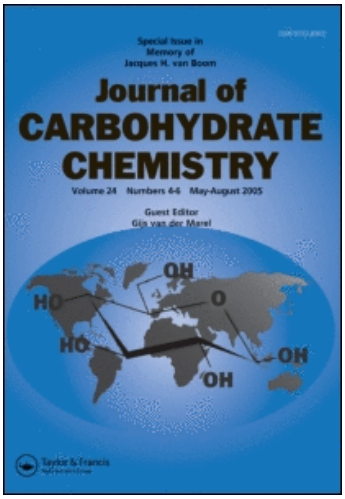

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FORMOSE REACTIONS. XXXI. SYNTHESIS OF DL-2-*C*-HYDROXYMETHYL-3-PENTULOSE FROM FORMALDEHYDE IN *N*,*N*-DIMETHYLFORMAMIDE-WATER MIXED SOLVENT (I)

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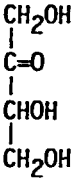
ABSTRACT

The formose reaction catalyzed by triethylamine and thiamine·HCl at high formaldehyde concentration in *N*,*N*-dimethylformamide-H_2O mixed solvent was found to give rise to DL-*glycero*-tetrulose or DL-2-*C*-hydroxymethyl-3-pentulose favorably. DL-2-*C*-Hydroxymethyl-3-pentulose and DL-*glycero*-tetrulose were isolated from formose and their spectral data are discussed. Under the reaction conditions, product distribution was affected by the ratio of *N*,*N*-dimethylformamide to H_2O. With an increase in the water content, the carbon number of the main product increased. The formaldehyde consumption and the maximum total yield were, however, decreased with an increase in the amount of water mainly due to rapid decomposition of thiamine in the solvent containing water.

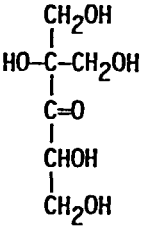
INTRODUCTION

Formose is a complex mixture of sugars, sugar alcohols, saccharic acids and so on produced from formaldehyde by base-catalyzed condensations, Cannizzaro reactions, and cross-Cannizzaro reactions. The formose reaction has received much attention in connection with the prebiotic synthesis of carbohydrates,[1] the microbial utilization of formose, and the industrial production of edible carbohydrates.[2-4] For these purposes, a high-yield production of desired sugars is required and, hence, selectivity in the reaction must be enhanced. Recently, the

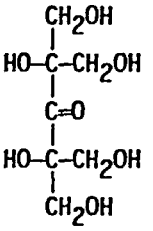
formose reactions[5,6] in *N*,*N*-dimethylformamide (DMF) catalyzed by 2-(dimethylamino)ethanol and thiamine·HCl, have been found to give rise to dihydroxyacetone and DL-*glycero*-tetrulose selectively at 1.1 M and 3.0 M of formaldehyde concentration, respectively. DL-*glycero*-Tetrulose was formed more favorably in the formose reaction catalyzed by triethylamine (TEA) than in that by 2-(dimethylamino)ethanol.[5] Furthermore, selective formation of 2,4-bis(hydroxymethyl)-3-pentulose (2,4-BH-3-P) in the formose reaction by choosing a suitable solvent ratio of water to DMF has been described in detail.[7] In our consecutive study on the formose reaction catalyzed by TEA and thiamine·HCl in DMF, it has been fortunately found that the distribution of products is able to be controlled by the amount of water added to the reaction mixture. We have preliminarily reported the favored formation of DL-2-*C*-hydroxymethyl-3-pentulose (2-H-3-P), which would be an important precursor of 2,4-BH-3-P,[7] in the formose reaction using DMF-H_2O mixed solvent, and its isolation and structure elucidation.[8]



DL-*glycero*-Tetrulose



2-H-3-P



2,4-BH-3-P

The present paper describes the separation and identification of DL-*glycero*-tetrulose and 2-H-3-P from the product mixture and how the product distribution (especially, the yield of 2-H-3-P and DL-*glycero*-tetrulose) is affected by the composition of the DMF-H_2O mixed solvent. The effects on the formaldehyde consumption are also mentioned. Furthermore, the product distribution was investigated during the course of the formose reaction starting with various reaction conditions.

