Synthesis of L-Pyranosides from 5-Enopyranosides by Diastereoselective Hydroboration/Oxidation

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Abstract: Improved synthesis of L-pyranosides utilizing diastereoselective hydroboration/oxidation of 5-enopyranosides was investigated. A unique phenomenon in the diastereoselectivity of the hydroboration was incidentally found. The method was successfully applied to the synthesis of L-iduronic acid.

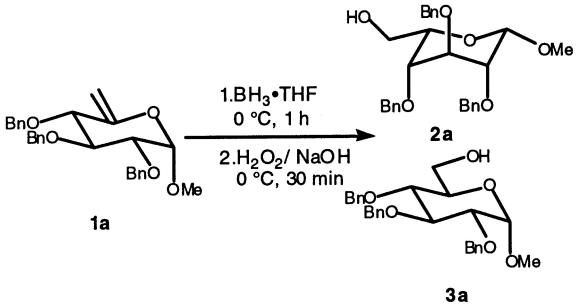
Key words: carbohydrates, diastereoselectivity, glycosides, hydroboration, synthesis

L-Sugars, which are typical components of bioactive natural products, play important roles in various biological processes.[1] Numerous studies have been performed on the synthesis of L-pyranose and L-furanose.[2] In previous papers, we described the novel synthesis of L-idose, L-altrose, L-gulose,[3] and L-ribose.[4] Our strategy was based on the Mitsunobu reaction,[5] which epimerizes the critical C-5 stereocenter and enables the efficient conversion of readily available D-sugars into L-sugars. Along this line, we herein report an alternative approach to L-pyranoside synthesis utilizing the diastereoselective hydroboration/oxidation of 5-enopyranosides.

Several reports have focused on the study of hydroboration/oxidation of 5-enopyranosides,[6] specifically on the conversion of D-glucoside into L-idose or L-iduronic acid, which is a typical component of mammalian glycosaminoglycans.[7] However, there appeared to be no previous systematic investigation of various pyranosides. We therefore examined the diastereoselective hydroboration/oxidation of methyl 5-enoglucoside, 5-enogalactoside, and 5-enomannoside.

Initially, methyl α-5-enoglucopyranoside **1a**[8] was reacted with 2 equivalents of BH_3·THF at 0 °C and then oxidized to provide predominantly L-idoside (73% yield, **2a**[9]:**3a**[10] = 2.1:1, Table 1, entry 1). To obtain a satisfactory yield, the amount of the reagent BH_3·THF was gradually increased.[11] Interestingly, an increase in BH_3·THF resulted in a high stereoselectivity of **2a** (Table 1). The reaction with 10 equivalents of BH_3·THF gave the remarkably high ratio of **2a**:**3a** = 11:1 (entry 6). It should be noted that the amount of the reagent significantly modified the distribution of the products. Such unusual results prompted us to examine the hydroboration/oxidation of 5-enogalactoside **1b** and 5-enomannoside **1c**. The results are summarized in Tables 2 and 3, respectively.

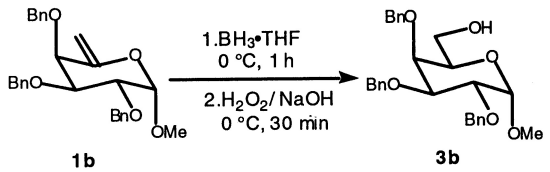
Table 1 Hydroboration/Oxidation of Methyl α-5-Enoglucoside **1a**



Entry	BH_3·THF (equiv)[a]	Yield (%)[b]	Ratio of **2a**:**3a**[c]
1	2.0	73	2.1: 1
2	3.0	82	2.9: 1
3	4.0	87	3.4: 1
4	5.0	88	3.8: 1
5	7.0	85	7.3: 1
6	10.0	85	11: 1

[a] All reactions were carried out in THF (0.1 M).
[b] Isolated yield of products (**2a** + **3a**).
[c] Ratios were determined by ^{1}H NMR spectroscopy.

Table 2 Hydroboration/Oxidation of Methyl α-5-Enogalactoside **1b**



Entry	BH_3·THF[a]	Yield (%)[b]
1	2.0	46
2	5.0	66
3	10.0	76

[a] All reactions were carried out in THF (0.1 M).
[b] Isolated yield.

