the solvent, the tosylated product was dissolved in 0.1 mL of absolute methanol and to the solution was added 0.3 mL of the 0.31 M methanolic solution of sodium methoxide to adjust the measured pH to 8-9. The resulting solution was heated at 70 °C for 2 h. The solution was neutralized (N H_2SO_4), concentrated to dryness in a nitrogen stream and acetylated as in 1a.

Reaction 2. 1,5-Anhydro-D-glucitol (4.9 mg = $3x10^{-5}$ mol) and TsCl (6.3 mg = $3.3x10^{-5}$ mol) were dissolved in 0.3 mL of pyridine and left for 24 h at room temperature, after which 0.3 mL of acetic anhydride was added and the mixture was again left for 24 h. Subsequently, 1.5 mL of chloroform and 2 mL of water were added; the chloroform layer was washed with a saturated aqueous $NaHCO_3$ solution, and dried over $MgSO_4$. The chloroform solution was filtered, concentrated to dryness in a nitrogen stream, and 0.2 mL of absolute methanol and 0.1 mL of the 0.032 M methanolic solution of sodium methoxide were added and the resulted solution heated at 70 °C for 2 h. The solution was cooled, neutralized (N H_2SO_4), concentrated to dryness in a nitrogen stream, and acetylated.

Reaction 3. 1,5-Anhydro-2,3,4-tri-*O*-benzoyl-6-*O*-tosyl-D-galactitol (20 mg = $3.2x10^{-5}$ mol), or -D-glucitol or -D-mannitol was dissolved in 0.2 mL of methanolic solution of sodium methoxide ($3.5x10^{-5}$ mol) and the solution heated at 68-70 °C for 2 h. With the 1,5-anhydro-D-galactitol derivative dissolved in 0.6 mL of $CHCl_3$ the reaction was conducted at room temperature for 3 days. The solutions were than neutralized (N H_2SO_4), concentrated to dryness in a nitrogen stream and acetylated.

The products of these reactions were analyzed by GC-MS.

Reactants. The following reactants were synthesized according to the referenced methods: 1,4-anhydro-D-glucitol,[11] 1,4-anhydro-D-mannitol,[12] 1,5-anhydro-D-galactitol,[13] 1,5-anhydro-D-glucitol,[13] 1,5-anhydro-D-manni-

tol,[14] 6-*O*-tosyl-2,3,4-tri-*O*-benzoyl-1,5-anhydro-D-glucitol,[16] -D-galactitol[15] and -D-mannitol.[16] *p*-Toleunesulphonyl chloride was freshly crystallized from ether.

The racemic **1,4-anhydro-D,L-galactitol** was synthesized as follows: 10 g of crystalline galactitol in 40 mL of concentrated HCl was refluxed for 24 h. The solution was then concentrated at diminished pressure to a dense syrup which was dissolved in 40 mL of water. After addition of 1 g of charcoal, the suspension was heated for 10 min; the charcoal was filtered off and the solution was concentrated at diminished pressure to a dense syrup which was dissolved in 50 mL of absolute ethanol. The precipitate was filtered off. After the filtrate was cooled, a crystalline product was obtained which, after repeated crystallization from ethanol, gave 2.6 g of colourless crystals. After careful washing with ether the melting point was determinated to be at 69-71 °C, (about 25 °C lower than the 1,4-anhydro-D-galactitol[15]). The compound was optically inactive. After acetylation the product displayed an identical mass spectrum and GC retention time as the authentic derivative of 1,4-anhydro-D-galactitol.

Gas chromatography. The instrument used was a CHROMATRON model GCHF 18.3 Gas-Chromatograph equipped with a flame ionization detector and a glass capillary column (40 m x 0.3 mm) coated with SP-2340 on barium carbonate. Hydrogen was used as a carrier gas. The temperature of the detector and the injection port were both held at 250 °C. The temperature program was: 100 °C, 2 °C/min.

Gas chromatography - mass spectrometry. Mass spectra were obtained on a Hewlett-Packard GC-MS System model 5992 B instrument equipped with a packed column (0.7 m x 0.2 cm) with a mixed phase of 2 % OV-101 and 0.2 % Carbowax 20M on Chromosorb WHP 80-100 mesh. The injection port temperature was 240 °C. The mass spectrometer was equipped with a jet separator. An electron beam of 70 eV was used for ionization

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