RESULTS AND DISCUSSION

Effect of Water Addition. As shown in Fig. 1a, it is known that dihydroxyacetone (DHA) is formed selectively in nonaqueous solvents from formaldehyde when thiazolium salts are used in the presence of a base.[5,9,10] We have already reported that, with an increase in the water content, the carbon number of the main product increased and, under the reaction conditions, 2.8 mL of TEA, H_2O/DMF ratio of 30/60 mL/mL, and 3 M of formaldehyde, the main products were DL-*glycero*-tetrulose and 2-H-3-P.[7] It was also pointed out that the formose reaction catalyzed by thiazolium salt in a H_2O-DMF mixed solvent gives 2,4-BH-3-P favorably in the presence of much formaldehyde.[7] The percentage of 2,4-BH-3-P increased smoothly with the progress of the reaction. During the initial stage, DL-*glycero*-tetrulose and 3-pentulose[11] decreased rapidly, then 2-H-3-P decreased along with an increase in 2,4-BH-3-P.

In the present paper, the distribution of products was examined at 1.0 M of formaldehyde by changing the H_2O/DMF ratio (Fig. 2). The total yield (mg/mL) is given by the summation of total products as measured by gas chromatography.

In this case, was also observed the same phenomenon as described previously,[7] that with an increase in the water content, the carbon number of the main product increased. 2,4-Bis(hydroxymethyl)-3-pentulose (2,4-BH-3-P) (30 %), 2-H-3-P (30 %), DL-*glycero*-tetrulose (25 %), and DHA (75 %) were favorably formed at an H_2O/DMF ratio of 50/50, 30/70, 13/87, and 0/100 mL/mL, respectively. Above 90/10 mL/mL of the H_2O/DMF ratio, 2,4-bis(hydroxymethyl)pentitol (2,4-BHP) was a main product, which was formed by cross-Cannizzaro reaction of 2,4-BH-3-P and formaldehyde.

Effects of water content on the HCHO consumption and the maximum total yield are shown in Fig. 3. The curve of the total yield as a

