Preparation of 2-Hydroxymethylated Aldose by the Stereospecific Rearrangement of Ketose

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A simple one-stage reaction system which yields 2-C hydroxymethylated aldopentose has been investigated. Four different 2-C branched aldopentoses (2-C hydroxymethylated D-arabinose, D-ribose (Hamamelose), L-lyxose, and D-xylose) were prepared from the corresponding ketoses (D-psicose, D-fructose, L-sorbose, and D-tagatose, respectively). These branched sugars were synthesized by a similar mechanism to the 2-C epimerization of aldose using a nickel complex. It was confirmed that the isomerization of ketose to the side-branched sugar proceeded in the ternary nickel complex through a sequence of stereospecific rearrangements in the sugar. The yields were dependent upon the structure of the substrate ketose and the nickel-ethylenediamine complex. *N*,*N*′-Dialkylated cyclohexanediamines were the most suitable ligands for preparing the 2-C hydroxymethylated branched chain sugar.

In our previous studies[1—7] it was confirmed that various types of aldoses were smoothly epimerized at 2-C by a nickel complex. The influence of the structure of the complex on this reaction has also been discussed. The nickel complex coordinating the *N*- and *N*′-alkylated ethylenediamine ligands showed an excellent epimerizing ability in methanol with high selectivity. It was revealed by a ^{13}C NMR examination that in the course of epimerization the anomeric carbon of a reactant aldose was converted into the 2-C carbon of the corresponding epimerized aldose, while the 2-C carbon of the reactant sugar was changed into the anomeric carbon of the product, and vice versa. In the reaction system, this reaction occurred via a reaction route different from the so-called Lobry–Alberda (LA) rearrangement (ene–diol rearrangement), that is, it proceeded through reversible enolization by an alkaline.

Based on this information, we expected that 2-C hydroxymethylated aldopentose could be obtained in a similar manner to that of the formation of the epimerized aldose, if ketohexose could be regarded as being an aldopentose possessing a hydroxymethyl group at the carbonyl carbon. In agreement with the expectation, the ternary complex readily carried out the rearrangement, and then yielded the corresponding 2-hydroxymethylated aldose.

This work has already been published in part as a preliminary communication. We have already briefly introduced this reaction in the preparation of hamamelose from fructose.[8] In the present paper, a highly efficient synthetic system used to prepare 2-C hydroxymethylated aldopentoses is discussed. The objective of the present work was to verify the previous result by studying in detail the isomerization of fructose and related homologue ketohexoses. We succeeded in obtaining four types of 2-C hydroxymethylated aldopentoses from the corresponding ketoses via a stereospecific rearrangement by the nickel complex.

In the present work, the reaction of four types of ketohexoses (D-psicose, D-fructose, L-sorbose, and D-tagatose) were studied under various conditions in order to elucidate the relationship between the two key processes, that is the coordination of the sugar to the nickel complex, and the rearrangement of the carbon skeleton of the sugars.

The system was compared to that of the epimerization of the aldose–nickel(II)–ethylenediamine complex, which have been well documented in previous literature.[2—7] Various alkyl-substituted acyclic and cyclic diamines were examined. The effect of the *N*-substitution and the chain length of *N*-alkyl group on the extent of the rearrangement to a branched chain sugar was studied in detail.

Results and Discussion

Preparation of 2-C Hydroxymethylated Sugar. The results for the rearrangement of fructose (**4**) are summarized in Table 1; those for the rearrangement of L-sorbose (**7**) into 2-C-hydroxymethyl-L-lyxose (**8**) are given in Table 2. The catalytic activities of the Nickel(II)–diamine complexes estimated in terms of the amount of the branched chain sugar prepared during the reaction as a possible parameter. Each reaction was conducted at 30 °C for 20 min in methanol.