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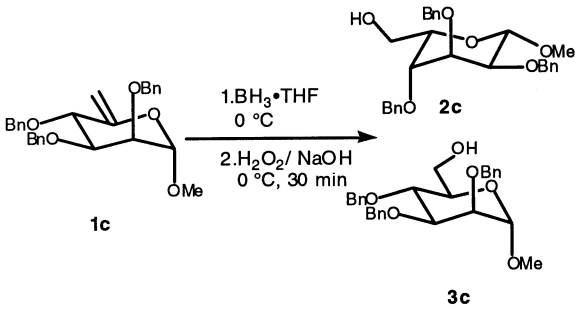
Table 3 Hydroboration/Oxidation of Methyl α-5-Enomannoside **1c**



Entry	BH_3·THF	Time (h)	Yield (%)[a]	**2c**:**3c**[b]
1	5.0	5	51	2.0: 1
2	10.0	3	73	2.4: 1

[a] Isolated yield of products (**2c** + **3c**).
[b] Ratios were determined by ^{1}H NMR spectroscopy.

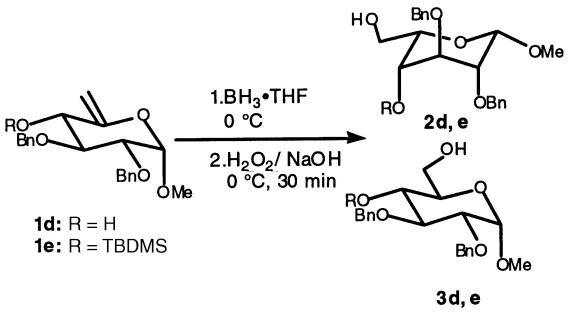
Interestingly, 5-enogalactoside **1b** gave contrasting results: only D-galactoside **3b**[12] was obtained and no L-altroside was observed. While the yield of **3b** increased with the addition of an excess amount of BH_3·THF, there was no change in the diastereoselectivity. The axial benzyloxy group at the C-4 position might cover the β-face of the double bond between C-5 and C-6 in galactoside. Therefore the borane reagent could attack only from the α-face to provide **3b** selectively. In contrast, the hydroboration/oxidation of 5-enomannoside **1c** with 5.0 equivalents of BH_3·THF gave predominantly L-guloside (51% yield, **2c**:**3c**[13] = 2.0:1, Table 3, entry 1). The production of **2c** was slightly increased when 10 equivalents of the reagent was used (entry 2).

From these results, it is possible that the hydroboration of 5-enoglucoside **1a** is an exceptional case, in which the amount of the reagent dramatically controls the diastereoselectivity in the reaction. To the best of our knowledge, this is a unique phenomenon observed in hydroboration reactions. We therefore investigated this further. For the moment, we focussed on the effect of the protective group at the C-4 position of 5-enoglucoside. The hydroboration/oxidation of 5-enoglucoside derivatives **1d**[14] and **1e** was examined (Table 4).

In the case of methyl α-5-enoglucoside **1d** bearing the 4-hydroxyl, the ratio of **2d** was increased based on the amount of borane reagent (Table 4, entries 1–3). However, a slight increase in the ratio was observed in the case of methyl α-5-enoglucoside **1e** bearing hindered TBDMS protection at the 4-position. Overall, it appears that the differences in the stereochemistry and in the protection of the carbohydrate somehow give rise to this unique phenomenon. Although our information on these interesting results is still limited, a detailed analysis of the reaction is underway in our laboratory and an extended discussion will be presented in the future.

After we established that the hydroboration/oxidation of methyl α-5-enoglucoside **1a** with excess amounts of

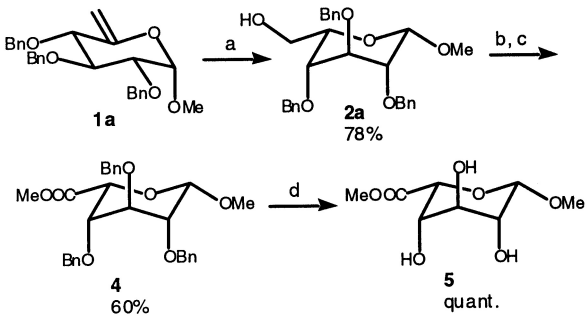
Table 4 Hydroboration/Oxidation of Methyl α-5-Enoglucoside **1d** and **1e**



Entry	R	BH_3·THF (equiv)	Time (h)	Yield (%)	**2**:**3**[a]
1	H	2.0	1	49[b]	3.5: 1
2	H	5.0	1	79[b]	4.2: 1
3	H	10.0	1	74[b]	5.2: 1
4	TBDMS	2.0	4.5	81[c]	1.4: 1
5	TBDMS	5.0	3	98[c]	1.5: 1
6	TBDMS	10.0	1.5	92[c]	2.1: 1

[a] Ratios were determined by ^{1}H NMR spectroscopy.
[b] Isolated yield of products (**2d**[14] +**3d**[15]).
[c] Isolated yield of products (**2e** + **3e**[14]).