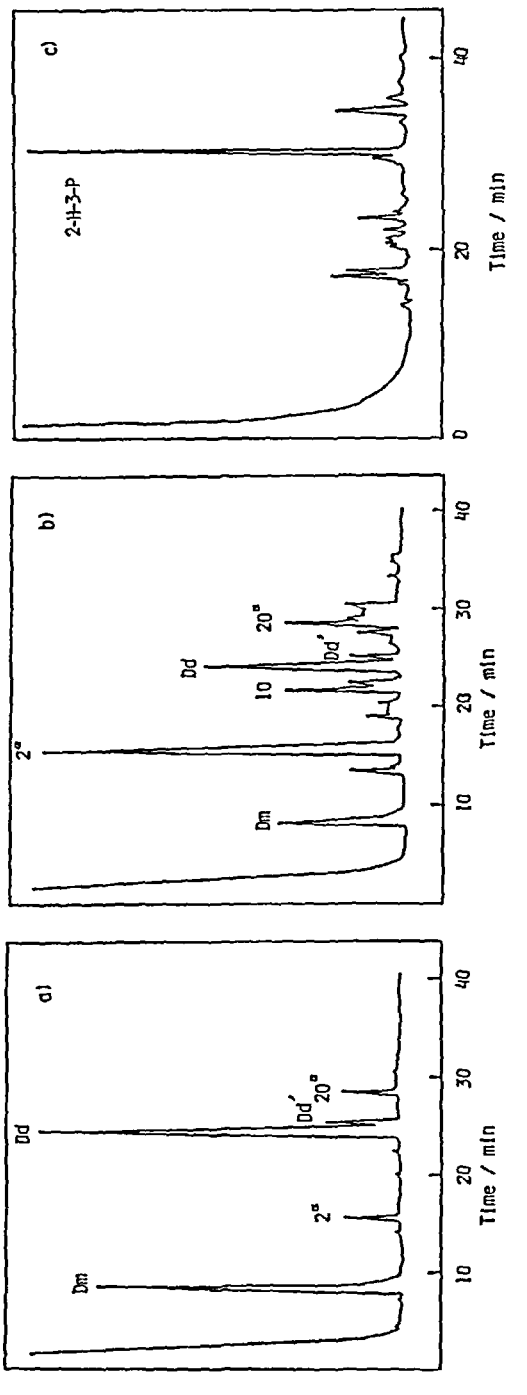


Fig. 1. GC elution patterns of per(trimethylsilyl)ated products obtained from selective formose reactions in:(a) *N,N*-dimethylformamide in the presence of 1.1 M formaldehyde, 28 mM thiamine·HCl, and 0.11 M 2-(dimethylamino)ethanol at 60 °C, (b) *N,N*-dimethylformamide in the presence of 3.0 M formaldehyde, 28 mM thiamine·HCl, and 0.15 M 2-(dimethylamino)ethanol at 110 °C, (c) 138 mL *N,N*-dimethylformamide and 17 mL water in the presence of 3.0 M formaldehyde, 50 mM thiamine·HCl, and 0.3 M triethylamine at 75 °C.
Dm, Dd, and Dd', monomer and diastereomeric dimers of dihydroxyacetone;
2^k, DL-*glycero*-tetrulose; 20^k, 2-(1,2-dihydroxyethyl)-5-(2-hydroxyethyl)-4-methyl thiazole.

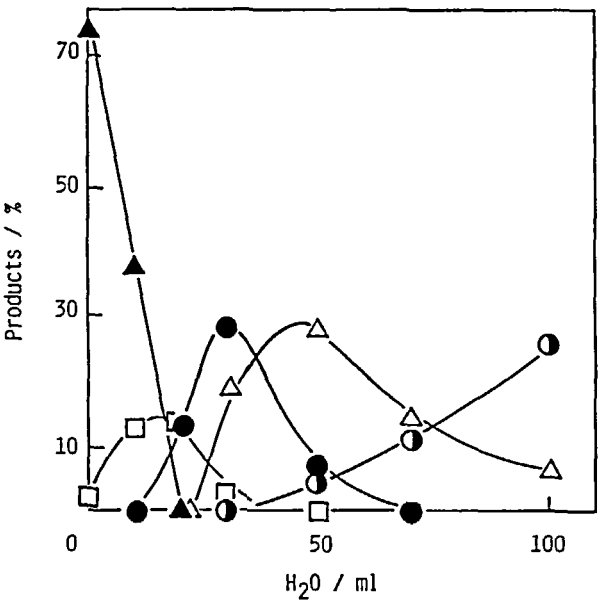


Fig. 2. Effect of H_2O content on the product distribution at the maximum total yield.
HCHO=100 mmol; thiamine·HCl=5 mmol; TEA=30 mmol; solvent, DMF and water; total volume, 100 mL; temp, 75 °C.
▲, DHA; □, DL-*glycero*-tetrulose; ●, 2-H-3-P; △, 2,4-BH-3-P; ◑, 2,4-BHP.

function of H_2O content was very similar to that of the HCHO consumption. This would suggest that the ratio of the amount of products detectable by GC to that undetectable was not affected by the amount of water in the solvent. Above 25/75 mL/mL of the H_2O/DMF ratio, the HCHO consumption decreased with an increase in the amount of water.

From the above discussions, the following conclusions can be given: the addition reaction of formaldehyde to DHA and cross-Cannizzaro reactions proceeded more smoothly with an increase in the water content; thiamine did not catalyze the aldol condensation of DHA with formaldehyde effectively; thiamine decomposed rapidly in solvents containing water.

