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# Selective Synthesis of Partially Protected D-Talopyranosides and D-Gulopyranosides via Catalytic Asymmetric Dihydroxylation: Multiplier Effects of Substrate Control and Catalyst Control

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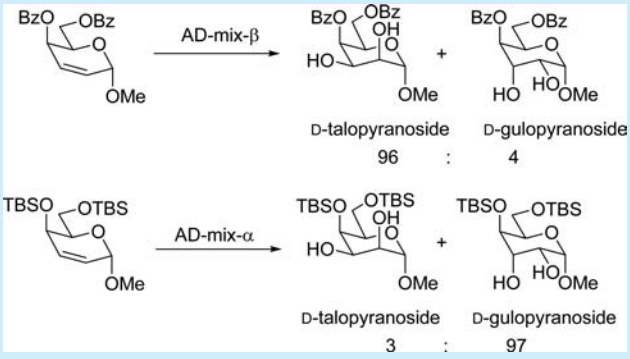
Supporting Information

**ABSTRACT:** Highly selective syntheses of D-talopyranosides and D-gulopyranosides have been achieved by utilizing the multiplier effects of substrate control and catalyst control. Through the combination of an *O*-benzoyl-protected substrate and the AD-mix-$\beta$ system, the D-talopyranoside was obtained in a ratio of 96:4. In contrast, the D-gulopyranoside was obtained in a ratio of 3:97 through the use of an *O*-*tert*-butyldimethylsilyl-protected substrate and AD-mix-$\alpha$.




Recently, rare sugars have attracted much attention in terms of their bioactivity, such as their ability to act as inhibitors of various glycosidases. For example, Izumori and co-workers reported that D-psicose (D-allulose) inhibits intestinal $\alpha$-glucosidase and suppresses the glycemic response after ingestion of carbohydrates and also inhibits motility, growth, and reproductive maturity of the L1 larvae of *Caenorhabditis elegans*.[1] In contrast, D-allose acts as a triggering molecule for rice defense via ROS generation and also suppresses gibberellin signaling through a hexokinase-dependent pathway in *Oryza sativa* L.[2] However, despite their importance in medicine and pharmacy, the bioactivity of other rare sugars has not been examined due to the difficulty in obtaining a sufficient amount for bioassays.

Izumori proposed the "Izumoring" strategy for the bioproduction of all hexoses including the 16 aldohexoses, 8 ketohexoses, and 10 hexitols using enzymatic and microbiological reactions.[3] By this method, some rare sugars, such as D-psicose and D-allose, have been produced on a large enough scale for bioassays. However, bioproduction of other rare sugars is not always easy. Synthesizing D-talose and D-gulose by this strategy is very difficult because these rare sugars are far from D-glucose in the "Izumoring" map, meaning multiple enzymes are required.

Several chemical syntheses have been reported; Mukaiyama and Kobayashi reported the synthesis of 6-deoxy-L-talose[4] and 6-deoxy-L-allose[5] using an asymmetric aldol reaction. Macmillan also reported the synthesis of L- and D-allose based on an L- (or D)-proline-catalyzed asymmetric aldol reaction followed by a Mukaiyama aldol addition.[6] O'Doherty and co-workers reported the synthesis of D- and L-mannose, gulose, and talose by dihydroxylation of unsaturated sugar derived from furfural.[7] Guaragna and co-workers reported the synthesis of L-altrose by the reaction of L-2,3-unsaturated carbohydrate with Oxone to give the epoxide, followed by hydrolysis with $HClO_4$.[8] Bystöm reported the synthesis of a $\beta$-D-mannoside and $\beta$-D-talosides using a double-parallel inversion method and a double serial inversion method from partially protected methyl $\beta$-D-glucoside and methyl $\beta$-D-galactoside, respectively.[9] For the synthesis of rare aldohexoses from ketohexoses, the use of 2-aminopyridine has also been reported.[10] We also reported the synthesis of D-allose using stereoselective reduction of bulky silyl-protected 1,5-anhydrohex-1-en-3-uloses using the $NaBH_4$–$CeCl_3{\cdot}7H_2O$ system.[11]

