Formose Reactions. XXVIII. Selective Formation of 2,4-Bis(hydroxymethyl)-3-pentulose in *N,N*-Dimethylformamide–Water Mixed Solvent

Yoshihiro SHIGEMASA,* Takaaki UEDA,† and Hiroyuki SAIMOTO
Department of Industrial Chemistry, Faculty of Engineering, Tottori University, Tottori 680

(Received June 7, 1989)

Dihydroxyacetone, DL-*glycero*-tetrulose, and 2,4-bis(hydroxymethyl)-3-pentulose (2,4-BH-3-P) were favorably formed in a formose reaction by choosing a suitable ratio of water to *N,N*-dimethylformamide used as solvent or a suitable [thiamine·HCl]/[HCHO] ratio. The formose reaction was strongly affected by the concentration of formaldehyde in the water layer. Under the reaction conditions studied, thiamine decomposed rapidly. 2,4-BH-3-P was isolated from the reaction mixture and characterized by MS, IR, and NMR techniques. A pathway for the formation of 2,4-BH-3-P was also proposed.

Formose is a complex mixture of sugars, sugar alcohols, saccharic acids and so on produced from formaldehyde by base-catalyzed condensation, Cannizzaro reaction, and cross-Cannizzaro reaction. 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, solvent effects on a formose reaction catalyzed by inorganic reagents have been studied from the standpoint of catalyst solubility and product distribution.5–7) To the best of our knowledge, the selectivity of products has been investigated only in aqueous and/or methanolic solvents,6–15) except for reactions catalyzed by thiazolium salts in *N,N*-dimethylformamide (DMF),16–18) which produce dihydroxyacetone (DHA)16,18) and DL-*glycero*-tetrulose19) selectively. Furthermore, 2,4-bis(hydroxymethyl)-3-pentulose (2,4-BH-3-P) and 2-hydroxymethyl-3-pentulose (2-H-3-P) were found to be formed selectively by adding a small amount of water to methanol7) or DMF solvent,20) respectively.

The present paper describes how the product distribution (especially, the yield of 2,4-BH-3-P), formaldehyde consumption, and the yield of organic acids are affected by the reaction conditions, such as solvent composition, formaldehyde concentration, and reaction temperature.

Experimental

General Procedure. In a typical experiment the reaction was conducted with 5.7 g of paraformaldehyde, 60 ml of DMF, 30 ml of water, 90 ml of triethylamine (TEA), and 3.0 g of thiamine·HCl at 75 °C with stirring (500 rpm) in a weak stream of nitrogen for 180 min. DMF was purified in the usual way.21) At intervals, 5 ml aliquots were withdrawn into 10 ml flasks and cooled in a cold bath (−60 °C) to ca. 0 °C. The reaction was practically terminated at this temperature. The aliquots were immediately separated into triethylamine (TEA) and H_2O layers, and the formaldehyde of both layers was determined according to a method of Bricker et al.,22) except for the use of optical density at 579 nm. The water layer contained more than 90% of the added formaldehyde.

The reaction mixture was concentrated under reduced pressure (25—30 °C/2 mmHg; 1 mmHg≈133.322 Pa) to a brownish syrup. The product distribution (%) was determined by GLC of their trimethylsilyl derivatives, as described previously.8,10) The total yield (mg ml^{-1}) of products was measured by the internal standard (trimethylolethane, $CH_3C(CH_2OH)_3$) method. The amount of formic acid and organic acids in the formose mixture was determined by a Shimadzu Isotachophoresis. ^{1}H and ^{13}C NMR spectra were taken on a JEOL JNM GX-270 spectrometer and chemical shifts were given by ppm from tetramethylsilane as an internal or external standard.