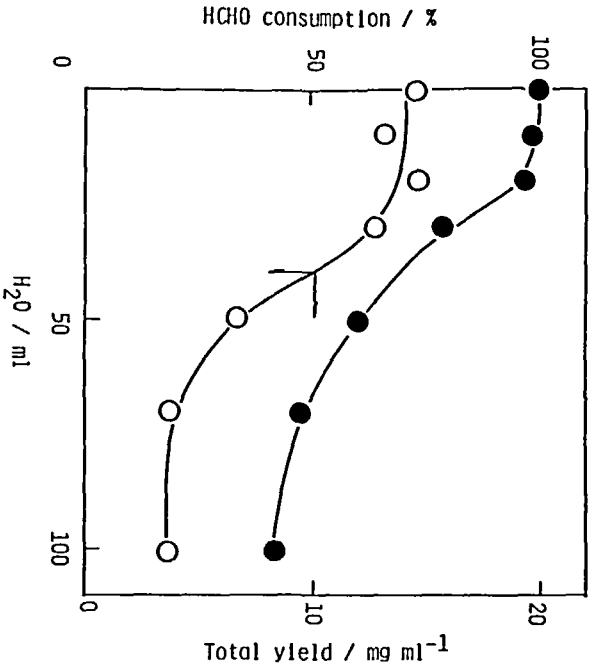


Fig. 3. Effect of H_2O content on the maximum total yield and HCHO consumption.
HCHO=100 mmol; thiamine·HCl=5 mmol; TEA=30 mmol; solvent, DMF and water; total volume, 100 mL; 75 °C; reaction time, 180 min.
○, Maximum total yield; ●, HCHO consumption.

Time-course of Product. Under various reaction conditions, time-courses of the yields of DHA, DL-*glycero*-tetrulose, 3-pentulose,[11] 2-H-3-P, and 2,4-BH-3-P were investigated and the results are shown in **Figs. 4, 5,** and **6.** As shown in **Fig. 4,** the percentage of 2-H-3-P increased with the progress of the reaction.

During the initial stage, DHA decreased rapidly, then DL-*glycero*-tetrulose decreased along with an increase in 2-H-3-P. The yield of 3-pentulose was maximum at 60 min, after then it decreased gradually. In this case, 2,4-BH-3-P was not a main product. **Fig. 5** shows the time-courses of products obtained from the formose reaction in which the

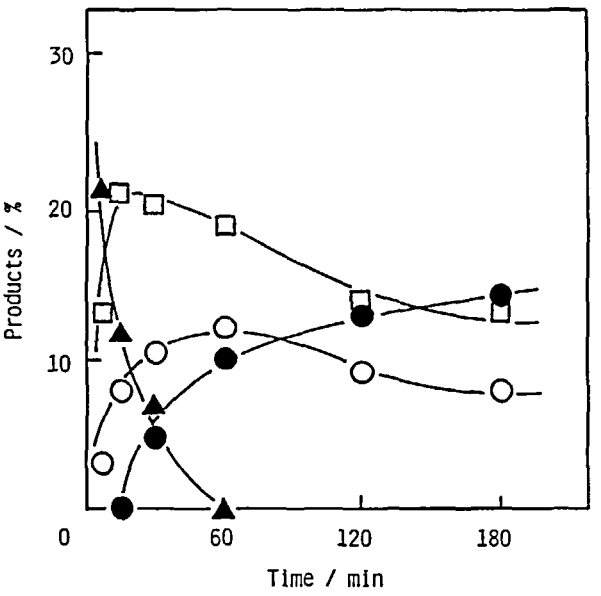


Fig. 4. Time-courses of products in the formose reaction: HCHO=100 mmol and TEA=30 mmol.
Thiamine·HCl=5 mmol; solvent, DMF containing 20 vol% water; total volume, 100 mL; temp, 75 °C.
▲, DHA; □, DL-*glycero*-tetrulose; ○, 3-pentulose; ●, 2-H-3-P.

amount of TEA was changed from 30 mmol (**Fig. 4**) to 120 mmol. At the initial stage, DL-*glycero*-tetrulose and 3-pentulose decreased rapidly and 2-H-3-P formed smoothly, after 60 min 2-H-3-P decreased gradually. In this case, DHA was a minor product throughout the reaction and the formation of 2,4-BH-3-P, which might be one of final products in the formose reaction, could be observed. **Fig. 6** shows the time-courses of products in the formose reaction changed from 100 mmol (**Fig. 4**) to 300 mmol of formaldehyde. Concerning DHA, DL-*glycero*-tetrulose, 3-pentulose, and 2-H-3-P, their formation behavior was similar to those in **Fig. 5**. On the other hand, 2,4-BH-3-P increased smoothly with the progress of the reaction and became a major product. These phenomena were