To our knowledge, there have been no reports on how to prepare D-gulopyranosides effectively nor any reports via the asymmetric dihydroxylation of unsaturated sugars derived from common pyranosides derived from D-glucose[12] and D-galactose using chiral catalysts. Here, we report novel and efficient methods for the selective syntheses of D-talopyranosides and D-gulopyranosides via catalytic asymmetric dihydroxylation[13] of protected unsaturated D-galactopyranoside derivatives. Among the ald-type hexoses, D-allose, D-talose, D-gulose, D-idose, and D-altrose are called rare sugars. Our strategy is shown in Scheme 1. If 1,2-unsaturated D-glucopyranoside were used as a substrate, dihydroxylative attack from the top would give D-mannopyranoside and attack from the bottom yields D-glucose (eq 1). Similarly, 2,3-unsaturated D-glucopyranoside would give D-mannopyranoside and D-allopyranoside, and 1,2-unsaturated D-galactopyranoside would yield D-talopyranoside and D-galactopyranoside (eq 2 and eq 3). We focused on using a 2,3-unsaturated D-galactopyranoside as the substrate because it yields

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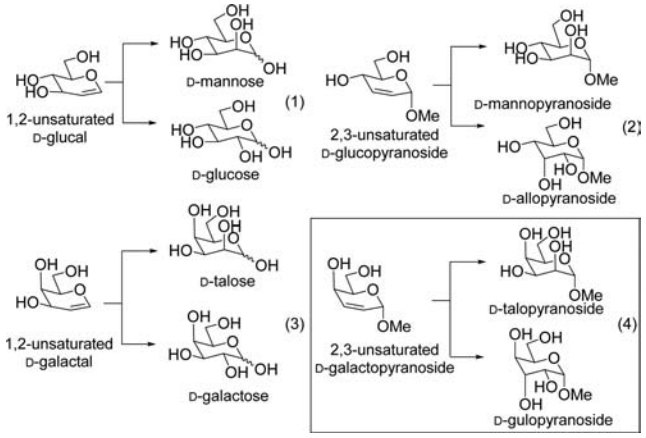
**Scheme 1. Stereoselective Dihydroxylation of Unsaturated D-Gulcose and D-Galactose Derivative**

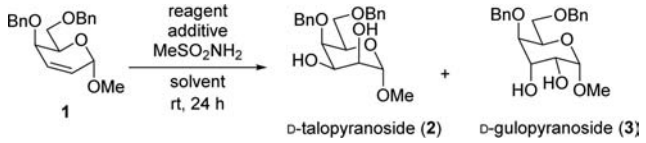



both D-talopyranoside and D-gulopyranoside (eq 4). Our focus was on substrate control versus chiral catalyst control in the diastereoselective dihydroxylation of 2,3-unsaturated D-galactal.

We first examined the reaction of methyl 4,6-di-*O*-benzyl-2,3-dideoxy-α-D-threo-hex-2-enopyranoside (**1**) with AD-mix-α and AD-mix-β (1.4 g/substrate mmol) at room temperature (30 °C) for 24 h in *t*-BuOH/$H_2O$ (1/1). Commercially available AD-mix-α (Aldrich) is composed of $K_2OsO_4{\cdot}2H_2O$, $(DHQ)_2PHAL$, $K_2CO_3$, and $K_3Fe(CN)_6$, and AD-mix-β (Aldrich) is composed of $K_2OsO_4{\cdot}2H_2O$, $(DHQD)_2PHAL$, $K_2CO_3$, and $K_3Fe(CN)_6$, respectively. Reaction of **1** with AD-mix-α (Table 1, entries 1 and 2) gave a dihydroxylated product in only 3% yield (**1** was recovered in 94% yield), and reaction of **1** with AD-mix-β was not observed. Addition of methanesulfonamide (1 equiv), $K_2OsO_4{\cdot}2H_2O$ (10 mol %), and $(DHQ)_2PHAL$ (10 mol %) to the AD-mix-α media, however, afforded dihydroxylated products methyl 4,6-di-*O*-benzyl-α-D-talopyranoside (**2**) and methyl 4,6-di-*O*-benzyl-α-D-gulopyranoside (**3**) in a 38:62 ratio in 71% yield (entry 3). Addition of methanesulfonamide (1 equiv), $K_2OsO_4{\cdot}2H_2O$ (10 mol %), and $(DHQD)_2PHAL$ (10 mol %) to the AD-mix-β reversed the selectivity (D-talopyranoside/D-gulopyranoside = 63:37) and gave both compounds in a combined 58% yield (entry 4). As the choice of chiral ligand ($(DHQ)_2PHAL$ or $(DHQD)_2PHAL$) determined which face of the double bond in **1** was attacked, this showed that the stereoselectivity was catalyst-controlled. The reaction of **1** with $K_2OsO_4{\cdot}2H_2O$ (11 mol %) and NMO (*N*-methylmorpholine *N*-oxide (1 equiv), entry 5) gave the D-talopyranoside and D-gulopyranoside in a ratio of 38:62 and only 20% yield (**1** was recovered in 73% yield). This indicated ligand acceleration in entries 3 and 4 and that attack from the bottom was preferred for the double bond in substrate **1**, leading to the formation of the D-gulopyranosides. Thus, the diastereoselectivity results from substrate control.

