Diastereoselective desymmetric 1,2-cis-glycosylation of meso-diols via chirality transfer from a glycosyl donor

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Chemical desymmetrization reactions of meso-diols are highly effective for the precise and efficient synthesis of chiral molecules. However, even though enzyme-catalyzed desymmetric glycosylations are frequently found in nature, there is no method for highly diastereoselective desymmetric chemical glycosylation of meso-diols. Herein, we report a highly diastereoselective desymmetric 1,2-cis-glycosylation of meso-diols found in myo-inositol 1,3,5-orthoesters using a boronic acid catalyst based on predictions of regioselectivity by density functional theory (DFT) calculations. The enantiotopic hydroxyl groups of the meso-diols are clearly differentiated by the stereochemistry at the C2 position of the glycosyl donor with excellent regioselectivities. In addition, the present method is successfully applied to the synthesis of core structures of phosphatidylinositolmannosides (PIMs) and glycosylphosphatidylinositol (GPI) anchors, and common β-mannoside structures of the LLBM-782 series of antibiotics.

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The desymmetrization of meso-diols is an attractive method for preparing chiral molecules bearing multiple stereogenic centers in one operation. Highly designed chiral catalysts possessing a nitrogen base on the chiral scaffold allow for the enantioselective functionalization\(^1,2\) of meso-diols by desymmetrization reactions, such as acylation\(^3\), silylation\(^4,5\), and sulfonylation\(^6\) (Fig. 1a). In addition, other approaches, such as oxidation\(^7–9\), Heck reaction\(^10\), and lipase-catalyzed selective acylation\(^11\) were also reported. However, the repertoire of enantio- or diastereoselective functionalization reactions of meso-diols is still limited. Therefore, to efficiently synthesize diversified valuable compounds from meso-diols, a new repertoire of desymmetric reactions has been in great demand. In this context, our interest was directed toward biosynthetic reactions that provide many biologically active natural products derived from meso-compounds. In nature, meso-compounds representing myo-inositol and 2-deoxystreptamine derivatives have been modified by enzymatic desymmetrization reactions, such as phosphorylation\(^12\) and glycosylation\(^13\). With regard to phosphorylation, Miller et al. focused on the analogy of key intermediates between

Fig. 1 Enantio- or diastereoselective functionalizations of meso-diols. a Highly enantioselective functionalizations of meso-diols using highly designed chiral catalysts. b Synthetic strategy for myo-inositol glycoside from a meso-diol. c Boronic-acid-catalyzed desymmetric 1,2-cis-glycosylations of meso-diols. X leaving group, P protecting group, Ar aryl, Glc glucose, Gal galactose, Rha rhamnose, Man mannose, Fuc fucose.
phosphorylation and acylation, and developed a pioneering highly enantioselective desymmetric phosphorylation of a myo-inositol derivative using chiral peptide catalysts discovered by screening a peptide library. Recently, Fukase and Fujimoto et al. have reported another method for desymmetric phosphorylation of a myo-inositol derivative. On the other hand, for glycosylation, despite the existence of many natural glycosides derived from meso-compounds, there is no method for the highly diastereoselective desymmetric glycosylation of meso-diols.

Highly diastereoselective desymmetric glycosylations of meso-diols can greatly increase the efficiency with which desymmetrized meso-compounds by glycosylations are prepared. As an example, the conventional synthetic strategy of myo-inositol glycoside is shown in Fig. 1b. In this strategy, myo-inositol glycosides were synthesized using a chiral auxiliary. A meso-diol derived from myo-inositol was first functionalized using a chiral auxiliary, followed by stereoselective glycosylation of the desired diastereomer and finally, removal of the chiral auxiliary to give the desired myo-inositol glycoside. However, most desymmetrization methods of myo-inositol derivatives using a chiral auxiliary proceeded with low regioselectivity, providing a mixture with an undesired diastereomer. In addition, at least three steps were required to introduce the sugar moiety into the desired position in the myo-inositol derivatives. In another approach, optically pure myo-inositis were synthesized from D-glucose through Ferrier rearrangement, however, a tedious multi-step operation was required. Thus, a highly diastereoselective desymmetric glycosylation of meso-diols would provide the desired myo-inositol glycosides in only one step.

