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C-2 Epimerization of Disaccharides by Calcium(II) - Monoamine Systems. A Direct Synthesis of (1→4)-Linked Disaccharides Having a D-Mannose Unit as a Reducing Terminal

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(1→4)- and (1→6)-linked disaccharides were epimerized at C-2 of the reducing terminal under mild conditions by calcium(II) - N-alkylated monoamine systems. Naturally rare (1→4)-linked heterodisaccharides having a D-mannose unit as a reducing terminal can be prepared in one step from disaccharides having a D-glucose unit which are abundunt in nature.

Carbohydrates have a wide spread of occurrence in nature and have many biological activities. Especially, naturally rare carbohydrates have received increasing attention in medical and immunological chemistries, because they were proved to be involved in glycoproteins, glycolipids, and antibiotics. So, it has been desired to develop simple and effective synthetic procedures for naturally rare mono- and disaccharides.

Previously, Bilik et al have shown that, in mildly acidic solutions of molybdate, aldoses epimerize at C-2 with the formation of a thermodynamic equilibrium mixture of the two epimers.[1,2] Further, a series of our recent works have demonstrated that nickel(II) complexes of N-alkylated diamines smoothly promote the C-2 epimerization of aldoses via a stereospecific rearrangement of the carbon skeleton.[3-5] However, in both cases, those compounds that do not have a free hydroxy group at C-4, e.g. (1→4)-linked disaccharides, were not epimerized at C-2, presumably because the substituents of C-4 hydroxy group prevent access of the carbohydrate skeleton to the metal centre. In the present study, by employing the combination of calcium(II) ion and N-alkylated monoamines, we have succeeded in the efficient C-2 epimerization of the reducing terminal of (1→4)-linked disaccharides which are abundant in nature.

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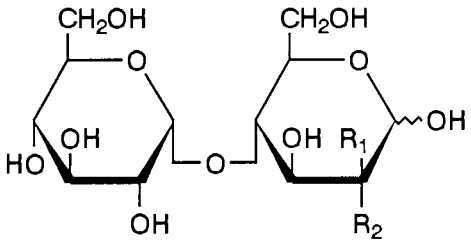

1 R_1=H, R_2=OH
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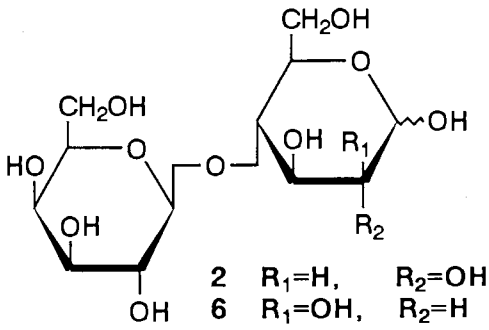

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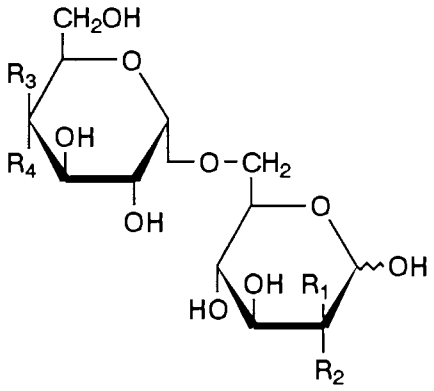

3 R_1=R_3=H, R_2=R_4=OH
4 R_1=R_4=H, R_2=R_3=OH
7 R_1=R_4=OH, R_2=R_3=H
8 R_1=R_3=OH, R_2=R_4=H

Disaccharides[6] (shown above) were treated with $CaCl_2 \cdot 2H_2O$ (1 equiv.) and N-alkylated amines (Et_3N, Et_2NH etc) (2 equiv.) in 100 mL of methanol at 60 °C for 10 min. Then the reaction mixture was dissolved in 100 mL of water and was kept at pH 7.0 with 1 mol dm^{-3} HCl for 30 min at room temperature. Subsequently the solution was treated with excess of Dowex 50WX-2(H^+ type) and Dowex MSA-1(HCO_3^- type). The resultant sugar components were analyzed by HPLC[3] and ^{13}C NMR[4,7] (Table 1).

