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Studies of the stereoselective reduction of ketosugar (hexosulose)

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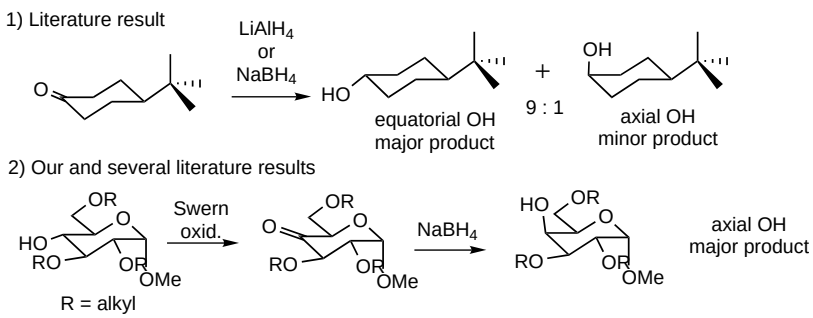
Abstract—The results from the studies of the stereoselective reduction of ketosugar (hexosulose) were reported. Combining our results and those reported in the literature, we summarize the factors in controlling the stereoselective reduction of ketosugars. These findings are valuable in the synthesis of various carbohydrate derivatives. © 2001 Published by Elsevier Science Ltd.

1. Introduction

Natural or non-natural carbohydrate mimetics,[1,2] such as fluorosugars, aminosugars, and deoxysugars, have attracted a growing interest due to their broad spectrum of application in chemistry, biochemistry, medicinal, and pharmaceutical fields. Our group is interested in studying the structure–activity relationship of aminosugars through a synthetic approach. Aminosugars are a group of structurally diverse unusual sugars bearing amino substitution from a normal sugar scaffold, and have been shown to closely relate to the activity of the aminosugar-containing antibiotics.[3–6] As part of our research, which involves the introduction of an amino (azido) group on the equatorial position of a hexose, it is necessary to epimerize the equatorial hydroxyl group into an axial configuration on the hexose scaffold, followed by a S_N2 azide substitution.

Typically our method of inverting the configuration of the hydroxyl group consists of a Swern oxidation to oxidize the hydroxyl group to a ketone that can then be reduced by $NaBH_4$ to a hydroxyl group of the opposite configuration. It has been our experience, which is fortified by other literature examples,[7–16] that the protecting groups on the α-hydroxyl groups of the ketone have an effect on whether the configuration of the resulting alcohol can be inverted or not. According to the literature results, the reduction of the 4-*tert*-butylcyclohexanone with $LiAlH_4$ or $NaBH_4$ favors the formation of a hydroxyl group with an equatorial configuration (Scheme 1.1).[17,18] Large nucleophile or hydride reducing agents, such as L-Selectride, favor the formation of an axial hydroxyl group. However, our results as well as some examples in the literature showed that $NaBH_4$ could reduce the ketohexoses and provide an axial hydroxyl group as the dominant product (Scheme 1.2). This paper summarizes our findings and discusses the conditions that allow for this transformation, the inversion from equatorial to axial hydroxyl group on a hexose, to occur.



Scheme 1. Stereoselective reduction of cyclohexanone moieties.

Keywords: ketosugar; hexosulose; stereoselective reduction; aminosugar.

