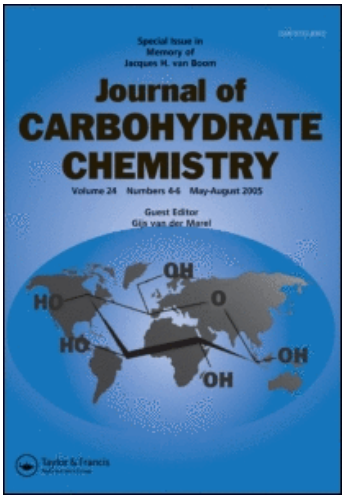

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Cyclization of Pentitols in Pyridine Via Their *O*-Tosyl Derivatives

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CYCLIZATION OF PENTITOLS IN PYRIDINE VIA THEIR O-TOSYL DERIVATIVES

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ABSTRACT

Heating of equimolar quantities of pentitols with *p*-toluenesulfonyl (tosyl) chloride in pyridine at 60 °C for 4 h afforded 1,4- or 2,5-monoanhydropentitols, which retained configuration of the asymmetric carbon atoms 2 or 4, together with small amounts of products with altered configuration at these centers. Variation of the reaction conditions by using a triple-molar excess of tosyl chloride and elevation of the temperature up to 115 °C gave mainly 1,4-anhydro-5-chloro-5-deoxy-pentitols and small amounts of 1,4-anhydro-2,5- and 3,5-dichloro-2,5- and 3,5-dideoxy-pentitols. The stereochemistry of the molecule of D-arabinitol was shown to favor the formation of 1,4:2,5-dianhydro-D-arabinitol, a compound with two tetrahydrofuran rings. All mixtures were separated by capillary GC, and their components were identified by co-injection of standards by GC-MS.

INTRODUCTION

Dehydration of alditols in an aqueous medium containing hydrochloric acid or sulfuric acid has been extensively studied.[1-16] The rate of acid catalyzed dehydration of alditols and the accompanying retention or inversion of configuration of the asymmetric carbon atoms are strongly influenced by the relative degree of protonation of primary and/or secondary

hydroxyl groups[12,15] as well as by the ease of abstraction of the water molecule from the oxonium ion formed.

In a basic medium, an analogous cyclization-dehydration process has been observed and studied both with alditols and monosaccharides[17-20] using their mono-*O*-tosyl derivatives as reactants.

Of particular interest to our research was the cyclization of a monosaccharide or polyol during *p*-toluenesulfonylation (tosylation) in dry pyridine, a reaction which has been previously observed.[21,22]

RESULTS AND DISCUSSION

Heating of equimolar quantities of pentitols with *p*-toluenesulfonyl (tosyl) chloride at 60 °C during 4 h gave 1,4- or 2,5- five-membered anhydro-compounds. With D-arabinitol as a reactant, 1,4-anhydro-D-arabinitol and 2,5-anhydro-D-arabinitol (equivalent to 1,4-anhydro-D-lyxitol), compounds with retained configuration of the C-4 and C-2 atoms, were found as the major products as determined by gas chromatographic (GC) analysis of their per-*O*-acetyl derivatives (FIG. 1a), in which a comparison was made with the retention times of known samples. Similarly, xylitol and ribitol were shown to afford 1,4-anhydro-D,L-xylitol (FIG. 1b) and 1,4-anhydro-D,L-ribitol, respectively (FIG. 1c). Simultaneously, small amounts of 1,4-anhydropentitols with inverted configuration at C-4 and C-2 (FIG. 1a, 1b, 1c) as well as 1,5-anhydropentitols (FIG. 1a) were found. The compounds were formed from pentitols presumably via their mono-*O*-tosyl derivatives. The most favorable reaction in this case should be one of *O*-tosylation of the terminal primary hydroxyl groups. Again, the cyclization occurs via intramolecular nucleophilic attack of the oxygen atom of an appropriate hydroxyl group on the carbon atom bound with the *O*-tosyl residue (Scheme 1). The excellent reactivity of the *O*-tosyl systems attached to primary terminal carbon atoms in linear pentitol derivatives is responsible for lack of well-shaped peaks of these compounds on the chromatograms (FIG. 1a, 1b, 1c).

Intramolecular cyclization, which occurs by intramolecular nucleophilic displacement, accounts for the number and configurations of the 1,4-anhydropentitols formed. In the case of the attack of the oxygen atom from the C-2-OH or C-4-OH groupings onto carbons C-5 or C-1, configuration is retained (cf. major products in Scheme 1), whereas during the attack of the oxygen atom from the C-1-OH or C-5-OH groupings onto the asymmetric C-4 or C-2 atoms, inversion of configuration results (Scheme 1).

