Published in final edited form as:

J Am Chem Soc. 2017 June 28; 139(25): 8570–8578. doi:10.1021/jacs.7b03198.

Regiodivergent Glycosylations of 6-deoxy-Erythronolide B and Oleandomycin-Derived Macrolactones Enabled by Chiral Acid Catalysis

Jia-Hui Tay[#], Alonso J. Argüelles[#], Matthew D. DeMars II[†], Paul M. Zimmerman^{#,*}, David H. Sherman^{‡,†,§,*}, and Pavel Nagorny^{#,§,*}

[#]Department of Chemistry, University of Michigan, Ann Arbor, MI 48109 United States

[†]Life Sciences Institute, University of Michigan, Ann Arbor, MI 48109 United States

[§]Department of Medicinal Chemistry, University of Michigan, Ann Arbor, MI 48109 United States

[‡]Department of Microbiology & Immunology, University of Michigan, Ann Arbor, MI 48109 United States

Abstract

This work describes the first example of using chiral catalysts to control site-selectivity for the glycosylations of complex polyols such as 6-dEB and oleandomycin-derived macrolactones. The regiodivergent introduction of sugars at the C3, C5 and C11 positions of macrolactones was achieved by selecting appropriate chiral acids as catalysts or through introduction of stoichiometric boronic acid-based additives. The BINOL-based CPAs were used to catalyze highly selective glycosylations at the C5 positions of macrolactones (up to 99:1 rr) whereas the use of SPINOL-based CPAs resulted in selectivity switch and glycosylation of the C3 alcohol (up to 91:9 rr). Additionally, the C11 position of macrolactones was selectively functionalized through traceless protection of the C3/C5 diol with boronic acids prior to glycosylation. The investigation of the reaction mechanism for the CPA-controlled glycosylations revealed the involvement of covalently linked anomeric phosphates rather than oxocarbenium ion pair as the reactive intermediates.

Graphical Abstract

*Corresponding Author: nagorny@umich.edu, davidhs@umich.edu, paulzim@umich.edu.

Supporting Information Available.

Experimental procedures and ¹H and ¹³C NMR spectra, are available free of charge via the Internet.

Keywords

Catalysis; Glycosylation; Regioselective; Macrolide Antibiotics; Chiral Phosphoric Acids

INTRODUCTION

Numerous bioactive natural products are glycosylated compounds including macrolide antibiotics where the sugar portion plays a central role in the biological activity and recognition of cellular targets. Glycosides can be viewed as chiral acetals, and the stereochemistry of the glycosidic linkage plays an important role in determining the physical, chemical, and biological properties of natural products.¹ Introduction of a glycosidic linkage to a complex natural product is a very delicate task as such compounds can often contain multiple reactive sites, and a reaction with a single sugar may result in a variety of isomeric glycoforms. However, when controlled by enzymes such as glycosyltransferases, such processes might proceed with remarkable levels of regio- and stereocontrol, and lead to the selective formation of one particular glycoform among the myriad of other possibilities.² Moreover, some glycosyltransferases from natural product pathways have shown remarkable versatility and flexibility toward a range of substrates.³

In contrast to Nature, accomplishing selective glycosylation of complex polyols in a reaction flask represents a formidable challenge. The strategies for selective glycosylation of natural products almost invariably involve additional protection/deprotection steps to prevent the formation of multiple regio- and stereoisomeric products during the glycosylation reaction.^{4,5} However, these additional selective protection/deprotection manipulations often represent a significant challenge by themselves, and the search for more convergent approaches, based on substrate-, reagent-, or catalyst-controlled glycosylation of unprotected polyols have received significant attention in recent years.⁶ While some remarkable examples of stereo-, chemo-, or regioselective glycosylation reactions have recently emerged,⁷ the available synthetic tools have limited versatility, and many challenges remain unaddressed. One of such challenges is achieving regiodivergent selective formation of glycosylated isoforms from the same initial polyols by judicious selection of catalysts or reaction conditions. Inspired by the seminal work of Miller and coworkers^{5a,b} and believing that the problem of regiocontrol could be addressed with the use of chiral catalysts that would change the environment around the glycosyl donor and affect the default reactivity pattern exhibited by the acceptor,⁸ our groups pursued studies focused on developing and applying such transformations.⁹ In order to demonstrate the power of this approach in a complex settings medicinally important 14-membered triol, 6-deoxyerythronolide B (6-dEB), was selected as our initial target.