(1→4)-Linked disaccharides having a D-glucose unit as a reducing terminal (**1** and **2**) epimerized at C-2 of the reducing unit to give epimaltose (**5**) and epilactose (**6**). Epimaltose (**5**) and epilactose (**6**) containing a D-mannose reducing terminal were also transformed to their C-2 epimers (**1**) and (**2**). N-Alkylated monoamines (Et_3N and Et_2NH) were proved to be more effective than diamine and aminoalcohol derivatives (N,N,N',N'-tetramethylethylenedimaine and N,N-dimethylaminoethanol). (1→6)-Linked disaccharides (**3**, **4**, **7**, and **8**) were similarly epimerized at C-2 of the reducing unit by a combination of Ca^{2+} and Et_3N. These reactions proceeded without any considerable side reactions such as decomposition into monosaccharide components and formation of ketoses. Only in the case of maltose (**1**) ⇌ epimaltose (**5**), a slight decomposition into D-glucose and D-mannose was observed (<5%). This is the first example of metal-promoted direct C-2 epimerization of (1→4)-linked disaccharides. By employing this simple procedure, naturally rare (1→4)-linked hetero-disaccharides having a D-mannose unit as a reducing terminal can be easily prepared from disaccharides having a D-glucose unit as a reducing terminal which are abundant in nature.

Table 1. Results of C-2 Epimerization of Disaccharides

Run	Substrate		Amine	Yield of C-2 epimers/% [a]	Recovery of substrate/% [a]
1	maltose	(**1**)	Et_3N	57 (**5**)	41[b]
2	maltose	(**1**)	Et_2NH	52 (**5**)	41[b]
3	maltose	(**1**)	N,N-$Me_2NCH_2CH_2OH$	50 (**5**)	48[b]
4	maltose	(**1**)	N,N,N',N'-Me_4en	37 (**5**)	47[b]
5	lactose	(**2**)	Et_3N	39 (**6**)	61
6	lactose	(**2**)	N,N,N',N'-Me_4en	4 (**6**)	86
7	isomaltose	(**3**)	Et_3N	31 (**7**)	47
8	melibiose	(**4**)	Et_3N	40 (**8**)	50
9	epimaltose	(**5**)	Et_3N	26 (**1**)	66[b]
10	epilactose	(**6**)	Et_3N	32 (**2**)	55
11	epiisomaltose	(**7**)	Et_3N	10 (**3**)	62
12	epimelibiose	(**8**)	Et_3N	11 (**4**)	79

a) Determined by HPLC, based on the substrate. b) Small amounts of D-glucose and D-mannose were detected (1-5%).

We have previously revealed that monosaccharides were epimerized at C-2 by nickel(II)-diamine[3] or calcium(II)-monoamine complexes[5] via novel stereospecific rearrangement of the carbon skeleton. In the present reaction, the epimerization proceeded rapidly in mild basic conditions, and the formation of ketoses was suppressed in very low yields. These similarities to the epimerization of monosaccharides by Ni^{2+}-diamine and Ca^{2+}-monoamine systems strongly suggest that the present transformation also involves the rearrangement of carbon skeleton resulting in inversion of the configuration at C-2 of the reducing unit. Unlike the nickel(II) and molybdate(VI) promoted epimerization, the bulky substituents of C-4 hydroxy group, glycopyranosyl groups, did not hinder the reaction in the Ca^{2+}-monoamine system, probably due to the strong interaction between Ca^{2+} and hydroxy groups[8] and the flexible coordination sphere around the calcium centre. These indicate that various utilizing systems might be developed by with appropriate choice of metal ions and amine derivatives. Further studies along this line are now in progress.

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6) Disaccharides used as a substrate and their systematic names are as follows;
maltose (**1**), O-α,D-glucopyranosyl-(1→4)-D-glucose;
lactose (**2**), O-β,D-galactopyranosyl-(1→4)-D-glucose;
melibiose (**3**), O-α,D-galactopyranosyl-(1→6)-D-glucose;
isomaltose (**4**), O-α,D-glucopyranosyl-(1→6)-D-glucose;
epimaltose (**5**), O-α,D-glucopyranosyl-(1→4)-D-mannose;
epilactose (**6**), O-β,D-galactopyranosyl-(1→4)-D-mannose;
epiisomaltose (**7**), O-α,D-glucopyranosyl-(1→6)-D-mannose;
epimelibiose (**8**), O-α,D-galactopyranosyl-(1→6)-D-mannose.

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