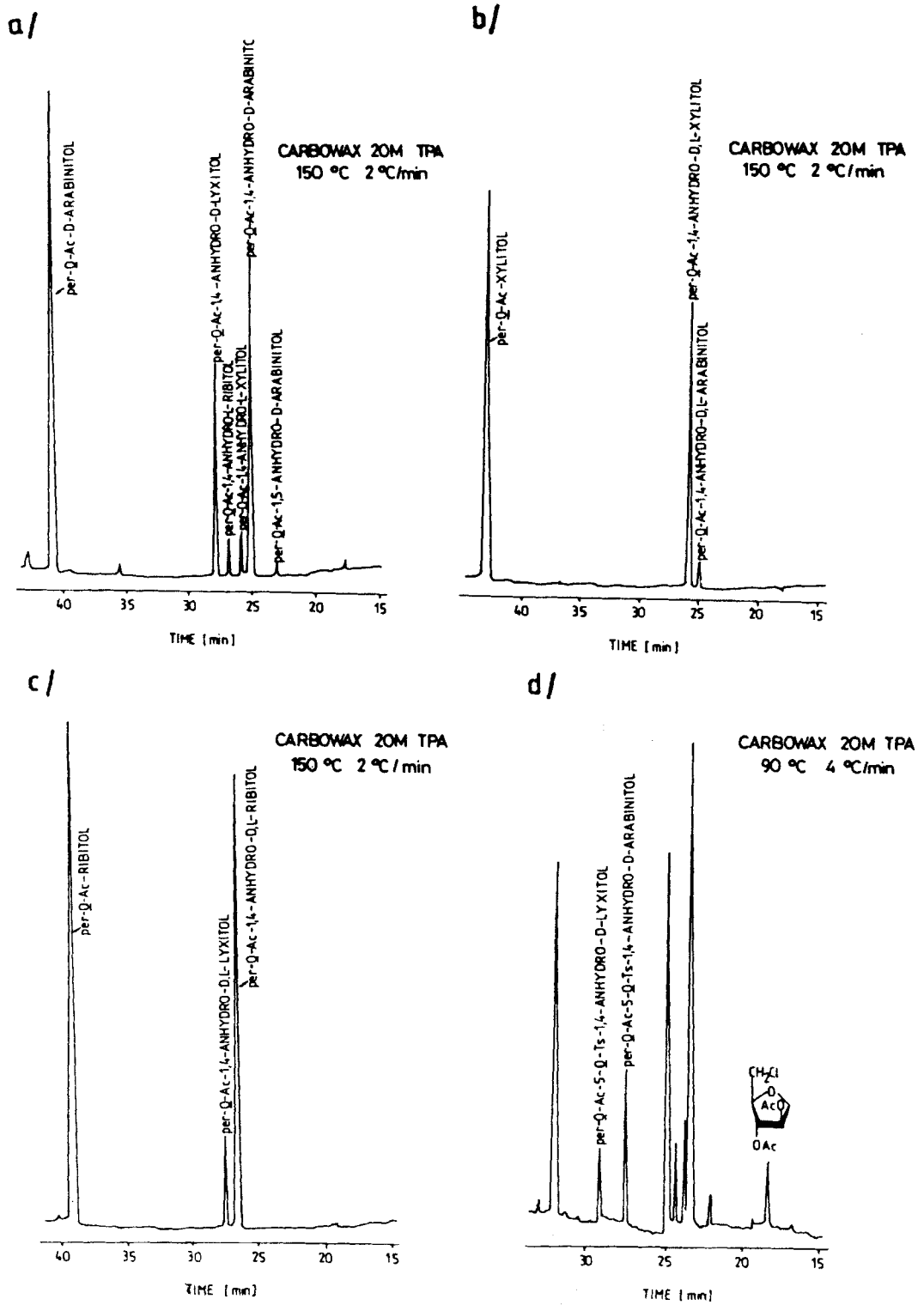


FIG. 1. a/ GC of dehydration products of D-arabinitol (according to reaction 1), b/ GC of dehydration products of xylitol (according to reaction 1), c/ GC of dehydration products of ribitol (according to reaction 1), d/ GC of dehydration products of D-arabinitol (according to reaction 2)

SCHEME 1

Raising the tosyl chloride concentration in the reaction mixture (molar ratio of the reactants 1:1.5) resulted in the formation of small amounts of 5-*O*-tosyl-1,4-anhydropentitols with the configuration of asymmetric carbon atoms retained. These products were 5-*O*-tosyl derivatives of products of the main dehydration pathways of pentitols with the D-arabino and D-lyxo configuration (FIG. 1d, Scheme 2).