Separation and Identification of Products. The reaction mixture (180 ml) was concentrated in vacuo at 40 °C to a brownish syrup (12.5 g) and dissolved into 250 ml of water. The solution was passed through an active-carbon column (3×30 cm), and concentrated in vacuo at 40 °C to a pale-yellow syrup (5.4 g). The syrup was chromatographed on a cellulose powder (Whatman CF-11) column (108×2.4 cm) with wet 1-butanol as eluent. The product corresponding to GLC peak number 23 was obtained as a colorless syrup (1.4 g; yield, 24.3 wt%), whose spectral data were in agreement with those of 2,4-bis(hydroxymethyl)-3-pentulose (2,4-BH-3-P).7)

Results and Discussion

Effects of Solvent Composition (H_2O/DMF). It is known that DHA is formed selectively in nonaqueous solvents from formaldehyde when thiazolium salts are used in the presence of a base.16–19) On the other hand, the reactions in H_2O gave sugars and sugar alcohols of carbon number 5 to 7 as the main products.7,8,12) In the present paper, the distribution of products was examined by changing the H_2O/DMF ratio, as shown in Fig. 1. DHA was selectively formed at over 80% yield in DMF. With an increase in the water content, the carbon number of the main product increased. When the water content was over 70—80 vol%, 2-(hydroxymethyl)glycerol (2-HG) and

---

† Present address: Sanyo-kokusaku Pulp Co., Ltd., Iwakuni, Yamaguchi 740.

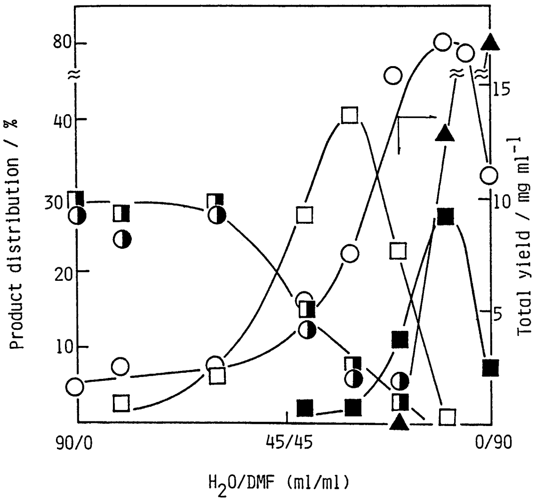


Fig. 1. Effect of H_2O content on the product distribution.
HCHO=180 mmol; [thiamine·HCl]=0.028 M; TEA=90 ml; temp, 75 °C; total volume=180 ml; reaction time=180 min. ○, total yield; ▲, DHA; DL-*glycero*-tetrulose; ◑, 2-HG; □, 2,4-BH-3-P; ◨, 2,4-BHP.

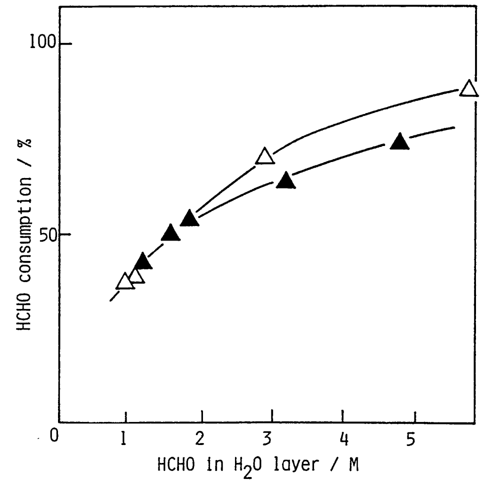


Fig. 3. Effect of formaldehyde concentration in H_2O layer on the formaldehyde consumption.
HCHO=180 mmol; thiamine·HCl=5 mmol; temp, 75 °C; reaction time=180 min. ▲, Total volume was varied and the ratio of H_2O/DMF/TEA ml/ml/ml was kept to 1/2/3. △, TEA volume was varied under H_2O/DMF=1/2 ml/ml and total volume was kept to 180 ml.

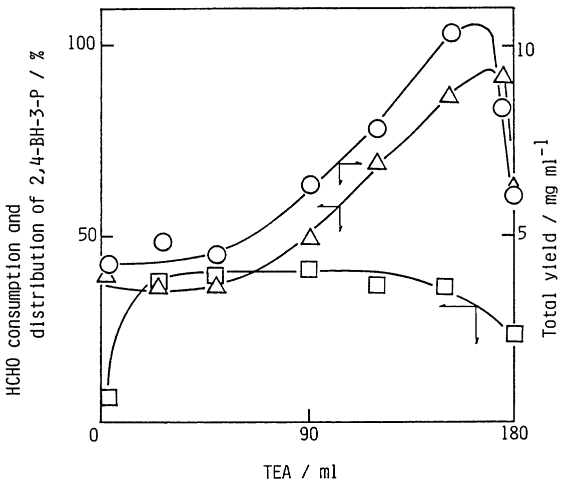


Fig. 2. Effect of the amount of triethylamine.
HCHO=180 mmol; [thiamine·HCl]=0.028 M; temp, 75 °C; H_2O/DMF=1/2 ml/ml, total volume=180 ml; reaction time=180 min. △, HCHO consumption; □, 2,4-BH-3-P; ○, total yield.