Influence of Structures of the Ligand Diamines. Various types of ligands, such as ethylene-

Table 1. Preparation of 2-*C*-Hydroxymethyl-D-ribose (Hamamelose) from D-Fructose

Ligands[a]	Fru	Ham	Glc	Man	Others
en	97	1	0	0	2
1,1′ en	90	10	0	0	0
2,2′ en	86	13	1	0	0
2,2 en	90	7	0	0	3
*i*3,*i*3′ en[b]	88	4	0	0	8
1,1,1′ en	81	14	1	2	2
1,1,2′ en	68	19	2	2	9
1,1,8′ en	75	19	0	3	3
2,2,2′ en	89	3	0	0	8
1,1,1′,1′ en	88	12	0	0	0
pn	93	1	0	0	6
2,2′ pn	69	27	0	0	4
mpn[c]	91	0	2	0	7
2,2′ mpn	93	5	0	0	2
chxn	93	2	0	0	5
1,1′ chxn	90	4	1	0	5
2,2′ chxn	59	41	0	0	0
3,3′ chxn	41	56	0	0	3
*i*4,*i*4′ chxn[d]	79	21	0	0	0
8,8′ chxn	54	46	0	0	0
NaOH	42	0	39	9	10

a) In the abbreviation of alkylated diamine, the first two numbers refer to the carbon number of *N*,*N*-dialkyl group, and the last number refers to that of *N*′-alkyl group. 1,1,8′-en refers to *N*,*N*-dimethyl-*N*′-octylethylenediamine. b) *N*,*N*′-Diisopropylethylenediamine. c) 1,2-Diamino-2-methylpropane. d) *N*,*N*′-Diisobutylcyclohexanediamine.

Table 2. Preparation of 2-Hydroxymethyl-L-lyxose from L-Sorbose

Ligands	L-Sor	2-HM-Lyx	Others
2,2′ en	77	19	4
1,1,1′ en	72	10	18
3,3′ chxn	62	21	17
8,8′ chxn	67	20	13

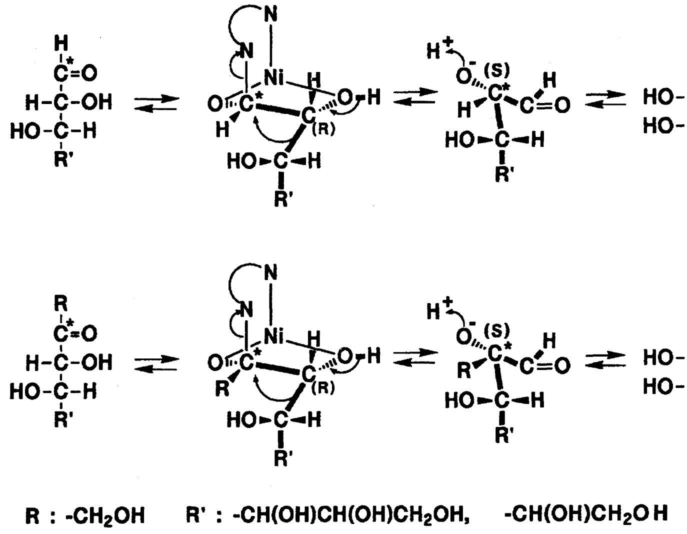
diamine (en), propylenediamine (pn), and cyclohexanediamine (chxn) derivatives, were tested for the reaction. A series of *N*,*N*′-dialkylated cyclohexanediamine (R,R′-chxn) were the most suitable ligands for preparing 2-C hydroxymethylated sugar. Especially hamamelose (**5**) was obtained in 56% yield with the Ni(II)-3,3′-chxn complex with high selectivity in a one-pot reaction. Very few by-products, such as glucose and mannose, were formed under ordinary conditions during the reaction. It is well known that monosaccharides are susceptible to alkaline solution by a variety of bases.[9] In this reaction, the solution containing the nickel–diamine complex was weak basic. These slight amounts of aldoses were prepared via a ene-diol intermediate provided by the abstraction of a hydrogen at 1-C, as the Lobry–Alberda reaction shows. As the reaction temperature increased, the amounts of by-products increased and an extended reaction time changed a colorless reaction mixture to dark brown.