The structures of **2** and **3** were determined by NOE analysis (Scheme 2). We then examined the effect of the protecting group on stereoselectivity.

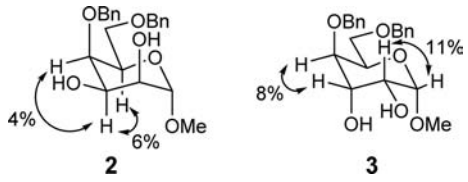
**Table 1. Dihydroxylation of Methyl 4,6-Di-*O*-benzyl-2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside (1)**[a]




| | | additive (mol %) | | | |
|---|---|---|---|---|---|
| entry | reagent | $K_2OsO_4{\cdot}2H_2O$ | ligand | yield[b,c] (%) | **2**:**3**[d] |
| 1 | AD-mix-α | 0 | 0 | 3 (94) | nd |
| 2 | AD-mix-β | 0 | 0 | 0 (100) | nd |
| 3 | AD-mix-α | 10 | 10[e] | 71 | 38:62 |
| 4 | AD-mix-β | 10 | 10[f] | 58 | 63:37 |
| 5[g] | none | 11 | 0 | 20 (73) | 38:62 |

[a]All reactions were carried out using 2,3-unsaturated D-galactopyranoside (**1**), reagent (1.4 g per substrate mmol), $MeSO_2NH_2$ (1 equiv), and additives as described in the table except for entry 5 in *t*-BuOH/$H_2O$ (1/1) at rt, 24 h. [b]Combined yield of **2** and **3** after silica gel column chromatography. [c]The value in the parentheses indicates the recovery of **1**. [d]The ratio of D-tallopyranoside and D-gulopyranoside was determined by both isolated yield and $^1H$ NMR analysis. The ratio after isolation agreed completely with the one by $^1H$ NMR analysis. [e]$(DHQ)_2PHAL$. [f]$(DHQD)_2PHAL$. [g]$K_2OsO_4{\cdot}2H_2O$ (0.11 equiv) and *N*-methylmorpholine *N*-oxide (1 equiv) were used.