6-dEB is a biogenic precursor to 14-membered macrolide antibiotics erythromycins A and B.¹⁰ Once produced, 6-dEB undergoes sequential glycosylations first at the C3 and then at the C5 position, which is an essential requirement for both the subsequent oxygenation at the C12 position, as well as for the antibiotic activity exhibited by erythromycins (Figure 1A). While recombinant techniques provide access to non-glycosylated 6-dEB,¹¹ the selective installation of sugars enzymatically represents a significant challenge.¹² To address this

challenge and to demonstrate that chemical catalysis could serve as a powerful tool for the regioselective glycosylation of complex natural polyols, we initiated studies directed to discovery of new methods that would allow direct and selective formation of all three regioisomeric glycosides from unprotected 6-dEB (Figure 1B). In particular, we were interested in identifying chiral catalysts that could mimic the function of EryBV and accomplish selective installation of the sugar at the C3 position in the presence of other functionalities. Indeed, our subsequent studies revealed that chiral acids such as chiral phosphoric acids (CPAs)^{13,14} or chiral disulfonimides could promote regiodivergent introduction of different sugars at both the C5 or C3 positions of 6-dEB and oleandomycin-derived 14-membered macrolactones **7**. In addition, conditions based on temporarily *in situ* masking of the C3/C5 diol as a cyclic boronate and subsequent glycosylation of the C11 position followed by unmasking the diol upon work up have been developed. These protocols have been used to generate various isomeric glycosides of 6-dEB and readily available oleandomycin B derivative **7** with 6-deoxysugars, a task that cannot be easily accomplished with existing achiral catalyst-based glycosylation or enzymatic methods. Remarkably, the mechanistic and theoretical studies contradict the traditionally proposed oxocarbenium ion-based reaction mechanism and are in line with the formation of covalently linked anomeric phosphate reaction intermediates (Figure 1C). This work represents the first example of chiral catalyst-controlled regioselective glycosylation and the methods developed in this study hold great potential for the non-enzymatic generation of glycosylated isoforms of complex natural polyols.

RESULTS AND DISCUSSION

To acquire sufficient amounts of 6-dEB for our studies, we employed an *E. coli* strain that had previously been engineered and optimized for high-level production of this biosynthetic intermediate.²⁴ Although the original study reported 6-dEB production titers as high as 129 mg/L in shake flask fermentation experiments, we were unable to reproduce these yields under the same conditions, typically acquiring ~5 mg/L of isolated material. Furthermore, quantification of 6-dEB production by LC-MS prior to culture extraction revealed that the low isolated yields were not due to loss of material from downstream workup, isolation, and purification procedures. After testing several alternative culturing conditions, we established a protocol that could reliably furnish 20–25 mg/L of the purified macrolactone (*cf.* SI). Thus, 200 mg of pure 6-dEB for glycosylation studies could be obtained in a facile manner following purification from a standard 9 L-scale fermentation.

Our subsequent studies commenced with investigating selective glycosylation of 6-dEB with 6-deoxyglucose derivative **A** (Table 1). To establish the inherent reactivity of the C3, C5, and C11 hydroxyls, control experiments where the reaction between 6-dEB and **A** was catalyzed by achiral catalysts (TMSOTf, (PhO)₂PO₂H, anhydrous *p*-TsOH and BF₃·OEt₂) were carried out (entries 1–5). The reaction with TMSOTf resulted in exclusive formation of the α -C5 product **2** (50% yield) along with the formation of *bis*-glycosylated product **3** (7% yield). The reaction with diphenylphosphoric acid (50 mol%) in dichloromethane and toluene (entries 2 and 3) proceeded with low conversion and provided the C5-glycoside (**2**) as the major product (24% and 30% yield respectively) along with minor quantities (5–6% yield) of the corresponding C3 product **1**. Despite its higher acidity, anhydrous *p*-TsOH was

not an effective catalyst for the glycosylation of 6-dEB and only trace amounts of products **1** and **2** (< 10%, 17:83 r.r.) was detected by NMR. Finally, the reaction catalyzed by $\text{BF}_3\cdot\text{OEt}_2$, (entry 5), a standard promoter for the glycosylation with trichloroacetimidates, proceeded in 59% yield to provide products **2** and **1** in 66:34 r.r. While all of the previous control reactions (entries 1–4) resulted in clean formation of the α -anomers, the reaction with $\text{BF}_3\cdot\text{OEt}_2$ as the catalyst led to the mixture of diastereomers of the C5-product **2** (α : β = 2.9:1). It should be noted that thus produced glycosides contain perbenzylated sugars, which can be converted in one step to the fully deprotected macrolactone glycosides by hydrogenolysis over Pd/C as exemplified by the debenzylation of **2** to **2A** (Eq. 1).