Increasing of both the tosyl chloride concentration (molar ratio 1:3) and the temperature (115 °C) opens up new perspectives for the reaction. There appears the possibility of repeated cyclization in 5-*O*-tosyl-1,4-anhydropentitols leading in principle to bicyclic compounds with either a tetrahydrofuran (formed via 2,5-dehydration) or an oxetane (formed via 3,5-dehydration) ring.

1,4:2,5-Dianhydro-D-arabinitol with two tetrahydrofuran rings in the molecule, appeared among the dehydration products of D-arabinitol. Its structure was elucidated by both the method of standard co-injection[23] and by inspection of its mass spectrum (FIG. 2a). The compound was formed either by intramolecular 2,5-cyclization of 5-*O*-tosyl-1,4-anhydro-D-arabinitol or 5-*O*-tosyl-1,4-anhydro-D-lyxitol (FIG. 2a, Scheme 3).

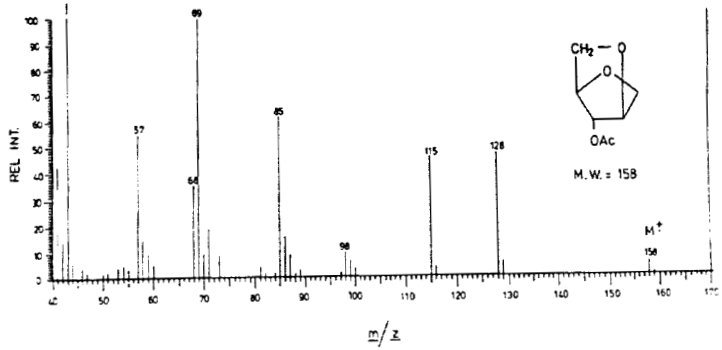
During dehydration of xylitol, dianhydro compounds were missing, apparently indicating the difficulties inherent in the formation of a 4-membered oxetane ring. A similar explanation can be offered for the absence of bicyclic species with the second oxetane ring among the dehydration products of D-arabinitol. These species could be formed either by 3,5-cyclization of 1,4-anhydro-D-lyxitol or 1,4-anhydro-L-xylitol (Scheme 1).

A competitive reaction relative to the intramolecular cyclization of 5-*O*-tosyl-1,4-anhydropentitols is that of nucleophilic substitution of the *O*-tosyl residue by the chloride ion liberated during tosylation. Its products are 5-chloro-5-deoxy-1,4-anhydropentitols (FIG. 3, Scheme 4). The number of these products agrees well with of 5-*O*-tosyl-1,4-anhydropentitols being formed. Their structure had previously been established by ^{1}H NMR spectroscopy[14] and are now confirmed by their mass spectra (FIG. 2b, Scheme 5).

The use of a large excess of tosyl chloride (molar ratio 1:3) led to a complex mixture of products (FIG. 3). The location of unidentified compounds of this mixture in the sequence of elution suggested the presence of dichloro-derivatives of the 1,4-anhydropentitols.

All the mass spectra of this group of compounds could be divided into two groups (FIG. 2c, 2d) according to the types of structural isomers of dichloro-dideoxy-1,4-anhydropentitols. A common, and at the same time diagnostic, feature for both types of the spectra is the presence of a

a/



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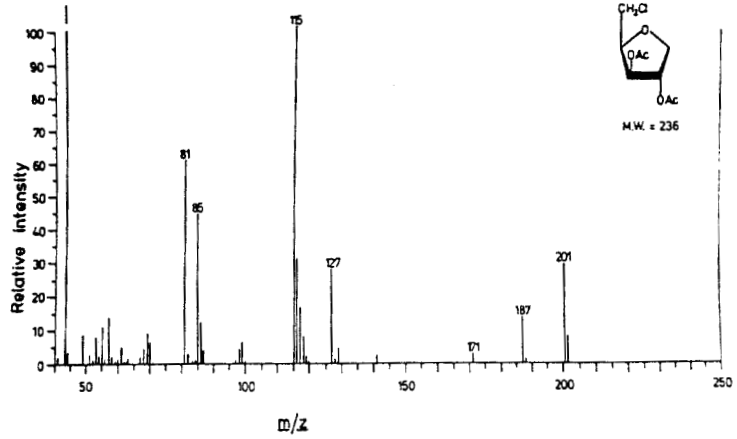