2,4-bis(hydroxymethyl)pentitol (2,4-BHP) were the main products.

From the above discussions, it could be concluded that the addition reaction of formaldehyde to DHA, Cannizzaro reaction, and cross-Cannizzaro reaction proceeded more smoothly with an increase in the amount of water. Thiamine did not catalyze the aldol condensation of DHA with formaldehyde effectively and decomposed rapidly in solvents containing water. 2,4-Bis(hydroxymethyl)-3-pentulose (2,4-BH-3-P) (43%) and DL-*glycero*-tetrulose (25%) were favorably formed at an H_2O/DMF ratio of 30/60 (ml/ml) and 10/80 (ml/ml), respectively. It was possible to control the product distribution in the formose reaction by changing the ratio of H_2O/DMF.

Effect of Triethylamine Concentration. Reactions were carried out under various TEA concentrations keeping the H_2O/DMF ratio at 1/2 (v/v) and the total volume of the reaction mixture at 180 ml. The results are shown in Fig. 2. Below 50 ml of TEA, the reaction mixture was homogeneous and only about 40% of the formaldehyde was consumed. In a range of TEA concentration from 50 to 150 ml, the distribution of 2,4-BH-3-P was constant (ca. 30—40%), but the formaldehyde consumption and the yield of 2,4-BH-3-P increased with an increase in the amount of TEA. The yield of 2,4-BH-3-P was maximum at ca. 150 ml of TEA. At 180 ml of TEA (DMF and H_2O were not added), the formaldehyde consumption and the distribution of 2,4-BH-3-P were 60 and 20%, respectively.

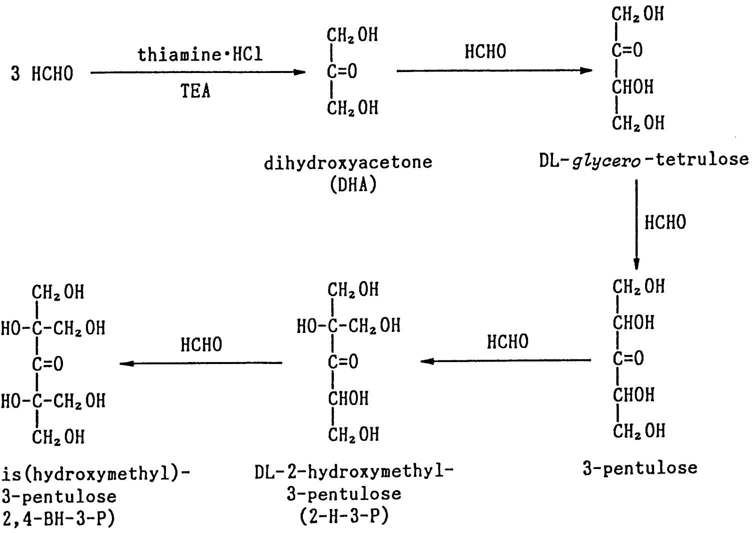
As described previously, most of the added formaldehyde was present in the H_2O layer, so that the concentration of the formaldehyde in the H_2O layer increased with increasing the amount of TEA and decreasing the amount of H_2O. Increasing the concentration of formaldehyde and thiamine in the H_2O layer would increase formaldehyde consumption. This assumption would be supported by the following experiments.

As shown in Fig. 3, the concentration of formaldehyde was changed using two different methods; these reactions were carried out in the presence of formaldehyde (180 mmol) and thiamine·HCl (5 mmol) at 75 °C. In both cases, the formaldehyde consumption increased with an increase in the formaldehyde concentration in the H_2O layer.