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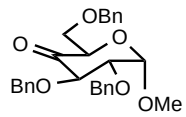
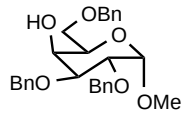
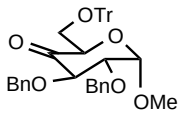
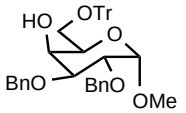
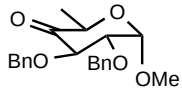
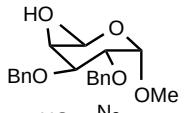
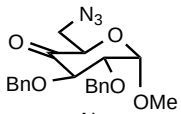
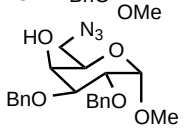
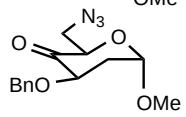
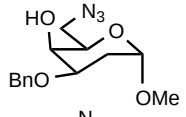
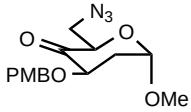
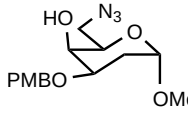
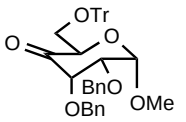
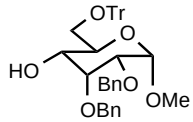
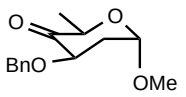
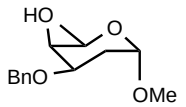
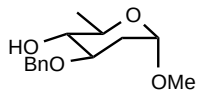
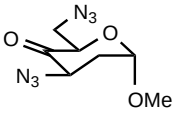
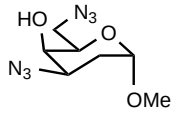
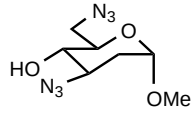
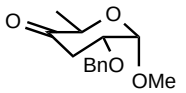
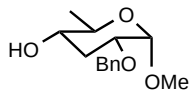
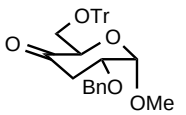
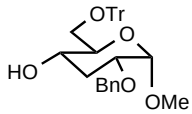
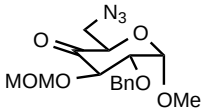
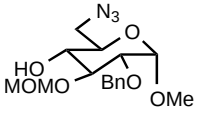
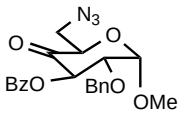
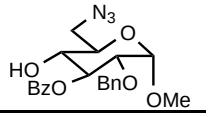
2. Results and discussion

Various hexose moieties[19] were converted into their corresponding ketosugars via Swern oxidation. The ketosugars were subjected to the $NaBH_4$ reduction without purification. The products were purified by column chromatography and the configuration of each sugar was assigned by the coupling constant from ^1H NMR.

Table 1. Stereoselective reduction of 4-ketosugars from the work of this paper

entry	ketosugars	products (% yield)	
		axial OH	equatorial OH
1		 80%	not isolated
2		 51%	not isolated
3		 94%	not isolated
4		 80%	not isolated
5		 65%	not isolated
6		 49%	not isolated
7		not isolated	 80%
8		 62%	 26%
9		 14%	 12%
10		not isolated	 99%
11		not isolated	 79%
12		not isolated	
13		not isolated	

We did not find any explanation in the literature regarding this reverse stereoselectivity. The only organized data comes from the reduction of 2-ketosugars.[11] Therefore, we decided to examine the results from our synthetic work, and those results reported in the literature. We discovered that the presence of *a vicinal equatorial alkoxyl group* is the pivotal criterion for the formation of an axial hydroxyl group during the $NaBH_4$ reduction, which is consistent with the observation for the stereoselective reduction of 2-ketosugars (Table 1, entries 1–6 and Table 2, entries 1 and 2). When no vicinal equatorial alkoxyl group is present as in the cases of deoxysugars, the sodium borohydride reduction will favor the formation of an equatorial hydroxyl group, which is consistent with the literature result for the reduction of the 4-*tert*-butylcyclohexanone (Table 1, entries 10 and 11). We also noticed that the azido group has little effect on the stereoselectivity of reduction (Table 1, entry 9). The substituents (BnO, TrO, H, or N_3) on the C-6 carbon have no effect on the stereoselectivity of the reduction of 4-ketosugars (Table 1, entries 1–4). However, one interesting example shows that when there is a free hydroxyl group on the C-6, the reduction favors the formation of the equatorial hydroxyl group, despite the presence of a benzyl group on C-3 (Table 3, entry 9). It was proposed that the C-6 hydroxyl group complexes with the reducing agent, $NaBD(OAc)_3$, and proceeds through a geometrically favored axial attack, which generated the observed equatorial hydroxyl group.