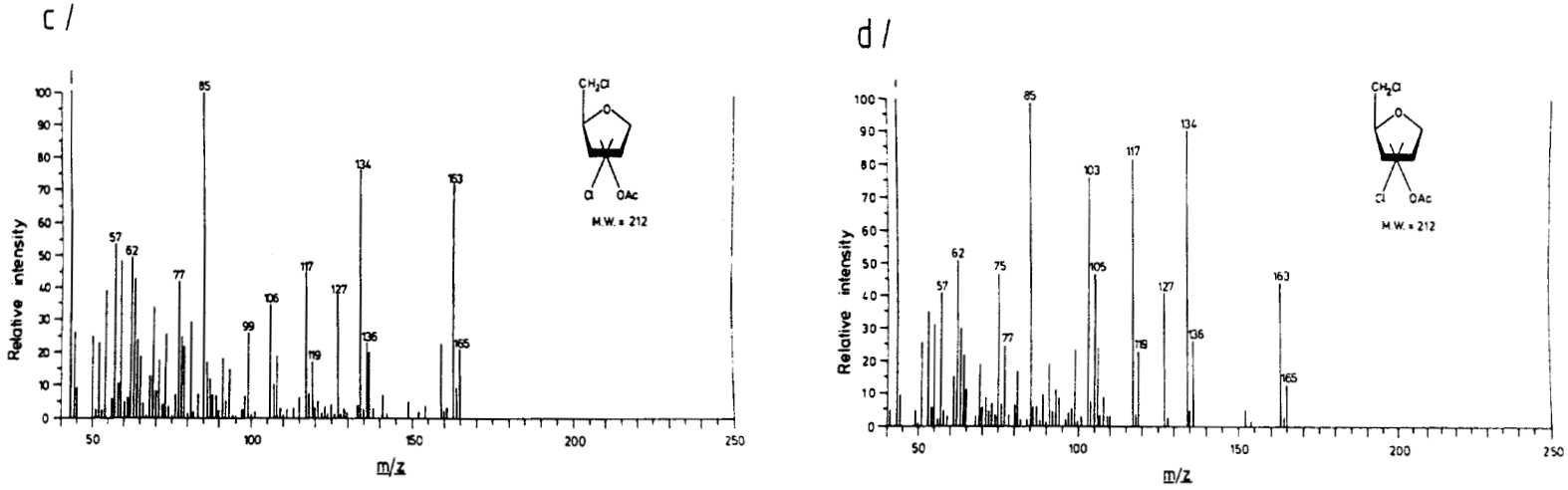
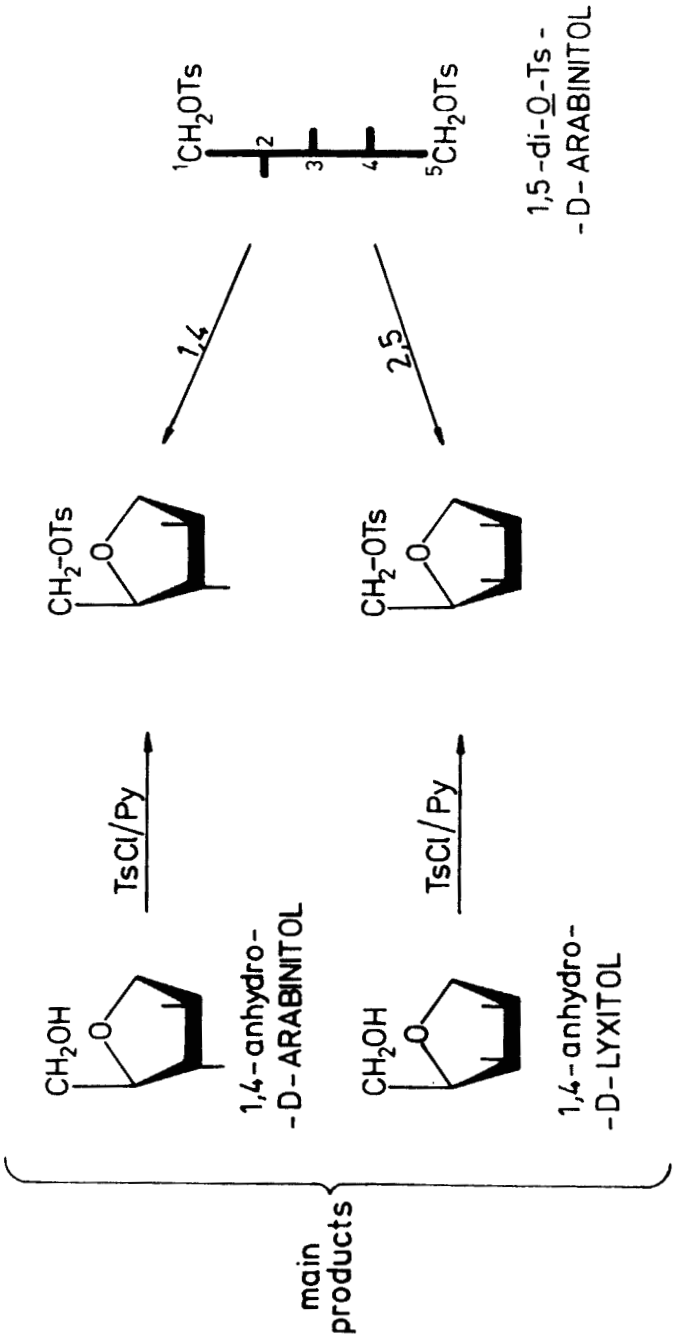
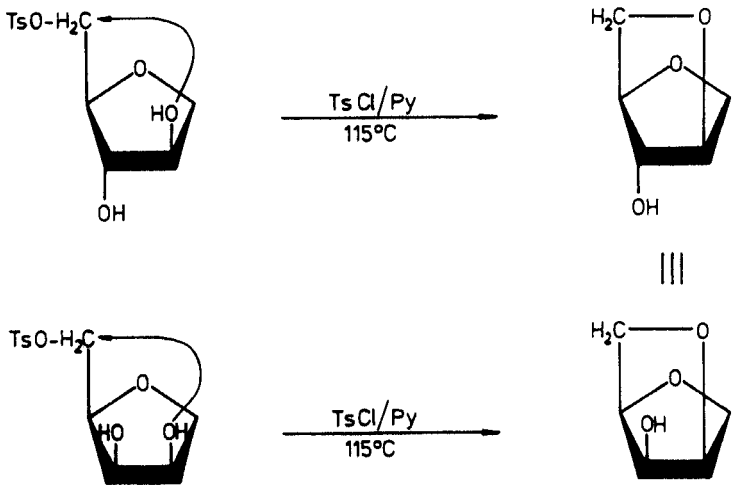