**Scheme 2. NOE Analysis of 2 and 3**




Tables 2 and 3 show the results of the reaction of benzoyl-protected (**4**) and *tert*-butyldimethylsilyl-protected 2,3-unsaturated D-galactopyranoside (**7**) with $K_2OsO_4{\cdot}2H_2O$ and NMO. When **4** and **7** were used as substrates, the yields were moderate, even after the addition of a stoichiometric amount of $K_2OsO_4{\cdot}2H_2O$ and an excess of NMO (55% and 35%, respectively, entry 2 in Table 2 and entry 2 in Table 3). However, the D-talopyranoside/D-gulopyranoside selectivity was up to 92:8 in the case of the benzoyl-protected D-galactopyranoside and up to 15:85 in the case of *tert*-butyldimethylsilyl-protected 2,3-unsaturated D-galactopyranoside. In order to improve the selectivity of this method, we examined the effect of the chiral ligand, the solvent, and other additives. The results are summarized in Tables 2 and 3. The highest D-talopyranoside selectivity (96:4) was obtained in 74% yield (entry 5 in Table 2) by the reaction of **4** with AD-mix-β (1.4 g/substrate mmol), $K_2OsO_4{\cdot}2H_2O$ (10 mol %), and $(DHQD)_2PHAL$ (10 mol %) in *t*-BuOH/$H_2O$ (1/1). The highest D-gulopyranoside selectivity was obtained (3:97) in 68% yield (entry 7 in Table 3) by the reaction of **7** with AD-mix-α (1.4 g/substrate mmol), $K_2OsO_4{\cdot}2H_2O$ (50 mol %), $(DHQ)_2PHAL$ (50 mol %), and $K_3Fe(CN)_6$ in THF/$H_2O$ (1/1).

The rate enhancement is explained as a "ligand acceleration effect",[15] and an increase of selectivity can be interpreted to match the pair of substrate control and catalyst control. The origin of stereoreversal by the choice of protecting group is explained in Scheme 3. In the case of *O*-benzoyl-protected substrate **4**, the benzoyl group oxygen coordinates with Os, and dihydroxylation occurs from the top side predominantly, affording the D-talopyranoside (substrate control). The addition of $(DHQD)_2PHAL$ (via AD-mix-β) increased the proportion of top side attack (catalyst control) as shown in Table 3. Conversely, in the case of *tert*-butyldimethylsilyl-protected substrate **5**, the bulky silyl moiety prevented top side attack, and the resulting product was the D-gulopyranoside, formed by



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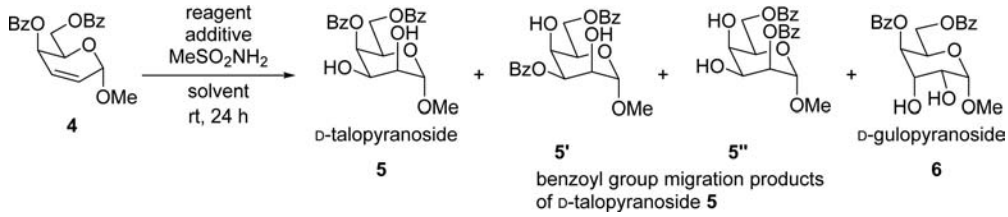
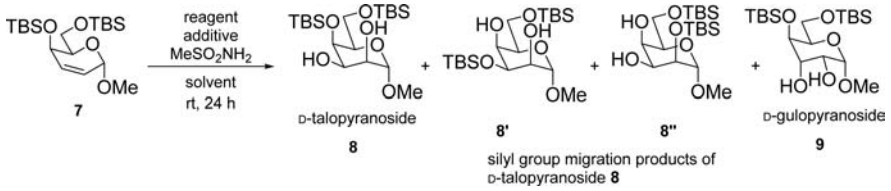
**Table 2. Catalytic Asymmetric Dihydroxylation of Methyl *O*-Benzoyl-2,3-unsaturated α-D-Galactopyranoside (4)[a]**




| | | additive (mol %) | | | product | |
|---|---|---|---|---|---|---|
| entry | reagent | $K_2OsO_4·2H_2O$ | ligand | solvent[b] | yield[c] (%) | D-talopyranoside/D-gulopyranoside[d] |
| 1 | none[e] | 10 | none | A | 40 | **5** + **5′** + **5″**:**6** = 80:20 |
| 2 | none[f] | 100 | none | A | 55 | **5** + **5′** + **5″**:**6** = 92:8 |
| 3 | AD-mix-α | 10 | 10[g] | B | 60 | **5** + **5′** + **5″**:**6** = 88:12 |
| 4 | AD-mix-α | 10 | 10[g] | A | 75 | **5** + **5′** + **5″**:**6** = 82:18 |
| 5 | AD-mix-β | 10 | 10[h] | B | 74 | **5** + **5′** + **5″**:**6** = 96:4 |
| 6 | AD-mix-β | 10 | 10[h] | A | 81 | **5** + **5′** + **5″**:**6** = 91:9 |