On the other hand, under reaction conditions which contained no nickel–diamine complex, but sodium hydroxide, fructose gave a mixture of unknown carbohydrates in addition to the corresponding isomerized aldoses, glucose and mannose. The aldoses must be prepared by an LA rearrangement of fructose via an enediol intermediate by an alkaline solution. At this stage, the equilibrium between the two epimers was in favor of glucose.[10]

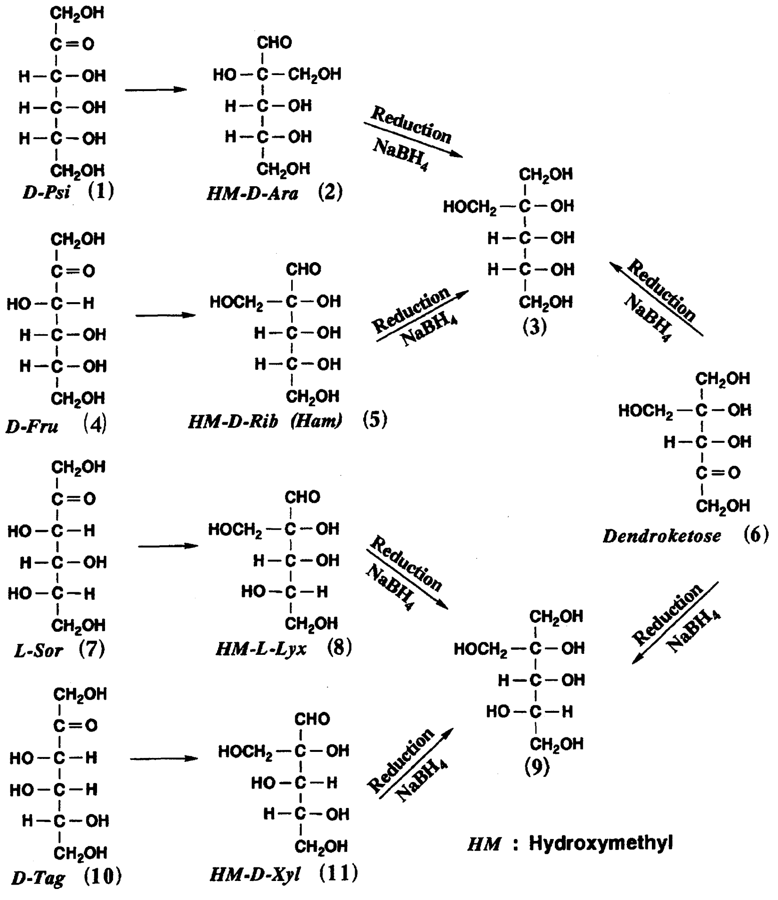
In a discussion about the influence of the diamine structure for the rearrangement of ketoses, we must consider two key steps by which the rearrangement would smoothly proceed. As stated in the reaction-mechanism section, the coordination of the substrate sugar to the nickel complex, i.e., the formation of the ternary complex, is one of the indispensable process for this reaction (Scheme 1). The size of the *N*,*N*-higher dialkylated group of diamines affects the rearrangement of ketoses. The reaction was more depressed as the steric hindrance around the amino group increased. These results in Table 1 could be ascribed to the lack of one of the most important steps, the coordination of ketose to the Ni–diamine complex.

At the same time, the rearrangement of the carbon skeleton between C-1 and C-2, and the release of the resulting isomerized sugar from the ternary complex, is an another key step of this reaction. If the ligand has a primary amino group, such as non-*N*-substituted ethylenediamine, the resulting ternary complex is so stable that the most significant rearrangement process of the carbon skeleton does not occur; that is, sugar does not isomerize. Previously, a ternary complex consisting of nickel, sugar (glucose, mannose, fructose) and a non-*N*-alkylated primary diamine (en, tn) was isolated, and its structure was determined by X-ray crystallography.[11] The results suggest that the progress of the rearrangement of ketoses and aldoses was affected by some factors that participated directly in the coordination of sugars and the elimination of diamine ligands. When a harmonic motion between coordination of the sugar and release of the ligand in the reaction system occurs, the reaction would proceed smoothly. In this context, although a primary amino group is unsuitable, a secondary or tertiary amino group substituted with a suitable alkyl group has advantages for the rearrangement of ketose.

Influence of the Configuration of the Substrate Sugar The coordination of sugar to a nickel complex is a very important process for preparing a branched chain sugar in high yield from ketose. One can readily understand that the steric configuration and conformation of a hydroxyl group of sugars has a significant effect on the formation of the ternary glycoside complex. Four types of 2-C hydroxymethylated aldopentoses including hamamelose were obtained from corresponding ketoses. Scheme 2 summarizes the results. The yields



Scheme 1. Reaction mechanism of the epimerization of aldose (upper half) and the formation of 2-C hydroxymethylated aldose (bottom half).