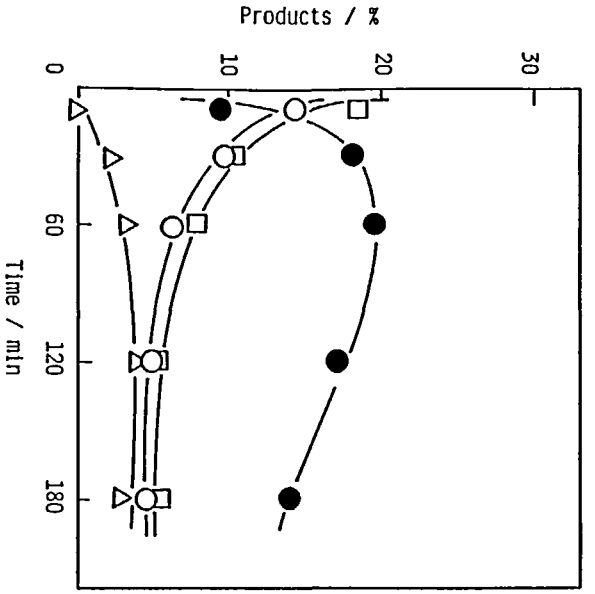


Fig. 5. Time-courses of products in the formose reaction: HCHO=100 mmol and TEA=120 mmol. Thiamine·HCl=5 mmol; solvent, DMF containing 20 vol% water; total volume, 100 mL; temp, 75 °C. □, DL-*glycero*-Tetrulose; ○, 3-pentulose; ●, 2-H-3-P; △, 2,4-BH-3-P.

similar to those[7] in the formose reaction starting from HCHO=500 mmol, [thiamine·HCl]=0.08 M, TEA=90 mL, DMF=60 mL, H_2O=30 mL, and temp=60 °C.

The effects of the TEA and formaldehyde concentration on the reaction will be precisely discussed in the following paper.[12] At the present time, however, we are able to confirm a pathway of the formation of formose which was proposed in the previous paper.[7]

EXPERIMENTAL

General Procedure for the Synthesis of DL-*glycero*-Tetrulose. The reaction was performed with an *N*,*N*-dimethylformamide (DMF) solution (180 mL) of 3.0 M formaldehyde (17.1 g) in the presence of 0.15 M 2-(di-

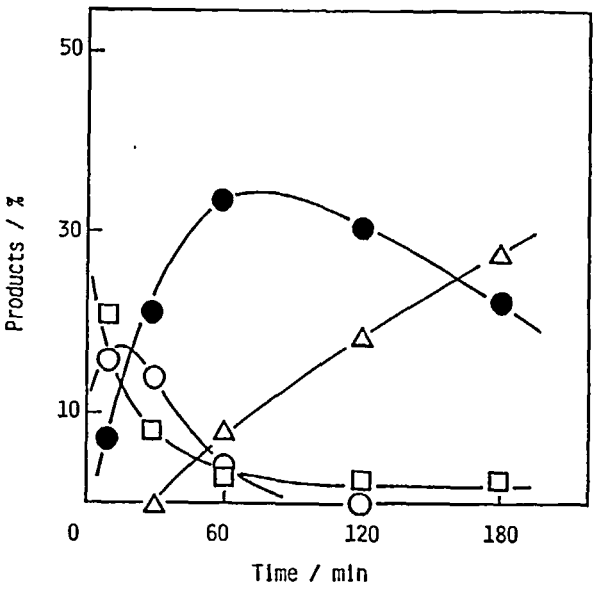


Fig. 6. Time-courses of products in the formose reaction: HCHO=300 mmol and TEA=30 mmol.
Thiamine·HCl=5 mmol; solvent, DMF containing 20 vol% water; total volume, 100 mL; temp, 75 °C.
□, DL-*glycero*-Tetrulose; ○, 3-pentulose; ●, 2-H-3-P; △, 2,4-BH-3-P.

methylamino)ethanol and 28 mM thiamine·HCl at 100 °C under nitrogen. DMF was purified in the usual way.[13] The amount of formaldehyde added was calculated from 0.95 times the amount of paraformaldehyde (Merck Co.) The other reagents were of an analytical grade.

General Procedure for the Synthesis of DL-2-*C*-Hydroxymethyl-3-pentulose. In a typical experiment, the reaction was performed with *N*,*N*-dimethylformamide (138 mL), H_2O (17 mL), and 3.0 M formaldehyde (17.1 g) in the presence of 1 M triethylamine (TEA) (25 mL) and 50 mM thiamine·HCl (3.0 g) at 75 °C with stirring (500 rpm) in a weak stream of nitrogen.