[a]All AD-mix reactions were carried out using reagent (1.4 g per substrate mmol), $MeSO_2NH_2$ (1 equiv), and additives at rt for 24 h. [b]A = THF/$H_2O$ (1/1). B = *t*-BuOH/$H_2O$ (1/1). [c]In the case of D-talopyranoside **5**, the benzoyl group transfer from the 4-position to the 3- (compound **5′**) and 2-position (compound **5″**) was observed, which was confirmed after benzoylation of other hydroxyl group that led the same compound. The yields indicate the combined yield of **5**, **5′**, **5″**, and **6** after silica gel column chromatography. The details are described in ref 14 and the Supporting Information. [d]The ratio of D-talopyranoside and D-gulopyranoside was determined by both the isolated yield and $^1$H NMR analysis. The ratio after isolation agreed completely with the one obtained by $^1$H NMR analysis. [e]*N*-Methylmorpholine *N*-oxide (1 equiv) was used in the absence of $MeSO_2NH_2$. [f]*N*-Methylmorpholine *N*-oxide (3 equiv) was used in the absence of $MeSO_2NH_2$. [g](DHQ)$_2$PHAL. [h](DHQD)$_2$PHAL.

**Table 3. Catalytic Asymmetric Dihydroxylation of Methyl *O*-(*tert*-Butyldimethylsilyl)-2,3-unsaturated α-D-Galactopyranoside (7)[a]**




| | | additive (mol %) | | | | product | |
|---|---|---|---|---|---|---|---|
| entry | reagent | $K_2OsO_4·2H_2O$ | ligand | $K_3Fe(CN)_6$ | solvent[b] | yield (%)[c] | D-talopyranosie:D-gulopyranoside[d] |
| 1 | none[e] | 10 | none | 0 | A | 9 | **8** + **8′** + **8″**:**9** = 22:78 |
| 2 | none[f] | 100 | none | 0 | A | 35 | **8** + **8′** + **8″**:**9** = 15:85 |
| 3 | AD-mix-α | 10 | 10[g] | 0 | B | 30 | **8** + **8′** + **8″**:**9** = 3:97 |
| 4 | AD-mix-α | 10 | 10[g] | 0 | A | 47 | **8** + **8′** + **8″**:**9** = 11:89 |
| 5 | AD-mix-α | 10 | 10[g] | 300 | B | 62 | **8** + **8′** + **8″**:**9** = 9:91 |
| 6 | AD-mix-α | 10 | 10[g] | 300 | A | 67 | **8** + **8′** + **8″**:**9** = 6:94 |
| 7 | AD-mix-α | 50 | 50[g] | 0 | B | 68 | **8** + **8′** + **8″**:**9** = 3:97 |
| 8 | AD-mix-β | 10 | 10[h] | 300 | A | 58 | **8** + **8′** + **8″**:**9** = 58:42 |

[a]All AD-mix reactions were carried out using reagent (1.4 g per substrate mmol), $MeSO_2NH_2$ (1 equiv), and additives at rt for 24 h. [b]A = THF/$H_2O$ (1/1). B = *t*-BuOH/$H_2O$ (1/1). [c]In the case of D-talopyranoside **8**, the silyl group transfer from the 4-position to the 3- and 2-positions was observed, which was confirmed after silylation of other hydroxyl group that led the same compound. The yields indicate the combined yield of **8** and its silyl migrated compounds (**8′** + **8″**) and **9**. Details are described in ref 14 and the Supporting Information. [d]The ratio of D-talopyranoside and D-gulopyranoside was determined by both the isolated yield and $^1$H NMR analysis. The ratio after isolation agreed completely with the one determined by $^1$H NMR analysis. [e]*N*-Methylmorpholine *N*-oxide (1 equiv) was used in the absence of $MeSO_2NH_2$. [f]*N*-Methylmorpholine *N*-oxide (3 equiv) was used in the absence of $MeSO_2NH_2$. [g](DHQ)$_2$PHAL. [h](DHQD)$_2$PHAL.

attack from the bottom side (substrate control). In this case, addition of (DHQ)$_2$PHAL (via AD-mix-α) increased the proportion of bottom side attacks (catalyst control) as shown in Scheme 3.