Scheme 2. Preparation of 2-C hydroxymethylated aldoses from the corresponding ketoses.

of 2-hydroxymethyl-D-ribose (**5**) and 2-hydroxymethyl-L-lyxose (**8**) were 56 and 25%, respectively. On the other hand, the yields of 2-hydroxymethyl-D-arabinose (**2**) and 2-hydroxymethyl-D-xylose (**11**) were extremely low. They were 2 and 5%, respectively. For a series of ketohexose, the contrast among the yields can be explained in terms of the relative configuration of the two hydroxyl groups of the substrate ketose. This suggested that a sugar–Ni complex interaction contributed in some way to coordination during the reaction. The 2-C branched chain sugars were produced at relatively high yield from two ketoses, D-fructose (**4**) and L-sorbose (**7**), whose two hydroxyl groups at 3-C and 4-C are aligned *threo*. On the other hand, two other ketoses,

1 and **10**, in which their two hydroxyl groups at 3-C and 4-C has an *erythro* relation, gave the corresponding isoemrized sugars in very low yields.

This indicates that the availability of the hydroxyl groups for coordination with the nickel–diamine complex is the principal factor that determines the extent of the rearrangement of ketose. These results suggested that the coordination of **1** and **10** to the nickel–diamine complex was more difficult compared to that of **4** and **7**. This is also in agreement with the fact that the configuration of hydroxyl groups in sugar was a controlling factor of the epimerization of aldoses.[4)]

Identification of the Isomerized Sugar. GLC Analysis. Each isomerized sugar was reduced to the corresponding alditol, which was in turn trimethylsilylated to prepare samples for a GLC analysis. It was not possible to distinguish a pair of enantiomers by the glass capillary column used here.

The structure of each alditol and the retention time were considered in order to identify the reaction products. We succeeded in identifying the reaction products by analyzing the gas chromatogram. For example, it is necessary to take α- or β-anomer, pyranose and furanose into consideration when sugars are analyzed directly. However, such considerations are not required for the alditols. The alditol derivatives were particularly suitable for the analysis of sugars of different structure types in this work. Theoretically, as shown in Scheme 2, **2** and **5** gave the same alditol **3** as **8**, and **11** gave **9**. The relative position of two hydroxyl groups at C(3) and C(4) allows only two isomers, *erythro* **3** and *threo* **9**, to be concerned. In addition, they could be compared to the alditols obtained from dendroketose (**6**), which was independently prepared by the dimerization of dihydroxy acetone.[12)] 2-C-(Hydroxymethyl)pentitols obtained by the reduction of **6** showed two peaks in their GLC. Their retention times were 10.04 and 10.35 min., respectively (Fig. 1). The retention time of alditol **3** obtained from the isolated hamamelose (**5**) was 10.35 min and that of **9** from **8** was 10.04 min. The retention times of the samples were in agreement with those of the alditols of known structure. The fact that both retention times of the alditols prepared in two different ways were consistent with each other is one piece of evidence used to validate our theory introduced in Scheme 2.

NMR Analysis. The structure of hamamelose (2-C-hydroxymethyl-D-ribose) (**5**) was proven by a direct comparison with an authentic sample, which was independently prepared according to Ho's method.[13)] In addition, some ^{13}C NMR data for hamamelose have been reported in the literature.[14)] The spectrum was in good agreement with that of the standard sample.

The structure of the isolated acetylated branched sugar, 2-C-hydroxymethyl-L-lyxose (**8**), was determined on the basis of the ^{1}H NMR spectral data (refer to Experimental section). The ^{1}H NMR spectrum of the crude reaction product suggested that it comprised a mixture of four types of isomers, which should be α- and β-anomers and furanose and pyranose isomers. The facts that four singlets were observed between $\delta=5.95$ and 6.75, which could be assigned to protons at the anomeric carbon, and that there were roughly twenty singlet peaks resulting from acetyl methyl groups at about $\delta=2.1$, proved the above arguments. Purification of the products was achieved by a triple silica-gel column chromatography eluted. One constituent (**8**-Acetate), after isolation from other isomers, was identified to be penta-*O*-acetyl-2-*C*-hydroxymethyl-β-L-lyxofuranose on the basis of the decoupled and NOE spectra. Notable NOEs were observed between H-3 and H-1/H-3 and one of H-2′. The acetoxyl group must occupy an equatorial position because of the rigid steric conformation of the furanose ring. The assigned stereochemistry was also confirmed from the equality of the coupling constants between H-4 and each of the two H-5s.