Analyses. At various time-intervals, aliquots (5 mL) of the reaction mixtures were transferred into a 10-mL flask and the reaction was quenched immediately by acidification with 9 M hydrochloric acid. These aliquots were analyzed for formaldehyde by the method of Bricker and Johnson,[14] except that the absorbance was measured at 579 nm, and were concentrated under reduced pressure (25-30 °C/1 mmHg, 1 mmHg ≈ 133.322 Pa) to a brownish syrup. The resulting compounds were analyzed as per(trimethylsilyl)ated derivatives by GC as described previously,[15] the patterns of which (**Figs. 1b** and **1c**) clearly indicated the favored formations of DL-*glycero*-tetrulose (20% by GC) and 2-H-3-P (30% by GC), respectively. The total yield (mg/mL) of products was measured by the internal standard [trimethylolethane, $CH_3C(CH_2OH)_3$] method.

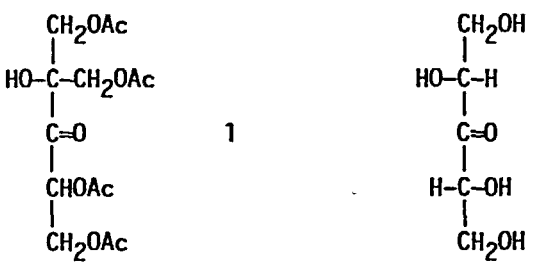
^1H and ^{13}C NMR spectra were taken on a JEOL JNM GX-270 spectrometer and chemical shifts are given in ppm from tetramethylsilane as an internal or external standard. IR spectra were determined on a Hitachi EPI-G2 spectrometer. GC-MS was performed in a JEOL JMS-DX303 mass spectrometer using a 1.2 m glass column with 1% OV-1 as stationary phase on Gas Chrom Q, 100-120 mesh.

Separation and Identification of DL-*glycero*-Tetrulose. The formose reaction was quenched at 180 min and the reaction mixture (180 mL) was concentrated to ca. 50 mL under reduced pressure (25-30 °C/1 mmHg). The concentrate was added to water (ca. 50 mL), extracted with diethyl ether, and the water layer was passed through a column of active carbon. Concentration of the filtrate gave a pale yellow syrup (12.1 g, DL-*glycero*-tetrulose: 21.3% by GC). DL-*glycero*-Tetrulose was isolated by repeating the column chromatography on cellulose powder with wet 1-butanol as eluent to give a colorless syrup (1.2 g, purity > 95% by GC): $[\alpha]_D^{28}$ 0° (*c* 0.65, methanol); IR (KBr) 3300-3400 (O-H) and 1730 cm^{-1}

(C=O); ^{1}H NMR (CD_3OD; int. standard, Me_4Si) δ 3.75 (d, 2H, J = 4 Hz, -HCOH-CH_2OH), 4.23 (t, 1H, J = 4 Hz, O=C-CHOH-), and 4.48 (s, 2H, O=C-CH_2OH); ^{13}C NMR (CD_3OD; int. standard, Me_4Si) δ 64.8 (t), 67.6 (t), 77.8 (d), and 212.8 (s), corresponding to 2 CH_2 and one CH groups, and one carbonyl C atom; MS (acetyl derivative; 70 EV) m/z 203 (1, M^+ - O=C-CH_3), 173 (1), 145 (6), 131 (2), 103 (12), 101 (13), 86 (2), 73 (6), 43 (100, O=C-CH_3); lit.[12] ^{1}H NMR of L-*glycero*-tetrulose (D_2O) δ 3.85 (d, 2H, J = 4 Hz, -HCOH-CH_2OH), 4.42 (t, 1H, J = 4 Hz, O=C-CHOH-), and 4.54 (s, 2H, O=C-CH_2OH). After reduction with sodium borohydride and trimethylsilylation with hexamethyldisilazane and trimethylchlorosilane, the gas chromatogram of the per(trimethylsilyl)ated derivatives showed two peaks, the retention times of which coincided with the peaks of per(trimethylsilyl)ated DL-threitol and *meso*-erythritol, respectively.