Table 1. Effect of the Amount of Triethylamine on the Formose Reaction[a)]

TEA	Time	HCHO cons.	Product yield[b)]/mg				Total yield[b)]
ml	min	%	*glycero*-Tetrulose	11^1	2-H-3-P	2,4-BH-3-P	mg
2.8	30	53	160	200	68	—	1100
	60	67	150	280	140	—	1300
	120	71	140	300	250	—	1500
	180	73	120	300	290	—	1700
10	30	67	54	66	650	310	2500
	60	74	45	36	750	610	3000
	120	84	53	—	490	730	2800
	180	92	47	—	320	900	3100
50	30	67	45	—	500	430	2200
	60	74	51	—	370	610	2300
	120	83	41	—	190	830	2600
	180	88	38	—	140	870	2600
90	30	66	39	14	350	360	1900
	60	73	42	10	270	570	2100
	120	83	—	—	390	1500	3300
	180	88	—	—	150	940	2800

a) HCHO=180 mmol, thiamine·HCl=9 mmol, DMF=60 ml, H_2O=30 ml, temp=75 °C.
b) The yield (mg) was measured by the internal standard (trimethylolethane) method.



Scheme 1. Possible pathway for the formation of 2,4-BH-3-P.

Table 1 also shows that the rate of formaldehyde consumption above 10 ml of TEA was constant, owing to the constant concentration of formaldehyde in the H_2O layer. At 2.8 ml of TEA, the main products were DL-*glycero*-tetrulose, GP-11^1 corresponding to GLC peak number 11^1, and 2-H-3-P. Above 10 ml of TEA, 2-H-3-P and 2,4-BH-3-P were the major products and the amount of 2,4-BH-3-P became greater than that of 2-H-3-P above 70% of formaldehyde consumption. We are presently undertaking to isolate and identify GP-11^1. We suppose that GP-11^1 would be 3-pentulose formed from DL-*glycero*-tetrulose and formaldehyde.

In Scheme 1, the possible pathway for the formation of 2,4-bis(hydroxymethyl)-3-pentulose (2,4-BH-3-P) in the formose reaction catalyzed by thiamine and TEA is proposed. During the first stage one mol of dihydroxyacetone (DHA) is formed from three mol of formaldehyde with thiamine and TEA;[16–18)] then the successive aldol condensations of formaldehyde and ketoses catalyzed by TEA give 2,4-BH-3-P as a final product.

Effects of Formaldehyde Concentration. Figure 4 shows the effect of the formaldehyde concentration on the formose reaction. Upon increasing the formaldehyde concentration, the formaldehyde conversion decreased; however, the amount of consumed formaldehyde increased. Formaldehyde was smoothly consumed for the first 30 min, after which formaldehyde was scarcely consumed. These results might be suggestive of a loss of the catalytic ability of thiamine, since the C-2 position of the thiazolium ring is substi-

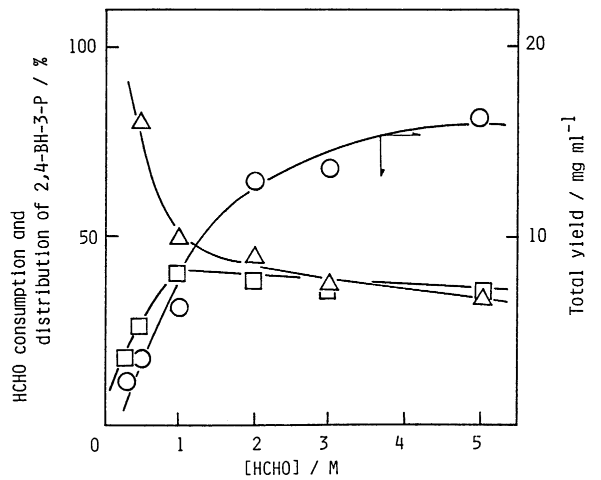


Fig. 4. Effect of formaldehyde concentration on formaldehyde consumption and the distribution of 2,4-bis(hydroxymethyl)-3-pentulose.
[Thiamine • HCl]=0.028 M; temp, 75 °C; TEA=90 ml; DMF=60 ml; H_2O=30 ml; reaction time=180 min. △, HCHO consumption; ○, total yield; □, 2,4-BH-3-P.