BH_3·THF afforded methyl β-L-idoside **2a** with high diastereoselectivity, we applied this method to the synthesis of L-iduronic acid (Scheme 1). As mentioned, the hydroboration of **1a** gave methyl β-L-idoside **2a** in good yield.[16] Oxidation of **2a** and successive esterification gave L-idopyranosiduronate **4**. Finally, O-debenzylation of **4** gave the desired methyl L-iduronic acid ester **5**.[17]



Scheme 1 *Reagents and conditions*: (a) BH_3·THF, THF, 0 °C, then H_2O_2, NaOH, 0 °C; (b) CrO_3, H_2SO_4, r.t.; (c) CH_2N_2, Et_2O, 0 °C; (d) $Pd(OH)_2$/C, H_2, MeOH, r.t.

In conclusion, we examined the hydroboration/oxidation of 5-enoglycopyranosides and developed an efficient method for the synthesis of L-idoside and L-guloside. This simple route to L-sugar was applied to the synthesis of L-iduronic acid. In the course of our study, we also found a unique form of diastereoselectivity controlled by the amount of reagent.

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were measured with a JASCO FT/IR-8000 spectrometer. HRFAB-MS were recorded with a JEOL SX-102A. ^{1}H NMR and ^{13}C NMR spectra were recorded at 600 MHz with a JEOL GSX-600 spectrometer using TMS as the internal standard. Chemical shifts were reported in ppm downfield from TMS. Optical rotations were measured with a JASCO DIP-370 in a 1 dm cell. Analytical and preparative TLC was conducted on precoated TLC plates (silica gel 60 F_{254}, Merck). Column chromatography was performed using Merck silica gel 60 N (100–210 μm). All anhydrous solvents were purified according to standard methods.

The TBDMS ether **1e** was prepared from **1d** by the usual silylation procedure.

Methyl 2,3-Di-*O*-benzyl-4-*O*-[*tert*-butyl(dimethyl)silyl]-6-deoxy-α-D-*threo*-hex-5-enopyranoside (1e)
$[\alpha]_D^{26}$ +2.23 (*c* = 0.73, $CHCl_3$).

IR (neat): 1667 cm^{-1} (C=C).

^{1}H NMR (600 MHz, CD_3OD): δ = 7.33–7.23 (10 H, m, C_6H_5), 4.86 (1 H, d, *J* = 11.3 Hz, PhCH_2), 4.80 (1 H, d, *J* = 1.7 Hz, H-6), 4.78 (1 H, d, *J* = 3.3 Hz, H-1), 4.76 (1 H, d, *J* = 11.3 Hz, PhCH_2), 4.67 (1 H, d, *J* = 11.6 Hz, PhCH_2), 4.66 (1 H, d, *J* = 1.7 Hz, H-6′), 4.63 (1 H, d, *J* = 11.6 Hz, PhCH_2), 4.00 (1 H, d, *J* = 8.3 Hz, H-4), 3.66 (1 H, dd, *J* = 3.3, 9.3 Hz, H-2), 3.63 (1 H, dd, *J* = 8.3, 9.3 Hz, H-3), 3.40 (3 H, s, CH_3), 0.94 (9 H, s, *t*-C_4H_9), 0.06 (3 H, s, CH_3), 0.04 (3 H, s, CH_3).

^{13}C NMR (150 MHz, CD_3OD): δ = 157.7 (C-5), 140.2, 139.5, 129.4, 129.2, 129.1, 128.9, 128.5 (C_6H_5), (100.0) (C-1), (97.6) (C-6), (82.9) (C-3), (81.3) (C-2), (76.5) (C-4), 74.2, 73.6 (PhCH_2), 55.7 (CH_3), 26.4 [*C*(CH_3)$_3$], 19.0 [C(*C*H_3)$_3$], –4.29 [Si(CH_3)$_2$].

HRMS (EI): *m*/*z* calcd for $C_{27}H_{38}O_5Si$: 470.2489; found: 470.2480.