Fig. 1. Gas chromatograpy of the TMS-lated of the reduced products from dendroketose (**6**).

Equilibrium between Fructose and Hamamelose. During a previous study of the epimerization of aldoses it was demonstrated that the transformation between two C-2 epimers was smoothly equilibrated. A similar reversible isomerization between fructose and hamamelose, which is ascribable to a rearrangement of the carbon skeleton of sugar, was discussed. The results are summarized in Fig. 2. The final solution compositions were identical when either fructose or hamamelose was used as the starting sugar. Under these conditions, the reaction reached equilibrium in 20 to 40 min.

Reaction Mechanism. In order to understand the reaction thoroughly, 2*-Fru (fructose, whose 2-C carbon was labeled with ^{13}C) was used as the starting sugar. Figure 3 shows the ^{13}C NMR spectrum of the reaction product, when 2*-Fru was treated with a nickel–*N*,*N*′-diethylcyclohexanediamine complex in methanol. The spectrum demonstrated that the product, hamamelose, had a labeled carbon at 2-C. Four peaks at about 75—

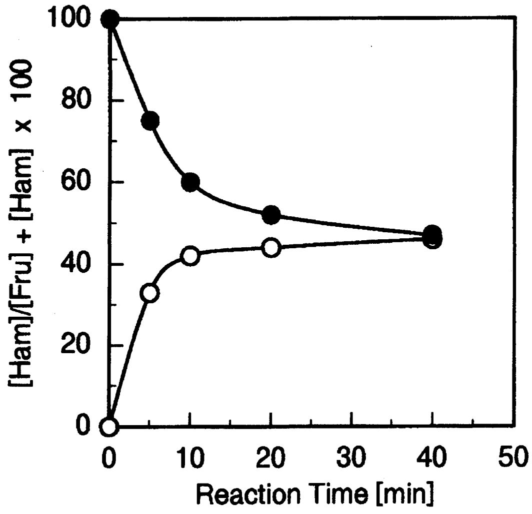


Fig. 2. Equilibrium between fructose and hamamelose. —○—: Fru→Ham, —●—: Ham→Fru.

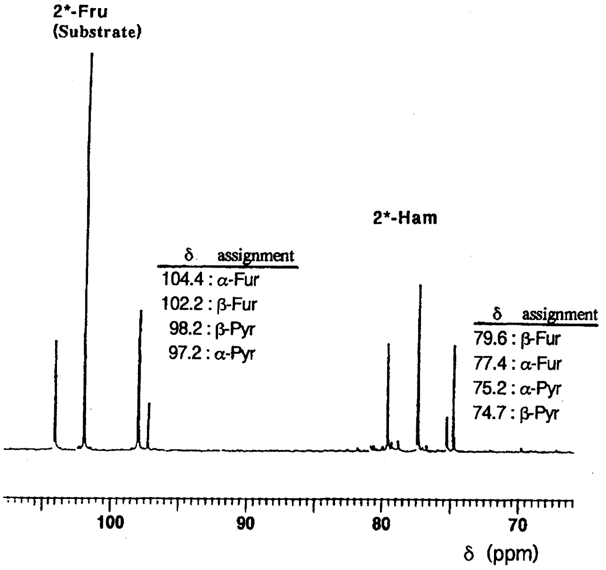


Fig. 3. ^{13}C NMR spectrum of the product obtained from fructose labeled with ^{13}C at C-2.

80 ppm were assigned to 2-C of hamamelose, as shown in Fig. 3.[14] This is the most important point, and it shows that the carbon sequence of fructose was rearranged between 2-C and 3-C, as indicated clearly in Fig. 3.