FIG. 2. Mass spectra of per-*O*-acetylated derivatives of : a/ 1,4:2,5-di-anhydro-D-arabinitol, b/ 5-chloro-5-deoxy-1,4-anhydroxylitol, c/ isomeric 5-chloro-5-deoxy-2(or 3)-chloro-2(or 3)-deoxy-1,4-anhydropentitol, d/isomeric 5-chloro-5-deoxy-2(or 3)-chloro-2(or 3)-deoxy-1,4-anhydropentitol.



SCHEME 2



SCHEME 3

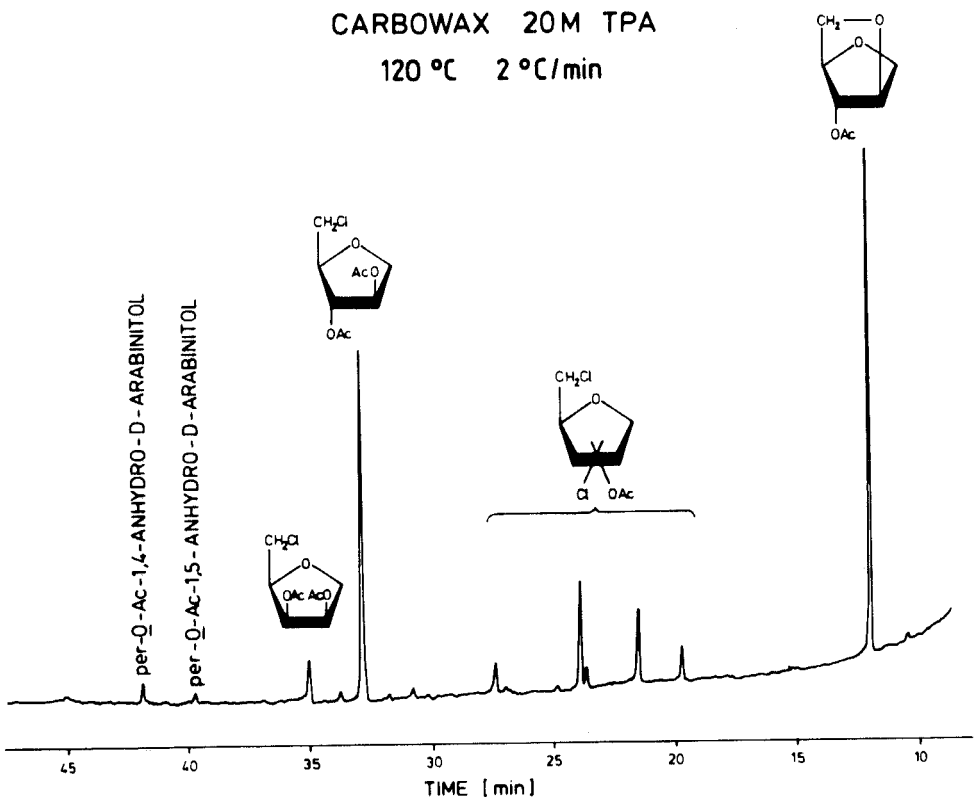
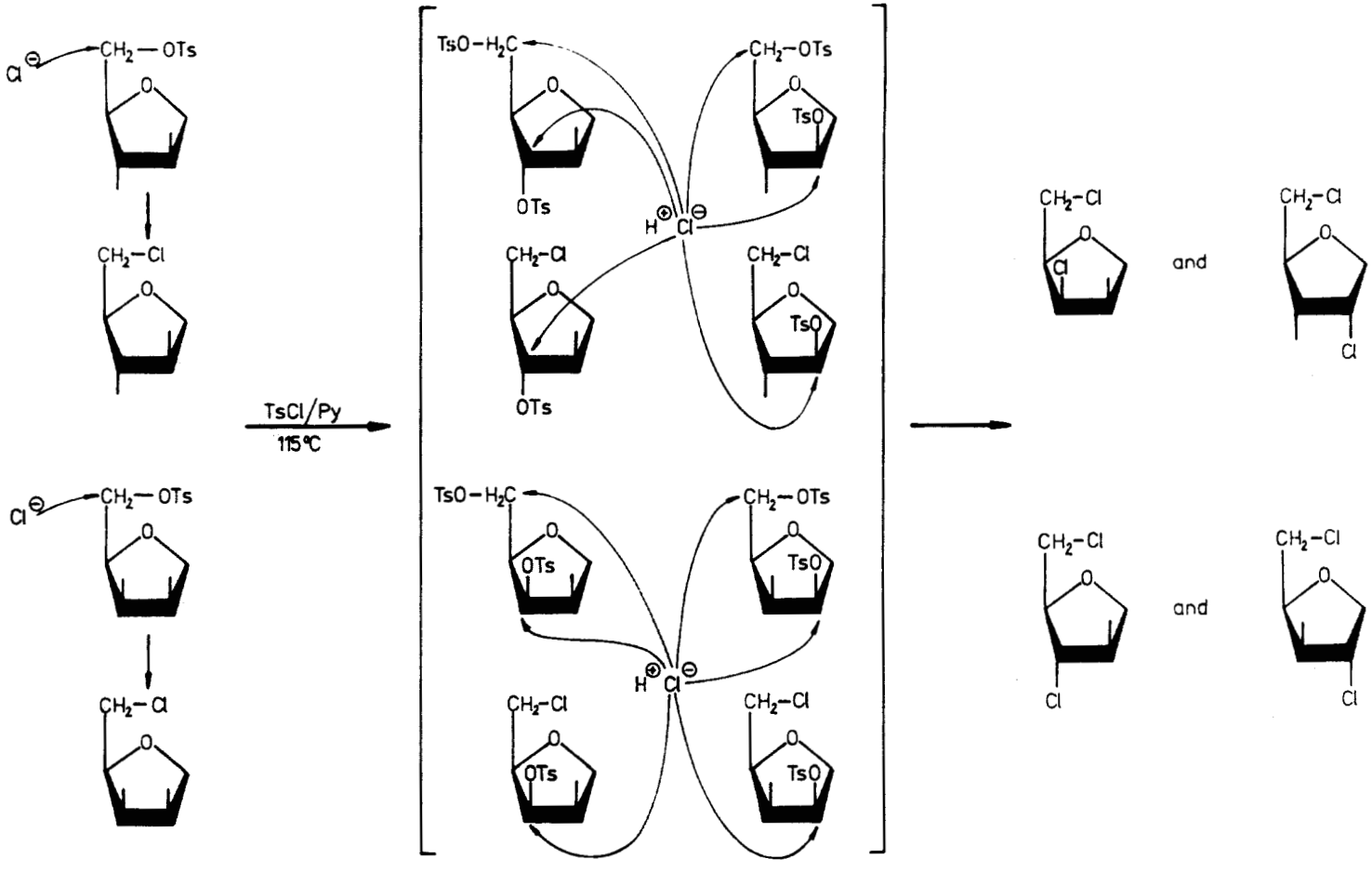
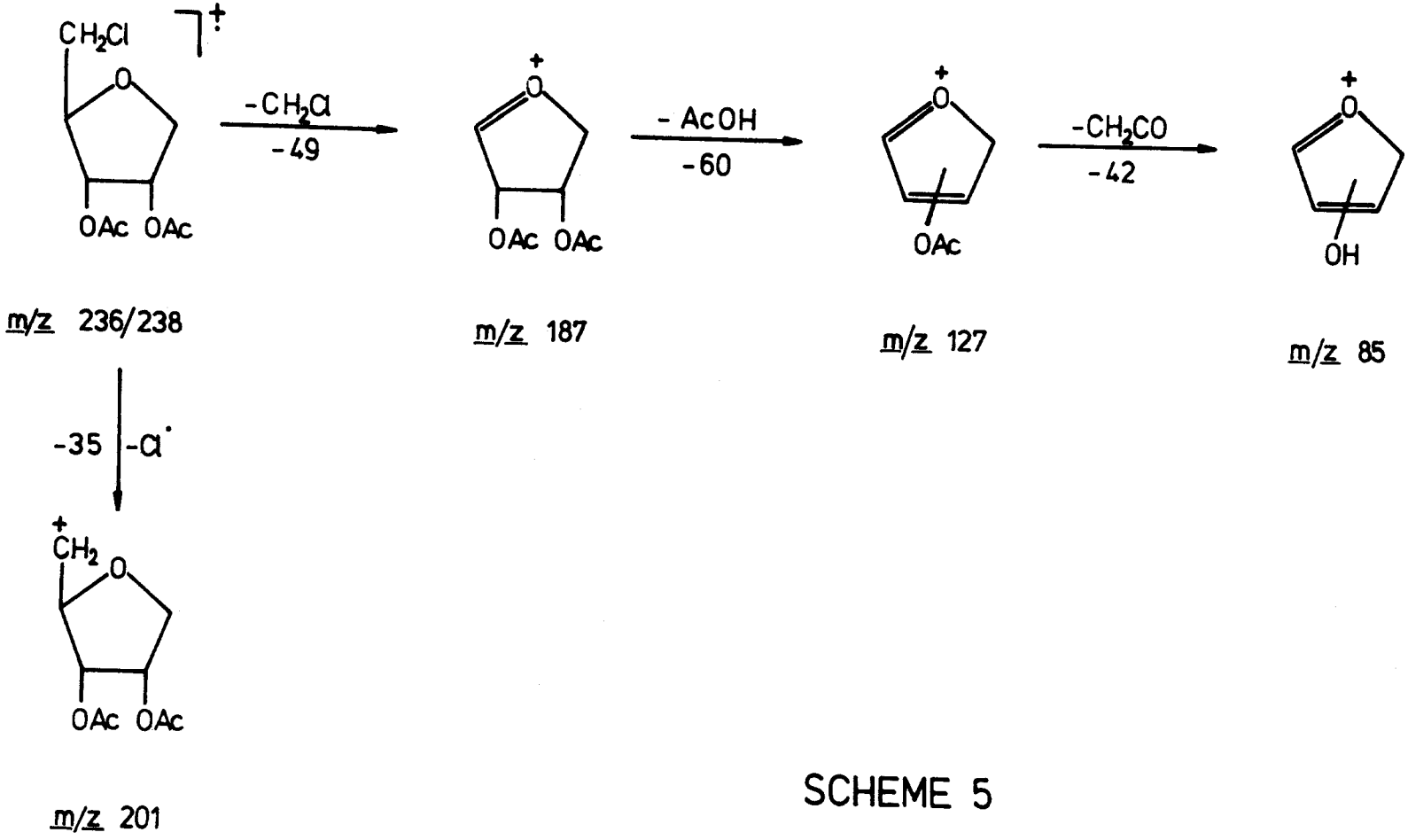