The presence of a vicinal benzoyl group favors the formation of the equatorial hydroxyl group, which is consistent with studies of the reduction of 2-ketosugars (Table 1, entry 13). However, we found a reported example in the literature where the presence of a vicinal benzoyl group offered an axial hydroxyl group from a 3-ketogalactose (Table 3, entry 7). Galactose is known to adopt a twisted chair conformation, which may explain this exceptional result. In addition, this result implies that in order to predict the stereoselectivity via the use of the vicinal equatorial alkoxyl group as the controlling factor for the formation of an axial hydroxyl group, a chair-like conformation of the hexosulose (ketosugar) is essential. When the conformation of a hexosulose is distorted from a chair-like one, the prediction regarding the presence of the vicinal equatorial alkoxyl group on the stereoselectivity starts to deviate. We also obtained similar results in Table 2, entry 3, where a significant amount of equatorial hydroxyl group was observed from a ketosugar with galactose-like configuration, despite the presence of a vicinal equatorial alkoxyl group on C-2. The importance of the chair conformation can also be noticed in the example of Table 1, entry 8. A conformationally more flexible 2,6-dideoxysugar gave only about a 2/1 ratio of axial OH/equatorial OH when subjected to the hydroxyl group inverting reactions.

To our surprise, the methoxylmethyl (MOM) group provides equatorial hydroxyl group as the dominant product (Table 1, entry 12). To our knowledge, this is the first example concerning the stereoselective reduction of a ketosugar with a MOM group participation. When the steric factor governs the selectivity as in the case of the reduction of 2-ketosugars on methyl α-D-glycoside (Table 2, entries 4 and 5), an equatorial hydroxyl group was obtained as expected. We also obtained the same result where a vicinal axial alkoxyl group on C-3 directed the formation of an equatorial hydroxyl group on C-4 by, presumably, steric effect (Table 1, entry 7). In general, the steric factor has a

Table 2. Stereoselective reduction of 2- and 3-ketosugars from the work of this paper

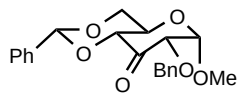
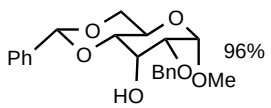
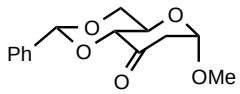
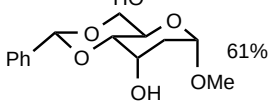
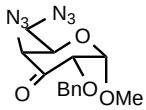
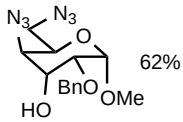
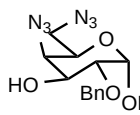
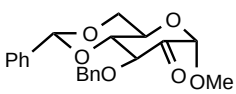
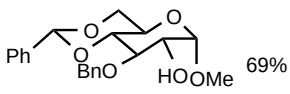
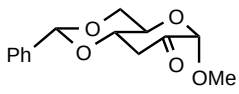
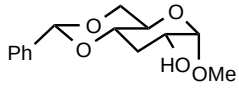
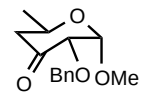
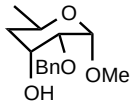
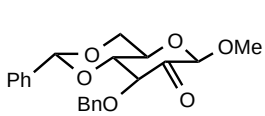
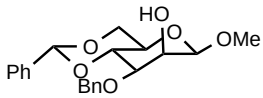
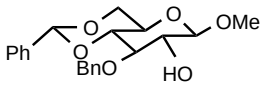
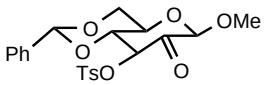
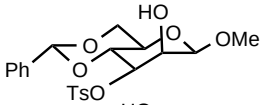
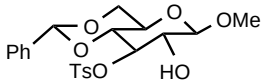
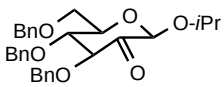
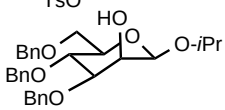
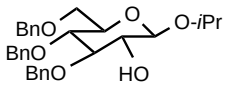
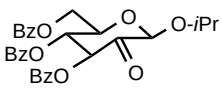
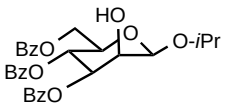
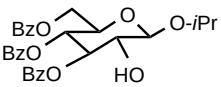
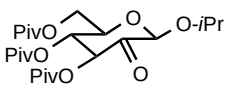
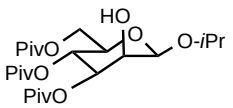
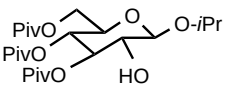
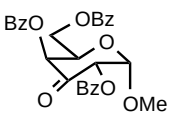
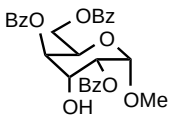
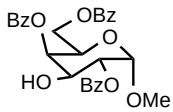
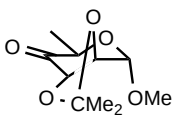
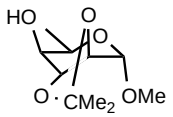
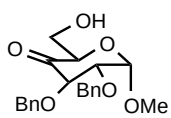
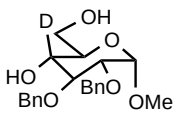
entry	ketosugars	products (% yield)	
		axial OH	equatorial OH
1		 96%	not isolated
2		 61%	not isolated
3		 62%	 14%
4		not isolated	 69%
5		not isolated	