The reaction mechanism of the 2-C hydroxymethylation of ketose is shown in Scheme 1 (bottom half) compared to that of the epimerization of aldose (top half). The NMR spectrum in Fig. 3 suggests that the rearrangement of the carbon skeleton across the ternary glycoside intermediate complex comprising nickel, *N*-alkylated diamine and ketose proceeds in a manner similar to that of the the eprimerization of aldose reported previously. The rearrangement takes place via a Ni^{2+} -involved five-membered chelate intermediate, in which the leaving diamine ligand and the migrating of 2-C, 3-C bond are arranged in an antiperiplanar relationship to create the reverse configuration at 2-C.

Experimental

General Measurement. The melting points were recorded on a Yanagimoto melting-point apparatus (MP-J3), and were uncorrected. IR spectra were taken with a JASCO spectrometer (FT/IR-5300). ^{1}H and ^{13}C NMR spectra were recorded with JEOL FX 90A (90 MHz for ^{1}H NMR and 22.5 MHz for ^{13}C NMR), JEOL GX 400 (400 MHz for ^{1}H) and JNM-GSX 270 (67.5 MHz for ^{13}C) instruments. The chemical shifts are reported in ppm downfield (δ) from the internal standard (TMS in $CDCl_3$, DMSO-d_6 and DSS in D_2O). Throughout this work, Merck precoated TLC plates (Silica-gel 60 F254, 0.25 mm, Art 5715) were used for the TLC analysis. For preparative column chromatography Wacogel C-200 was employed.

GLC data were obtained by a GL Science Model GC-380 instrument with flame-ionization detectors. A capillary column (0.25 mm i.d.×25 m, OV-1 bonded) was set at 190 °C isothermally, and the injector temperature was higher by 50 °C than the column temperature. Samples were injected using a Hamilton Model 7001. Under a given set of operating conditions, the retention time served as a method for qualitative identification.

Material. Commercial sugars of the highest quality available were used. D-Psicose, D-fructose, L-sorbose, and D-tagatose were examined. The ^{13}C-enriched fructose at C-2, [2-^{13}C]-Fru, was purchased from ISOEC Inc., Ohio. 4-Hydroxymethyl-1,3,4,5-tetrahydroxy-2-pentanone, 2-C-(Hydroxymethyl)-2-ketopentose, Dendroketose (**6**) was prepared according to the method of Matsumoto.[12] A variety of branched chain sugars such as (**2**), (**5**), (**8**), (**11**), and (**6**) were reduced by sodium borohydride by a conventional method.[15] All other reagents used were of highest commercial grade, and were used without further purification.

The diamine ligands were either commercial products or prepared in a similar manner as in previously published works[2,4] *N*,*N*-Dimethylethylenediamine, propylenediamine, and cyclohexanediamine were reacted with the corresponding aldehyde; the resulting Schiff's bases were reduced with sodium borohydride, *N*-acylated diamines were reduced with lithium aluminium hydride in dry THF. The diamines were purified by distillation in vacuo. The boiling points of newly prepared diamines are summarized below. (°C/mmHg, 1mmHg=133.322 Pa). 1,1,8′-en, 87—88/0.05; 2,2′-pn, 64—66/33; 2,2′-mpn, (*N*,*N*-diethyl-1,1-dimethylethylenediamine), 64—66/29; 1,1′-chxn, 77—80/7; 2,2′-chxn, 50—52/0.2; 3,3′-chxn, 120—122/5; *i*4,*i*4′-chxn, 128—131/7.8; 8,8′-chxn, 132—138/0.2. Their structure and purity were determined on the basis of an elementary analysis as well as their IR and NMR spectra in addition to TLC and physical-constant measurements. ^{1}H NMR spectrum of 1,1,8′-en (90 MHz; 20mg/0.35 ml $CDCl_3$, Me_4Si) is shown here as an example. $\delta=0.89$ (3H, t, $J=7$Hz, $C\underline{H}_3(CH_2)_7$-), 1.25 (10H, br s, $CH_3(C\underline{H}_2)_5$-), 1.51 (2H, m, $CH_3(CH_2)_5C\underline{H}_2CH_2$), 2.14 (1H, br s, $N\underline{H}$), 2.23 (6H, s, N $(C\underline{H}_3)_2$), 2.42, 2.69 (2H×2, two t, $J=7$ Hz, $NC\underline{H}_2C\underline{H}_2N$), 2.61 (2H, t, $CH_3(CH_2)_5CH_2C\underline{H}_2$-).