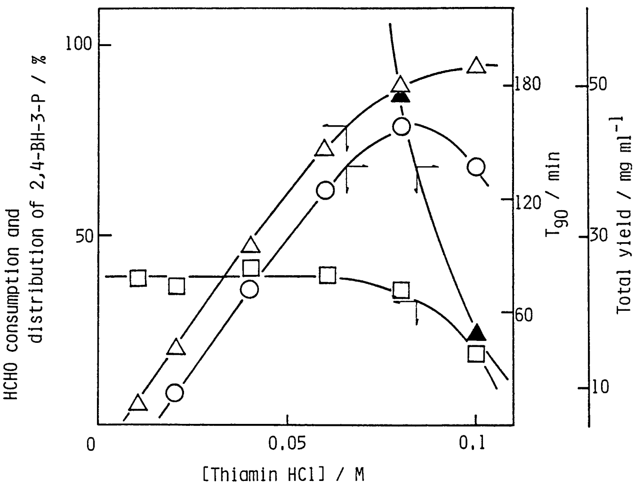


Fig. 5. Effect of thiamine • HCl concentration.
HCHO=540 mmol; temp, 75 °C; TEA=90 ml; DMF=60 ml; H_2O=30 ml; reaction time=180 min. △, HCHO consumption; □, 2,4-BH-3-P; ○, total yield; ▲, T_{90}.

tuted with a polyhydric alcohol group and thiazolium salt changes to thiazole.[23]

Above 1.0 mol dm^{-3} of the formaldehyde concentration, the distribution of 2,4-BH-3-P was constant, ca. 40%. The amount of 2,4-BH-3-P increased with an increase in the formaldehyde concentration. The yield of 2,4-BH-3-P, which was a major product in methanol,[7] gradually increased throughout the reaction. Thiamine catalyzes the formation of DHA from formaldehyde[16–18] and a base-catalyzed addition of formaldehyde to DHA would form 2,4-BH-3-P. Hence, the [thiamine]/[HCHO] ratio would be an important factor in determining the product distribution.

Formic acid was scarcely formed and the yield was below 6 mol%. 2,4-Bis(hydroxymethyl)pentitol (2,4-BHP), which was a major product in water,[8] was a minor product in DMF. It might be estimated that the Cannizzaro reaction and the cross-Cannizzaro reaction of 2,4-BH-3-P with formaldehyde hardly proceeded under these reaction conditions.

Effect of Thiamine • HCl Concentration. The formose was scarcely formed in DMF by inorganic bases such as $Ca(OH)_2$, $Ba(OH)_2$, etc.[18] The formose reaction in DMF was effectively catalyzed by thiazolium salts.[16–19,23] Figure 5 shows the effects of the thiamine • HCl concentration. With an increase in the thiamine concentration, formaldehyde was consumed more smoothly and T_{90} shortened, which was the reaction time when formaldehyde consumption reached 90%.

As the concentration of thiamine • HCl increased, the total sugar yield increased and reached to a maximum at 0.08 mol dm^{-3} of thiamine, then decreased. When the amount of thiamine • HCl was below 0.08 mol dm^{-3} at 540 mmol (3 mol dm^{-3}) of formaldehyde, the distribution (%) of 2,4-BH-3-P was constant (ca. 40%) and the yield (mg ml^{-1}) increased with an increase in the thiamine concentration. When the amount of thiamine • HCl was above 0.08 mol dm^{-3}, the distribution and the yield of 2,4-BH-3-P decreased with an increase in the thiamine concentration. 2-Hydroxymethyl-3-pentulose (2-H-3-P),[20] furthermore, increased with increasing the thiamine concentration.

The effects of the thiamine concentration on formaldehyde consumption, the yield of 2,4-BH-3-P, and the total sugar yield at 180 mmol (1 mol dm^{-3}) of formaldehyde were similar to those at 540 mmol of formaldehyde.

These results indicate that the [thiamine]/[HCHO] ratio would be an important factor affecting the formation of 2,4-BH-3-P. With increasing the thiamine concentration, the formation rates of 2-H-3-P and dihydroxyacetone (DHA) from formaldehyde would increase and most formaldehyde would be consumed owing to their presence. Consequently, 2,4-BH-3-P cannot form from 2-H-3-P, owing to a deficiency of formaldehyde. A similar phenomenon, that 2-H-3-P and DHA was formed as major products, was observed in the case of a low formaldehyde concentration.