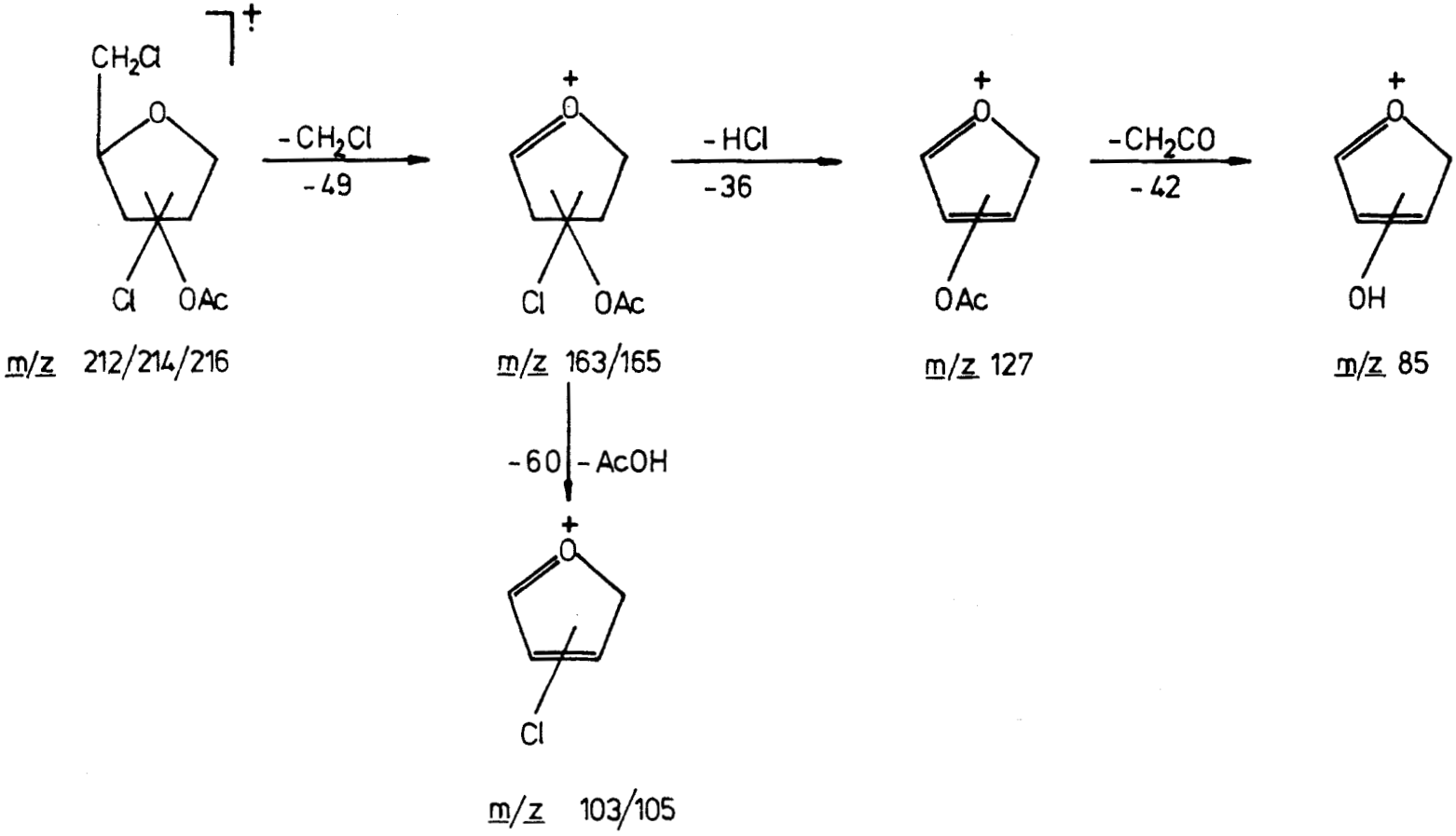
FIG. 3. GC of dehydration products of D-arabinitol (according to reaction 3).