In the development of a desymmetric glycosylation of meso-diols, it is challenging to completely and simultaneously control both the α/β stereoselectivity of the anomeric center and the regioselectivity of the glycosylation site. Efficient stereoselective glycosylation methods have been developed for the α/β stereoselectivity. However, there is no efficient desymmetric glycosylation method that can predict and concisely control the regioselectivity in the reaction with meso-diols. Although several cases of desymmetric α-mannosylations of meso-diols have been reported so far, the regioselectivities were low to moderate. In addition, the regioselectivities of these glycosylations using other substrates are unpredictable because detailed reaction mechanisms and transition states during the glycosylations are still unclear.

In this context, we focus on our organoboron-catalyzed 1,2-cis-glycosylations of 1,2-anhydro donors and mono-, di-, and poly-ol sugar acceptors. The combination of a 1,2-anhydro donor...
and a boronic or borinic acid catalyst in the glycosylation gives excellent 1,2-cis-stereoselectivities. In addition, the S$_3$i-type mechanism and the transition states are supported by mechanistic studies. Thus, we expect that the glycosylation of a 1,2-anhydro donor and a meso-diol using a boronic acid catalyst will give a 1,2-cis-glycoside with high stereoselectivity via the S$_3$i-type mechanism, and the regioselectivity will be predictable by analyzing transition states with density functional theory (DFT) calculations. Herein, we report a highly diastereoselective glycosylation using a catalytic amount of a 1,2-anhydro donor with excellent regio- and stereoselectivities without forming any other regio- and stereoisomers (10–12) (Supplementary Figs. 2, 3, and 6–8, Supplementary Tables 2 and 3). This observed regioselectivity was good agreement with the calculation result using the model compounds (Fig. 2a). Since 1,2-anhydro donor 7 was the only chiral source in this glycosylation, the absolute configuration of stereogenic center(s) in the glycosyl donor was an origin of the excellent regioselectivity of this glycosylation.

**Results**

**Desymmetric glycosylations of myo-inositol derivatives.** To investigate our hypothesis, we first selected 1,2-anhydro-β-D-glucose 1, 2-O-methyl-myco-inositol 1,3,5-orthoesters (2), and 4-nitrophenylboronic acid (3) as the glycosyl donor, meso-diol acceptor, and arylboronic acid, respectively, and investigated the transition states by DFT calculations (Fig. 2a, Supplementary Fig. 41). It was found that donor 1 could approach the boron atom from either the convex or concave face of boronic ester 4, forming reasonable transition states in which the anomeric center of the donor is near the oxygen atom of the 4 position (TS-Glc-Convex) or 6 position (TS-Glc-Concave), respectively. The difference in activation energy was found to be 0.6 kcal mol$^{-1}$. These results indicated that the glycosylation at the 6 position via TS-Glc-Concave was favored over glycosylation at the 4 position via TS-Glc-Convex. The activation energy difference was caused by the ring strain in the envelope conformation of the dioxaborinane TS-Glc-Convex. The activation energy difference was used to predict the preferred glycosylation pathway. The predicted results were in good agreement with the experimental results.

**Substrate scope of the protecting groups in the desymmetric glycosylation using 1,2-anhydro-D-glucose.** Bz benzoyl, Ph phenyl, TBDPS tert-butyldiphenylsilyl.
This result indicated that the chirality of the glycosyl donor was completely transferred to the meso-diol, leading to the clear differentiation of enantiopure hydroxyl groups in meso-diols.

The effect of protecting groups of the meso-diol using 13–15 was also examined (Fig. 3). The corresponding α(1,6)-d-glucosides 20–22 were obtained as single isomers in high yields (Supplementary Figs. 2, 4, and 9–12, Supplementary Tables 4–9). In addition, even when triol 16 possessing a more reactive hydroxyl group at 2 position was used, α(1,6)-d-glucoside 23 was obtained with excellent diastereoselectivity (Supplementary Tables 10 and 11). This result indicated that the activation of 4,6-diol by the boronate ester formation was more important for the glycosylation than the innate reactivity of hydroxyl group. Next, the effect of protecting groups of the glycosyl donor using 17–19 (synthesis of 18 was described in Supplementary Fig. 1) was examined. In these cases, also, the desymmetric glycosylations proceeded effectively to give the corresponding α(1,6)-d-glucosides 24–26 with high regio- and 1,2-cis-stereoselectivities in high yields (Supplementary Figs. 2, 5, and 13–15, Supplementary Tables 12–17). These results clearly indicated that the
regioselectivity of the present glycosylations was not affected by the protecting groups.