Regardless of the concentration of thiamine, formaldehyde was also smoothly consumed for the first 30 min and scarcely, or very slowly, after 60 min because of the rapid decomposition of thiamine • HCl (as described previously). A further addition of thiamine after 60 min promoted the formose reaction again, as follows.

About 30% of formaldehyde was consumed by starting with 0.02 mol dm^{-3} of thiamine • HCl and 1.0 mol dm^{-3} of formaldehyde at 75 °C for 60 min; a further addition of 0.02 mol dm^{-3} of thiamine • HCl at 60 min caused a 60% consumption of formaldehyde for

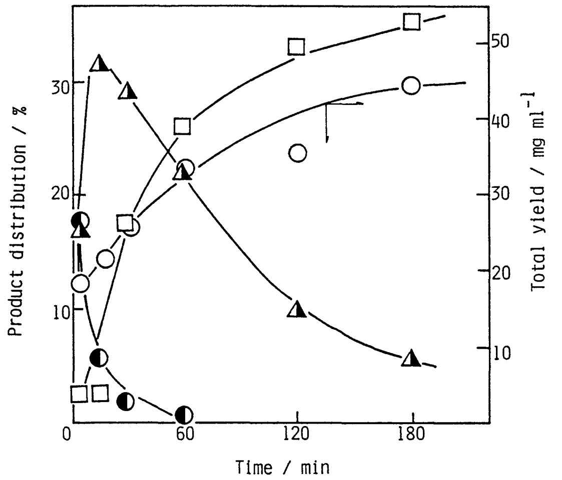


Fig. 6. Time courses of products.
HCHO=540 mmol; [thiamine • HCl]=0.08 M; temp, 75 °C; TEA=90 ml; DMF=60 ml; H_2O=30 ml. ◐, GP-11[1]; ▲, 2-H-3-P; □, 2,4-BH-3-P; ○, total yield.

Table 2. Effect of Temperature on the Formose Reaction[a)]

Temp	HCHO cons.	Product distribution/%		Total yield[b)]
°C	%	2-H-3-P	2,4-BH-3-P	mg ml^{-1}
40	25	42	15	2.7
50	29	25	32	4.4
60	37	7	37	4.6
70	45	3	31	7.6
80	61	3	35	11.0

a) HCHO=180 mmol, thiamine • HCl=5 mmol, TEA= 90 ml, DMF=60 ml, H_2O=30 ml, time=180 min.
b) The yield (mg ml^{-1}) was measured by the internal standard (trimethylolethane) method.

120 min; by further adding the same amount of thiamine • HCl at 120 min, 90% of the formaldehyde was consumed. About 60 and 90% of the formaldehyde were, furthermore, consumed for 60 min by starting with 0.04 mol dm^{-3} and 0.06 mol dm^{-3} of thiamine • HCl, respectively. It is estimated that under these reaction conditions thiamine • HCl would decompose rapidly and lose its catalytic ability.[23)]

Time-Course of Product. Figure 6 shows time-courses of the yields of GP-11[1], 2-H-3-P, and 2,4-BH-3-P. The percentage of 2,4-BH-3-P increased smoothly with the progress of the reaction. During the initial stage, DL-*glycero*-tetrulose and GP-11[1], which would be 3-pentulose, decreased rapidly; then, 2-H-3-P decreased along with an increase in 2,4-BH-3-P.

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. DL-*glycero*-Tetrulose, 3-pentulose (GP-11[1]), 2-H-3-P, and 2,4-BH-3-P would be formed in this order by successive additions of formaldehyde to DHA, as shown in Scheme 1.

Effect of Temperature. The effects of temperature (40—80 °C) on the formose reaction are summarized in Table 2. At temperatures above 50 °C, 2,4-BH-3-P was a main product, but 2-H-3-P increased with decreasing the reaction temperature. As the reaction temperature increased, formaldehyde was consumed more rapidly.

This work was partially supported by a Grant-in-Aid for Scientific Research No. 61303011 from the Ministry of Education, Science and Culture.