Separation and Identification of DL-2-*C*-Hydroxymethyl-3-pentulose. After 1 h, the reaction mixture, for which reaction conditions are described above, was neutralized and concentrated to ca. 50 mL under reduced pressure (25-30 °C/1 mmHg), then the concentrate was passed through a column of active carbon (3x30 cm) with water as eluent. Concentration of the filtrate gave a pale-yellow syrup (14.2 g, 28% of 2-H-3-P by GC). 2-H-3-P (1.3 g, a colorless syrup) was isolated by repeating column chromatography on cellulose powder (Whatman CF-11) with wet 1-butanol as eluent: IR (neat) 3300-3400 (O-H) and 1710 cm^{-1} (C=O); ^{1}H NMR (D_2O; int. standard, sodium 2,2-dimethyl-2-silapentane-5-sulfonate) δ 3.61 [d, 2H, J = 11.7 Hz, -C(OH)(HCHOH)(HCHOH)], 3.83 [d, 1H, J = 11.7 Hz, -C(OH)(HCHOH)(HCHOH)], 3.83 [dd, 1H, J = 5.4 and 12.2 Hz, -HC(OH)-(HCHOH)], 3.85 [d, 1H, J = 11.7 Hz, -C(OH)(HCHOH)(HCHOH)], 4.00 [dd, 1H, J = 3.4 and 12.2 Hz, -HC(OH)(HCHOH)], and 4.86 [dd, 1H, J = 3.4 and 5.4 Hz, O=C-CH(OH)-]; ^{13}C NMR (D_2O, int. standard, sodium 2,2-

dimethyl-2-silapentane-5-sulfonate) δ 64.9 (t), 66.4 (t), 67.4 (t), 78.5 (d), 86.8 (s), and 217.4 (s), corresponding to 3 CH_2, one CH, and one quarternary C groups, and one carbonyl C atom. After acetylation with acetic anhydride in pyridine, the acetylated product 1 was isolated by thin layer chromatography on silica gel with methanol-benzene (1:10 v/v) at R_f = 0.26. The product 1 was obtained as a colorless syrup: IR (neat) 3400-3450 (O-H), 2920, and 1740 cm^{-1} (C=O); ^1H NMR ($CDCl_3$ int. standard, Me_4Si): δ 2.09, 2.10, 2.13, and 2.16 (4s, 12H, 4 $-C=OCH_3$), 3.95 (s, 1H, -OH), 4.25 and 4.27 [d, 1H, J = 11.7 Hz, -C(OH)(HCH-OAc)(HCH-OAc) and -C(OH)(HCH-OAc)(HCH-OAc)], 4,38 and 4.40 [d, 1H, J = 11.7 Hz, -C(OH)(HCH-OAc)(HCH-OAc) and -C(OH)(HCH-OAc)(HCH-OAc)], 4.42 [dd, 1H, J = 5.9 and 12.2 Hz, -HC(OAc)-HCH-OAc], 4.65 [dd, 1H, J = 2.9 and 12.2 Hz, -HC(OAc)-HCH-OAc], and 5.82 [dd, 1H, J = 2.9 and 5.9 Hz, -HC(OAc)-HCH-OAc]; ^{13}C NMR ($CDCl_3$ int. standard, Me_4Si) δ 20.4 (q), 20.6 (2q), 20.7 (q), 61.7 (t), 65.9 (t), 66.7 (t), 74.3 (d), 77.2 (s), 170.0 (s), 170.6 (s), 170.9 (s), 171.6 (s), and 203.9 (s) corresponding to 4 O=C-CH_3, 3 CH_2, one CH, one quaternary C, and 4 O=C-CH_3 groups and one carbonyl C atom; MS (70 EV) m/z 349 (MH^+, 3), 331 ($MH^+ - H_2O$, 31), 217 (44), 173 (76), 131 (86), 61 (100). Thus, the structure of the product 1 was established as DL-1,4,5,6-tetra-*O*-acetyl-2-*C*-hydroxymethyl-3-pentulose. GC-MS of pertrimethylsilylated derivative of 2-H-3-P (70 EV) m/z 540 (M^+, 2), 525 ($M^+ - CH_3$, 4), 435 ($M^+ - CH_3 - Me_3Si$-OH, 31), 309 (97), 308 (92), 218 (92), 156 (97), 73 (24).



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