**Construction of a prediction model.** We hypothesized that the regioselectivity was mainly affected by the C2 configuration of the glycosyl donor, and constructed a prediction model for the regioselectivities using (2R)-epoxide donors, such as 1,2-anhydro-D-glucose, D-galactose, and L-rhamnose, and (2S)-epoxide donors, such as 1,2-anhydro-D-mannose and L-fucose, as shown in Fig. 4a. According to this model, it was expected that the glycosylations of (2R)-epoxide donors would occur at the 6 position via boat-type transition states. On the other hand, in the cases of 1,2-anhydro donors possessing S configuration at the C2 position, the regioselectivity would be reversed and the glycosylations would occur at the 4 position.

To validate this prediction model, we analyzed the boronic acid 3 catalyzed glycosylations of meso-diol 2 with several 1,2-anhydro glycosyl donors 27–29 by DFT calculations (Fig. 4b). Using 1,2-anhydro-L-rhamnose 27, two transition states were found in which the donor approached from the concave and convex faces of boronic ester 4, i.e., TS-Rha-Concave which leads to β(1,6)-L-rhamnose 30 and TS-Rha-Convex which leads to β(1,4)-L-rhamnose 31. As with 1,2-anhydro-D-glucose 1, TS-Rha-Concave was favored over TS-Rha-Convex by 2.8 kcal mol\(^{-1}\) due to a similar ring strain of the envelope conformation, indicating that β-rhamnosylation using 1,2-anhydro-L-rhamnose would occur at the 6 position. Also, when 1,2-anhydro-D-mannose 28 and L-fucose 29 possessing the S configuration at the C2 position were used, the approach of these donors from the concave face to the boron atom was favored, similar to the (2R)-epoxide donor, and the anomeric center of the glycosyl donor was positioned near the 4 position in the favored TSs (TS-Man-Concave and TS-Fuc-Concave) as expected, indicating that β-mannnosylation and α-fucosylation would proceed regioselectively at the 4 position. These predictions of regioselectivities by DFT calculations were in good agreement with the prediction model, suggesting that the regioselectivity of the present glycosylation reaction was attributed to the stereochemy at C2 of the glycosyl donor.

In fact, we investigated the glycosylations of several 1,2-anhydro donors and meso-diol 8 (Fig. 5). Using 1,2-anhydro-D-galactose 36, similarly to 1,2-anhydro-D-glucose 7, α(1,6)-D-galactoside 40 was obtained in high yield with high regio- and stereoselectivities (Supplementary Figs. 16–18, Supplementary Tables 18 and 19). The use of 1,2-anhydro-L-rhamnose 37 gave β(1,6)-L-rhamnose 42 as a single isomer as expected (Supplementary Figs. 19–21, Supplementary Tables 20 and 21). Also, when 1,2-anhydro-D-mannose 38 was used, β-mannnosylation occurred at the 4 position in 8 according to our prediction model, and β(1,4)-D-mannoside 43 was obtained with complete regio- and stereoselectivities.
Application to acyclic meso-diols. Next, as a preliminary attempt, we examined the desymmetrical glycosylations of acyclic meso-diols, which possess high conformational flexibility, to show the possibility of the present glycosylation method (Eq. 6). The results showed that when acyclic meso-diols 45 and 48 were used, the glycosylations proceeded smoothly to provide the corresponding 1,2-cis-glycosides in high yields with moderate and excellent regioselectivities, respectively, and excellent 1,2-cis-α-stereoselectivities (Supplementary Figs. 30–37, Supplementary Tables 28–31). Although the rationale of regioselectivities was still unclear, these results showed the possibility that this glycosylation method could be applicable to acyclic meso-diols. Further investigations using several acyclic meso-diols is now in progress in our laboratory.