References

1) N. W. Gabel and C. Ponnamperuma, *Nature (London)*, **216**, 453 (1967).

2) T. Mizuno and A. H. Weiss, *Adv. Carbohydr. Chem. Biochem.*, **29**, 173 (1974).

3) Y. Shigemasa, *Yuki Gosei Kagaku Kyokai Shi*, **36**, 667 (1978).

4) M. Goto and T. Sakai, *Yuki Gosei Kagaku Kyokai Shi*, **41**, 588 (1983).

5) E. Pfeil and G. Schroth, *Chem. Ber.*, **85**, 293 (1952).

6) V. A. Likholobov, A. H. Weiss, and M. M. Sakharov, *React. Kinet. Catal. Lett.*, **8**, 155 (1978).

7) Y. Shigemasa, S. Akagi, R. Nakashima, and S. Saito, *Carbohydr. Res.*, **80**, C1 (1980); Y. Shigemasa, S. Akagi, E. Waki, and R. Nakashima, *J. Catal.*, **58**, 296 (1979), **69**, 58 (1981); Y. Shigemasa, H. Sakai, and R. Nakashima, *Nippon Kagaku Kaishi*, **1982**, 1626.

8) Y. Shigemasa, O. Nagae, C. Sakazawa, R. Nakashima, and T. Matuura, *J. Am. Chem. Soc.*, **100**, 1309 (1978); Y. Shigemasa, M. Kawahara, C. Sakazawa, R. Nakashima, and T. Matuura, *J. Catal.*, **62**, 107 (1980).

9) T. Matsumoto and S. Inoue, *J. Chem Soc., Perkin Trans. 1*, **1982**, 1975.

10) Y. Shigemasa, Y. Matsuda, C. Sakazawa, and T. Matuura, *Bull. Chem. Soc. Jpn.*, **50**, 222 (1977).

11) S. Irie, *Chem. Lett.*, **1984**, 2153.

12) Y. Shigemasa, A. Matsuba, N. Ueda, R. Nakashima, K. Harada, N. Takeda, M. Suzuki, and S. Saito, *Carbohydr. Res.*, **134**, C4 (1984).

13) Y. Shigemasa, T. Hamada, M. Hirabayashi, E. Waki, R. Nakashima, K. Harada, N. Takeda, and M. Suzuki, *Chem. Lett.*, **1981**, 899; M. Irie, K. Fukuyama, T. Tsukihara, Y. Katsube, Y. Shigemasa, and R. Nakashima, *Acta Crystallogr., Sec. C*, **41**, 1814 (1985).

14) T. Matsumoto, M. Yamane, and S. Inoue, *Chem. Lett.*, **1984**, 1819.

15) Y. Shigemasa, K. Oogaki, N. Ueda, R. Nakashima, K. Harada, N. Takeda, M. Suzuki, and S. Saito, *J. Carbohydr. Chem.*, **1**, 325 (1982).

16) T. Matsumoto, H. Yamamoto, and S. Inoue, *J. Am. Chem. Soc.*, **106**, 4829 (1984).

17) J. Castells, F. Geijo, and F. Lopez-Calahorra, *Tetrahedron Lett.*, **21**, 4517 (1980); *Carbohydr. Res.*, **116**, 197 (1983).

18) Y. Shigemasa, H. Matsumoto, Y. Sasaki, N. Ueda, and R. Nakashima, *J. Carbohydr. Chem.*, **2**, 343 (1983); *Bull. Chem. Soc. Jpn.*, **57**, 2761 (1984).

19) Y. Shigemasa, A. Okano, H. Saimoto, and R. Nakashima, *Carbohydr. Res.*, **162**, C1 (1987).

20) Y. Shigemasa, T. Ueda, and H. Saimoto, *J. Carbohydr. Chem.*, **8**, 669 (1989).

21) "Shin Jikken Kagaku Kohza," ed by T. Tachibana, Maruzen, Tokyo (1975), Vol. 1, p. 457.

22) C. E. Bricker and H. R. Johnson, *Ind. Eng. Chem.*, **17**, 400 (1945).

23) H. Saimoto, K. Kotani, Y. Shigemasa, M. Suzuki, and K. Harada, *Tetrahedron Lett.*, **30**, 2553 (1989).