Hydroboration/Oxidation; Methyl 2,3,4-Tri-*O*-benzyl-β-L-idopyranoside (2a) and Methyl 2,3,4-Tri-*O*-benzyl-α-D-glucopyranoside (3a); Typical Procedure
To a solution of **1a** (32.0 mg, 0.07 mmol) in anhyd THF (1 mL) was added a 1.08 M solution of borane in THF (0.66 mL, 0.72 mmol) at 0 °C, and the mixture was stirred at 0 °C for 1 h. Then, 30% H_2O_2 (1 mL) and aq 2 N NaOH (1 mL) were successively added and the mixture was stirred for 30 min and extracted with EtOAc. The EtOAc extract was washed with aq sat. NH_4Cl, dried (Na_2SO_4), and evaporated. Purification by chromatography on silica gel (hexane–EtOAc, 2:1) gave 28.4 mg of the product (85%, **2a**:**3a** = 11:1).

Methyl *O*-2,3,4-Tri-*O*-benzyl-α-D-galactopyranoside (3b)
$[\alpha]_D^{24}$ +10.8 (*c* = 0.76, $CHCl_3$).

IR (neat): 3436 cm^{-1} (OH).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.42–7.25 (15 H, m, C_6H_5), 4.97 (1 H, d, *J* = 11.7 Hz, PhCH_2), 4.89 (1 H, d, *J* = 11.7 Hz, PhCH_2), 4.84 (1 H, d, *J* = 12.0 Hz, PhCH_2), 4.75 (1 H, d, *J* = 11.7 Hz, PhCH_2), 4.71–4.68 (2 H, m, PhCH_2, H-1), 4.63 (1 H, d, *J* = 12.0 Hz, PhCH_2), 4.05 (1 H, dd, *J* = 3.7, 10.0 Hz, H-2), 3.94 (1 H, dd, *J* = 2.7, 10.0 Hz, H-3), 3.87 (1 H, d, *J* = 2.7 Hz, H-4), 3.74–3.68 (2 H, m, H-6, H-6′), 3.45–3.52 (1 H, m, H-5), 3.36 (3 H, s, CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.5, 138.2, 138.0, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 127.4 (C_6H_5), 98.8 (C-1), 79.1 (C-3), 76.5 (C-2), 75.1, 74.4, 72.9 (Ph*C*H_2), 73.6 (C-4), 70.3 (C-5), 62.4 (C-6), 55.4 (CH_3).

HRMS (EI): *m*/*z* calcd for $C_{28}H_{32}O_6$: 464.2199; found: 464.2204.

Methyl 2,3,4-Tri-*O*-benzyl-β-L-gulopyranoside (2c)
$[\alpha]_D^{23}$ +21.1 (*c* = 0.77, $CHCl_3$).

IR (neat): 3457 cm^{-1} (OH).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.35–7.09 (15 H, m, C_6H_5), 4.85 (1 H, d, *J* = 12.1 Hz, PhCH_2), 4.76 (1 H, d, *J* = 8.0 Hz, H-1), 4.74 (1 H, d, *J* = 12.1 Hz, PhCH_2), 4.58 (1 H, d, *J* = 12.1 Hz, PhCH_2), 4.54 (1 H, d, *J* = 12.1 Hz, PhCH_2), 4.36 (1 H, d, *J* = 11.8 Hz, PhCH_2), 4.22 (1 H, d, *J* = 11.8 Hz, PhCH_2), 3.95 (1 H, ddd, *J* = 1.4, 4.7, 7.2 Hz, H-5), 3.82 (1 H, dd, *J* = 7.2, 11.3 Hz, H-6), 3.79 (1 H, dd, *J* = 3.3, 3.6 Hz, H-3), 3.59 (1 H, dd, *J* = 3.3, 8.0 Hz, H-2), 3.56 (1 H, dd, *J* = 4.7, 11.3 Hz, H-6′), 3.55 (3 H, m, CH_3), 3.38 (1 H, dd, *J* = 1.4, 3.6 Hz, H-4).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.7, 138.2, 137.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5 (C_6H_5), 102.0 (C-1), 76.4 (C-3), 75.0 (C-2), 74.5 (C-4), 73.5, 73.4, 73.1 (PhCH_2), 72.2 (C-5), 62.4 (C-6), 56.7 (CH_3).

HRMS (EI): *m*/*z* calcd for $C_{28}H_{32}O_6$: 464.2198; found: 464.2184.

Methyl 2,3-Di-*O*-benzyl-4-*O*-[*tert*-butyl(dimethyl)silyl]-β-L-idopyranoside (2e)
$[\alpha]_D^{21}$ +20.5 (*c* = 0.47, $CHCl_3$).