Synthesis of core structures of PIMs and GPI anchors. Overall, we developed the highly diastereoselective desymmetric 1,2-cis-glycosylation, which can be applied to synthesize various 1,2-cis-glycosides. Next, we focused on the representative myo-inositol glycosides, PIMs and GPI anchors (Fig. 7a). Although several synthetic strategies have been developed for PIMs and GPI anchors, which possess α-mannose and α-glucosamine at 6 position of myo-inositol, respectively, there are few efficient methods for highly regio- and stereoselective introduction of these sugars. Therefore, the efficient synthesis of core structures of PIMs and GPI anchors using the present glycosylation as a key step was examined (Fig. 7b, Supplementary Figs. 38 and 39). Initially, selective triflation of 9 and displacement using CsOAc, followed by deprotection of TBS group, afforded α(1,6)-d-mannoside 50. Mannosylation at the 2 position in inositol moiety provided core structure 52 of PIMs. In addition, protection of 9 using benzoyl and methoxymethyl (MOM) groups, followed by deprotection of benzoyl group, gave 53. Finally, oxidation and oximation, followed by reduction, afforded core structure 54 of GPI anchors. These results indicated that the present glycosylation method could lead to synthesize PIMs and GPI anchors effectively.

Synthesis of common structure of the LLBM-782 series. Finally, we applied the glycosylation method to the synthesis and structural determination of a common mannosyl inositol structure of the LLBM-782 series of antibiotics. The β configuration of the anomeric center was supported by the $^1$J_{CH} value of LLBM-782a$_2$ (163.9 Hz). However, in general, it is difficult to judge the anomeric configuration to be α or β using this ambiguous $^1$J_{CH} value. Therefore, in order to determine the anomeric configuration of the LLBM-782 series, we planned to synthesize common β-mannoside structure 55β of the LLBM-782 series using the present glycosylation method, and compare it to mannoside 55, which was provided by base hydrolysis of LLBM-782a$_2$, as shown in Fig. 8a. The synthetic scheme of 55β is shown in Fig. 8b (Supplementary Fig. 40). Desymmetrical glycosylation of 1,2-anhydro-α-mannose 56 and meso-diol 8 proceeded efficiently to provide β(1,4)-d-mannoside 57 in high yield as a single isomer.
Fig. 8 Synthetic scheme of mannoside 55β. a Chemical structures of LLBM-782 series and mannoside 55 produced by base hydrolysis of LLBM-782α; b Synthesis of mannoside 55β using the present glycosylation method. PMB p-methoxybenzyl, DMF dimethylformamide.

General procedure for desymmetric glycosylation. To a solution of meso-diols (0.02–0.05 mmol, 1.0 equiv.) and p-nitrophenylboronic acid (3) (4–10 μmol, 0.2 equiv.) in dry THF (0.2 M to meso-diols) was added a solution of 1,2-anhydro donor (0.03–0.15 mmol, 1.5–3.0 equiv.) in dry THF (0.2 M to 1,2-anhydro donor) at the temperature indicated under Ar atmosphere. After the reaction mixture was stirred for 3 h, the reaction was quenched by addition of 0.05 M NaBO3 aq. (8.8 mmol, 85%) in dry THF (0.1 M) at the temperature indicated. After the reaction mixture was stirred for 3 h, the reaction was quenched by addition of 0.05 M NaBO3 aq. (8.8 mmol, 85%) in dry THF (0.1 M) at the temperature indicated. After the reaction mixture was stirred for 3 h, the reaction was quenched by addition of 0.05 M NaBO3 aq. (8.8 mmol, 85%) in dry THF (0.1 M) at the temperature indicated. The crude material was purified by column chromatography on SiO2.

Data availability

The data supporting the findings of this study are available within the paper and its Supplementary Information and Supplementary Data 1 files.

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Methods

Materials. For 1H- and 13C-NMR spectra of compounds in this study, see Supplementary Information (Supplementary Figs. 42–125). For the detailed synthetic procedures and methods of DFT calculations, see Supplementary Information. For the data of DFT calculations, see Supplementary Dataset 1.

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