Table 3. Stereoselective reduction of ketosugars from the reported work

entry	ketosugars	products (% yield)			note
		axial OH	ratio of $OH_{(ax)}/OH_{(eq)}$	equatorial OH	
1		 77%		not isolated	ref. 7,8
2			10 : 1		ref. 9
3			2 : 1		ref. 10
4			50 : 1		ref. 11
5			5 : 2		ref. 12
6			3 : 1		ref. 13
7			9 : 1		ref. 14
8		not reported		 98%	ref. 15
9		 93%		not reported	ref. 16

greater influence on the stereoselectivity of a ketosugar reduction than the presence of vicinal equatorial alkoxyl group, which has a more dominant effect than the vicinal deoxygenation.

Based on our and the literature reported results, we summarize the factors in controlling the stereoselective reduction of ketosugars as the following: (1) A chair-like conformation is essential, although not critical, for the prediction of favored stereoselectivity. (2) The presence of a protected vicinal axial hydroxyl group favors the formation of an equatorial hydroxyl group due to the steric effect. (3) In the absence of steric factors, the presence of *a vicinal equatorial alkoxyl group*, such as BnO, PMBO, benzylidene, or isopropylidene, favors the formation of an axial hydroxyl group. (4) The presence of vicinal acyl groups (Bz, Piv, or Ts groups), MOM group, or CH_2 funcitionality from deoxygenation reduces or inverses the preference for the formation of the axial hydroxyl group. (5) Vicinal azido group has no effect in controlling the stereoselectivity of the reduction of ketosugars. (6) The protecting groups on the C-6 of a 4-ketosugar have no effect on the stereoselectivity of the reduction of ketosugar except when a free hydroxyl group is present. In which case, the C-6 hydroxyl group has a greater effect in controlling the stereoselectivity of the reduction of a 4-ketosugar than a vicinal equatorial alkoxyl group does.

In general, the summarized results from this paper provide a practical method for synthesizing various carbohydrate derivatives. We are currently employing these findings for the preparation of biologically interesting azide-substituted hexoses in regiospecific and stereospecific fashions.

General procedure for Swern oxidation and $NaBH_4$ reduction. To a solution of $(COCl)_2$ (0.52 mL, 6.0 mmol) in 20 mL anhydrous CH_2Cl_2 at −78°C, anhydrous DMSO (0.85 mL, 12 mmol) was added and the resulting solution was stirred for 20 min allowing the temperature to warm up to −65°C. To the reaction flask, a solution of hexose (3.0 mmol) in 5 mL CH_2Cl_2 was added. The reaction mixture was stirred for 30 min allowing the temperature to warm up to −45°C. To this solution, dried DIPEA (4.2 mL, 24 mmol) was added, and the reaction was allowed to warm up to 0°C in 1 h. After completion of the reaction (monitored by TLC, hexane/ethyl acetate = 1/1), the reaction mixture quenched with 1N HCl and diluted with CH_2Cl_2 or EtOAc. The organic layer was washed with pH 7 buffer (three times) and dried over Na_2SO_4. After removal of solvent, the crude product was obtained usually as viscous oil. The crude ketosugar from previous step was dissolved in MeOH (20 mL) and cooled to 0°C, then solid $NaBH_4$ (9.0 mmol) was added in small portions. After being stirred for overnight, the reaction was quenched by addition of 1N $HCl_{(aq)}$. After removal of most of the solvent, the reaction mixture diluted with EtOAc, washed with 1N HCl, water, saturated $NaHCO_{3(aq)}$, brine, then dried over Na_2SO_4. After removal of solvent and purification with gradient column chromatography the product was obtained usually as clear oil.

Acknowledgements

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19. The complete syntheses of these hexoses will be reported separately.