SCHEME 4



SCHEME 5



SCHEME 6

fragment ion *m/z* 163/165 (3:1, M-CH_2Cl), thus revealing chlorine atom in the tetrahydrofuran ring (Scheme 6).

These compounds probably resulted from *O*-tosylation of the secondary hydroxyl groups, thus leading to the formation of di-*O*-tosyl derivatives of 1,4-anhydropentitols carrying the *O*-tosyl groups at C-5 as well as C-2 or C-3. Nucleophilic substitution of the *O*-tosyl residues for chlorine atoms affords 5-chloro-5-deoxy-2(or 3)-chloro-2(or 3)-deoxy-1,4-anhydropentitols (FIG. 3, Scheme 4).

EXPERIMENTAL

Reaction 1. In a screw-capped glass ampoule were placed, 7.7 mg (0.05 mmole) of the appropriate pentitol (D-arabinitol, xylitol or ribitol), 9.5 mg (0.05 mmole) of *p*-toluenesulfonyl chloride (tosyl chloride) and 0.5 mL of dry pyridine. This mixture was maintained at 60 °C for 4 h and then cooled to room temperature. Pyridine was removed in a stream of nitrogen, and 0.5 mL of freshly distilled acetic anhydride and ca. 10 mg of anhydrous sodium acetate were added. The mixture was heated at 100 °C for 1 h and analyzed by capillary GC.

Reaction 2. The above-described procedure was employed with the exception that the quantity of tosyl chloride was increased to 14.25 mg (0.075 mmole).

Reaction 3. Procedure 1 was modified by using a still larger quantity of tosyl chloride (28.5 mg = 0.15 mmole) and the heating time at 115 °C was extented up to 24 h. The products were analyzed by capillary GC and by GC-MS.

Gas-liquid chromatography. The instrument used was CHROMATRON Gas-Chromatograph GCHF 18.3, which was equipped with a flame ionization Carbowax 20M TPA (0.15 μm on barium carbonate). Hydrogen was used as a carrier gas. The temperature of both the detector and the injection port was held at 250 °C.

Mass spectrometry. Products of reaction 3 were analysed on a GC-MS System Model 5992 B Hewlett Packard instrument equipped with a column (0.7m x 0.2 cm i.d.) packed with a mixed phase of 2% OV-101 and 0.2% Carbowax 20M. The injection port temperature was 240 °C.

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