IR (neat): 3451 cm^{-1} (OH).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.33–7.24 (10 H, m, C_6H_5), 4.79 (1 H, d, *J* = 11.3 Hz, PhCH_2), 4.70 (1 H, d, *J* = 12.1 Hz, PhCH_2), 4.69 (1 H, d, *J* = 11.3 Hz, PhCH_2), 4.59 (1 H, d, *J* = 12.1 Hz, PhCH_2), 4.52 (1 H, d, *J* = 3.8 Hz, H-1), 3.94–3.89 (1 H, m, H-5), 3.88–3.84 (3 H, m, H-3, H-6, H-6′), 3.81 (1 H, dd, *J* = 5.5, 7.7 Hz, H-4), 3.47 (3 H, s, CH_3), 3.45 (1 H, dd, *J* = 3.8, 7.9 Hz, H-2), 0.86 (9 H, s, *t*-C_4H_9), 0.05 (3 H, s, CH_3), 0.02 (3 H, s, CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.6, 138.2, 137.5, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9 (C_6H_5), 100.1 (C-1), 78.5 (C-3), 78.0 (C-2), 74.8 (C-5), 74.8, 73.7 (PhCH_2), 71.9 (C-4), 62.9 (C-6), 57.0 (CH_3), 25.8 [*C*(CH_3)$_3$], 18.0 [C(*C*H_3)$_3$], –4.67 [Si(CH_3)$_2$].

HRMS (FAB-NBA + NaI): *m*/*z* calcd for $C_{27}H_{40}O_6SiNa$: 511.2492; found: 511.2492.

Dimethyl 2,3,4-Tri-*O*-benzyl-β-L-idopyranosiduronate (4)
To a solution of **2a** (120 mg, 0.26 mmol) in anhyd acetone (3 mL) was added a solution of CrO_3 (69.7 mg, 0.70 mmol) in 3.5 M H_2SO_4 (1 mL) at 0 °C. The solution was stirred at 0 °C for 10 min and then at r.t. for 1 h. After filtration, the filtrate was extracted with $CHCl_3$, and the extract was dried (Na_2SO_4) and evaporated. The crude carboxylic acid (104.5 mg, 0.22 mmol) thus obtained was dissolved in CH_2Cl_2 (2 mL), and an excess amount of diazomethane in Et_2O was added to the mixture. After stirring the mixture at 0 °C for 90 min, the solvent was evaporated. The residue was purified by silica gel chromatography (hexane–EtOAc, 10:1) to give 76.3 mg of **4** (60%); $[\alpha]_D^{26}$ +29.0 (*c* = 1.10, $CHCl_3$).

IR (neat): 1688 cm^{-1} (C=O).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.26–7.15 (15 H, m, C_6H_5), 4.68 (1 H, d, *J* = 12.7 Hz, PhCH_2), 4.58 (1 H, d, *J* = 12.7 Hz, PhCH_2), 4.57 (1 H, d, *J* = 12.1 Hz, PhCH_2), 4.50–4.48 (3 H, m, H-5, PhCH_2), 4.41 (1 H, d, *J* = 12.1 Hz, PhCH_2), 4.23 (1 H, d, *J* = 3.6 Hz, H-1), 3.97–3.95 (1 H, dd, *J* = 5.5, 7.6 Hz, H-3), 3.65 (3 H, s, CH_3), 3.61 (3 H, dd, *J* = 3.6, 5.5 Hz, H-2), 3.41–3.39 (4 H, m, H-4, CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.5 (C=O), 138.5, 138.0, 137.9, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6 (C_6H_5), 100.9 (C-1), 75.7 (C-3), 74.5 (C-4), 73.7, 73.5, 72.9 (PhCH_2), 56.9 (CH_3), 51.9 ($COCH_3$).

HRMS (EI): *m*/*z* calcd for $C_{29}H_{32}O_7$: 492.2148; found, 492.2132.

Dimethyl β-L-Idopyranosiduronate (5)
To a solution of **4** (71.9 mg, 0.15 mmol) in anhyd MeOH (1.5 mL) was added $Pd(OH)_2$/C (14.4 mg). After stirring the mixture under a H_2 atmosphere for 22 h, the catalyst was removed by filtration. The

filtrate was evaporated to give **5** (31.9 mg, quant). The analytical and spectral data are in confirmation with the reported values.[17]

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