As for benzoyl group and silyl group migration, we observed the formation of migration products during the reaction.

In conclusion, highly selective synthesis of methyl D-talopyranoside and methyl D-gulopyranoside dervatives has been achieved through catalytic asymmetric dihydroxylation. Complete reversal of diastereoselectivity of the double bond in protected 2,3-unsaturated D-galactopyranoside was accomplished by the choice of protecting group, which led to the selective formation of D-talopyranoside and D-gulopyranoside. When benzoyl-protected 2,3-unsaturated D- galactopyranoside was used as a substrate, D-talopyranoside was obtained predominantly. In contrast, the reaction of *tert*-butyldimethylsilyl-protected 2,3-unsaturated D-galactopyranoside under the same conditions afforded D-gulopyranoside in a selective manner. The multiplier effects of substrate control and catalyst control through the combination of an *O*-benzoyl-protected substrate and AD-mix-β systems produced D-talopyranoside in a ratio of 96:4. In contrast, D-gulopyranoside was obtained in a



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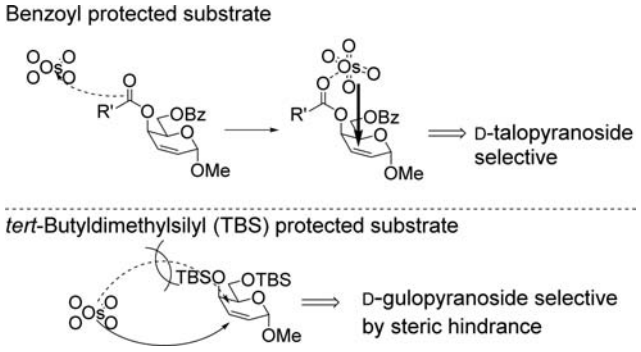
**Scheme 3. Origin of Stereoreversal: Protecting Group Dependency**




ratio of 3:97 through the combination of an *O-tert*-butyldimethylsilyl-protected substrate and AD-mix-$\alpha$. *It should be mentioned that this is the first example for the synthesis of two rare sugars of* D*-talopyranoside and* D*-gulopyranoside using the matching pair of multiplier effects of substrate control and catalyst control.* Further studies of the diastereoselectivity mechanism and syntheses of other rare sugars based on this strategy are ongoing in our laboratory.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03000.

General experimental procedures, characterization details, and $^{1}H$ and $^{13}C$ NMR spectra of products (PDF)

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### Notes

The authors declare no competing financial interest.

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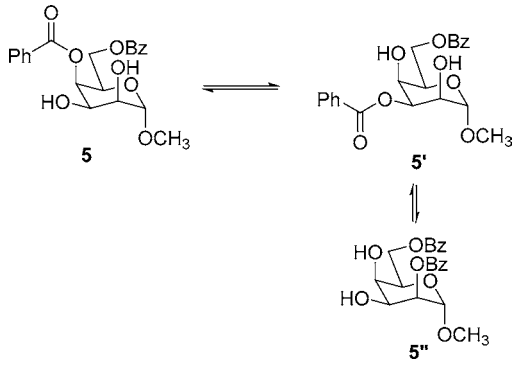
(14) In the formation of methyl 4,6-di-*O*-benzoyl-$\alpha$-D-talopyranoside (**5**), the 4-positional benzoyl group was transferred to the 3- and 2-position leading to formation of methyl 3,6-di-*O*-benzoyl-$\alpha$-D-talopyranoside (**5′**) and methyl 2,6-di-*O*-benzoyl-$\alpha$-D-talopyranoside (**5″**) as shown below. This was confirmed by full benzoylation after all deprotection and benzoylation; therefore, the yield was determined as a mixture of **5**, **5′**, and **5″**. A similar observation occurred in silyl-protected product **8**.

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