Other spectra were also in a fair agreement with the theoretical ones. Lower homologues such as 1,1′-en, 2,2′-en, 2, 2-en, 1,1,1′-en, and 1,1,1′,1′-en were purchased from Tokyo Kasei Chemicals Co., Tokyo. The chirality of the diamines, based on their asymmetric carbon, such as pn and chxn derivatives, were not taken into account in this study.

Preparation of 2-C-hydroxymethyl Aldopentoses. In a typical experiment, 1 mmol $NiCl_2 \cdot 6H_2O$ and 2 mmol of each of diamine derivative were placed in a round-bottom flask containing 15 ml of methanol. After the addition of 1 mmol of ketose, the reaction mixture was kept at 30 °C for 20 min with stirring during the reaction. The reaction time varied depending on the reaction conditions. The resulting ternary complex was easily decomposed to its constituents by neutralization of the product solution with 1 M-HCl (1 $M=1\ mol\,dm^{-3}$). The product solution was treated with Dowex 50 W×2 (H^+ type) and Dowex 2×8 ($HCO_3{}^-$ type) ion-exchange resin columns to deionize the reactant ions. A work up of the elution, and following qualitative and quantitative analyses of the resulting sugars were carried out. Trimethylsilyl derivatives were prepared using reagents developed by Sweely,[16] hexamethyldisilazane together with chlorotrimethylsilane, in pyridine solution at room temperature. TMS derivatives were extracted with chloroform and washed with water. Chloroform was removed in vacuo at 40 °C with a rotary evaporator, and the sample was dissolved in hexane.

Preparation and Isolation of the Total Acetate of the Branched Aldose (8). The reaction product gave two types of the glycoside complex: One was a raw-material sugar complex; the other was the product sugar complex. They were separated into each different ternary-complex by Sephadex LH-20 column chromatography. Separation by methanol elution depended on the kind of sugar comprising the complex, the substrate ketose or the product side-chain branched sugar. The following cleavage of the isolated complex and the preparation of a free sugar were carried out in a similar manner as described above. The acetylation of the hydroxyl groups of aldose (**8**) was accomplished according to a conventional manner. For instance, the treatment of **8** with acetic anhydride in pyridine followed by leaving standing at 40 °C for 8 h yielded a total acetate of **8** at 32% yield. In order to improve this rather inefficient acetylation, 4-dimethylaminopyridine was added to the above-mentioned reaction system. The reaction was complete after 5 h to yield (**8** acetate) at 53% yield. Pure 1,2,2′,3,5-penta-*O*-acetyl-2-*C*-hydroxymethyl-*β*-L-lyxofuranose was obtained as one of the components by silica-gel column chromatography of the acetate using a mixed eluate of hexane and ethyl acetate (5/1 v/v). The preparative chromatography was repeated three times in order to obtain very pure acetate.

Elemental Analysis: Found: C, 48.96; H, 6.02%. Calcd for $C_{16}H_{22}O_{11}$: C, 49.23; H, 5.64%. ^1H NMR (400 MHz, $CDCl_3$) $\delta=6.37$ (1H, s, H-1), 5.57 (1H, d, $J_{3-4}=5.2$ Hz, H-3), 4.92, 4.70 (each 1H, d, $J_{\mathrm{gem}}=13.5$ Hz, H-2), 4.91—4.95 (1H, m, H-4), 4.19 (1H, dd, $J_{\mathrm{gem}}=13.1$ and $J_{5-4}=3.0$ Hz, one of H-5), 3.67 (1H, ddd, $J_{\mathrm{gem}}=13.1$, $J_{5-4}=3.0$ Hz and $J_{5-3}=0.9$ Hz, the other of H-5), 2.13, 2.12, 2.11, 2.10, 2.01 (3H×5, five s, CH_3CO); ^{13}C NMR (270 MHz, $CDCl_3$) $\delta=170.11$, 169.62, 169.22, 169.08, 168.79, 96.22, 89.63, 68.20, 66.65, 61.32, 60.23, 21.47, 21.00, 20.83, 20.77, 20.72.

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