(1)

With these results in hand, our subsequent studies were focused on evaluating various chiral catalysts (**6–12**) with the objective of increasing the selectivity and yield of the C5-glycoside **2**.¹⁵ The evaluation of catalysts **4a–d** in nonpolar solvents (entries 6–11) helped to identify catalyst (**S**)-**4d** as the catalyst of choice (entry 11) that promoted the formation of α -C5 glycoside **2** in an excellent yield and selectivity (98% yield, 99:1 r.r.) and without the formation of *bis*-glycoside **3**. In addition, commercially available *bis*-sulfonimide (**R**)-**5d** could also promote highly selective formation of **2** albeit in lower yield (71% yield, entry 12). The biosynthesis of Erythromycin A from 6-dEB involves initial selective glycosylation at the C3 position catalyzed by EryBV (Figure 1A). However, our results indicate that the non-enzymatic version of this transformation is not accessible as the C5 hydroxyl of 6-dEB is inherently more reactive than the C3 position.¹⁶ Therefore, one of the important objectives in our following studies was to discover a catalyst that could mimic EryBV function and promote a C3-selective glycosylation directly from 6-dEB. The aforementioned studies indicated that the use of catalyst (**R**)-**4d** with DCM as the solvent (entry 9) resulted in ~1:1 C5:C3 selectivity and thus we decided to explore structurally similar catalysts with the objective of enhancing selectivity for the formation of **1** (entries 13–19). Considering that (**R**)-**4d** possesses 3,3'-aryl substituents functionalized at the 3,5-positions of the phenyl ring (i.e. 3,5-(CF_3)₂Ph-), BINOL-based catalysts **4e** and **4f** with similar substitution of the phenyl ring were examined (entries 13 and 14). To our delight, catalyst (**R**)-**4f** (Ar = 3,5-F-Ph) indeed promoted the selective formation of **1** for the first time (51% yield, 69:31 r.r.). In further attempts to optimize the reaction yield and selectivity, SPINOL-based catalysts **6** were examined (entries 15–19). Such catalysts possess a less flexible backbone with a different angle between substituents, which may result in a better differentiation of the diastereomeric transition states and hence higher selectivities in comparison to the BINOL based catalysts.¹⁷ Gratifyingly, catalyst (**S**)-**6f** (with a stereochemical configuration identical

to (**R**)-**4f** and Ar = 3,5-F-Ph) promoted selective formation of the C3 glycoside **1** in higher yield and selectivity (82% yield, 73:27 r.r.) when the reaction was in dichloromethane at room temperature (entry 19). In addition, the use of enantiomeric catalyst (**R**)-**6f** resulted in a selectivity switch and enhanced formation of the C5-glycosylated product **2** (entry 15, 75% yield, 93:7 r.r.). These results strongly indicate that the chiral catalyst configuration plays a determining role for whether the C5 (entry 15) or C3 (entry 19) position of 6-dEB is functionalized. Although with lower selectivity than observed in nature with EryBV, catalyst (**R**)-**6f** overrides the inherent preference for the C5 glycosylation exhibited by 6-dEB and directs glycosylation to proceed at the C3-position.

The optimization studies depicted in Table 1 led to the development of selective reactions between 6-dEB and 6-deoxyglucose derivative **A** that resulted in the C3-product **1** (73:27 r.r., >99:1 α : β , 82% yield) or the C5-product **2** (99:1 r.r., >99:1 α : β , 98% yield). In order to demonstrate that regiodivergent glycosylation of 6-dEB leading to all possible regioisomeric forms is possible, the development of a protocol allowing single step generation of the C11 glycoform of 6-dEB (**8a**) was pursued next (Scheme 1). Based on the prior glycosylation studies (Table 1), the C11 hydroxyl appeared to be the least reactive hydroxyl functionality in 6-dEB. We surmised that since the C3 and C5 hydroxyls are in 1,3-*syn* relationship, they could be selectively masked to form a cyclic boronic acid ester, which, in theory, could be formed *in situ* and cleaved upon work up without introducing additional steps. While such strategy has been successfully implemented in carbohydrate synthesis,¹⁸ we are unaware of its use for the single-pot selective glycosylation of 14-membered macrolactones or other non-carbohydrate-based natural products. Upon careful selection of the reaction conditions, the traceless *in situ* protection of 6-dEB with phenylboronic acid followed by glycosylation with **A** was accomplished to provide the corresponding C11 glycoside. This single pot sequence was completed by peroxide work up that cleaved boronate and resulted in **8a** in 62% yield (99:1 r.r., 3.7:1 β : α).

With selective methods for the introduction of a sugar at all three positions of 6-dEB leading to glycosylated macrolactones **1**, **2**, and **8a** (Table 2) in hand, the scope and limitations of these methods were investigated. To demonstrate that catalysts (**S**)-**4d** and (**S**)-**6f** could promote the reactions with other 6-deoxysugars, the reaction of 6-dEB and *D*-fucose derivative **B** using chiral catalyst-controlled glycosylation (conditions I and II, Table 2) was examined. As before, in the control experiment with TMSOTf as the promoter, the highly selective formation of C5 product **8c** was observed in 69% yield along with significant amounts (31% yield) of *bis*-glycosylated product (*cf.* SI-Table 2). This strongly contrasts with the (**S**)-**6f**-catalyzed reaction (conditions I) that allowed achieving the formation of the C3 product **8b** that was not observed in the control experiment (56:44 r.r., >99:1 α : β , 87% yield). As before, applying the BINOL-based catalyst (**S**)-**4b** resulted in exclusive formation of the C5 glycoside **8c** (>99:1 r.r., 1.7:1 α : β , 82% yield) with no *bis*-glycosylation product observed in the reaction mixture.

Our studies turned next to demonstrating that the methods identified in Table 1 and Scheme 1 could be applicable to the glycosylation of macrolactones other than 6-dEB. Thus, we identified a related 14-membered macrolactone **7** as a substrate that is structurally similar to 6-dEB, yet displays a dissimilar reactivity pattern due to the variant functionalities at the C8

position. In addition, this readily accessible oleandomycin derivative was selected due to its stability to spontaneous hemiacetalization documented for other deglycosylated oleandomycin derivatives.¹⁹ Interestingly, macrolactone **7** exhibited a markedly different reactivity profile in comparison to 6-dEB in reactions with achiral and chiral catalysts. When exposed to TMSOTf (conditions IV), macrolactone **7** and donor **A** reacted to produce the mixture of the C5 product **8d** (99:1 r.r., 1.6:1 = α : β , 31% yield), and hemiacetalized C3 side product **8e** (99:1 r.r., 1:1 = α : β , 31% yield). These results suggest that the C3 and C5 hydroxyls are equally reactive, and that an unselective glycosylation is followed by hemiacetalization of the C3 product to form **8e**. Similarly, the reactions catalyzed by CPAs followed a different trend as both (*R*)- and (*S*)-CPA catalysts were found to be C3-selective. The highest selectivity for the reaction of **7** and **A** was observed for the catalyst (*R*)-**6f**, while its enantiomer (*S*)-**6f** also promoted a C3-selective glycosylation of **7**; albeit with lower regioselectivity (*cf.* SI-Table 3). Thus, the use of (*R*)-**6f** led to regioselective formation of the C3 glycoside **8f** (71:29 r.r., 1:1 = α : β , 80% yield), while the reaction with (*S*)-**6f** provided 39% of **8f** (3.4:1 = α : β) and 21% of C5-glycosylated product **8d** with no hemiacetalization side product **8e** observed. In attempts to accomplish selective C5 glycosylation, catalysts (*S*)-**4d** and (*R*)-**5d** were explored (*cf.* SI-Table 3), and (*R*)-**5d** catalyzed the selective formation of the C5 product **8d** (70:30 r.r., 3.4:1 = α : β , 79% yield). Similar trends were observed for the glycosylation of **7** with fucose derivative **B**. In a control reaction, **7** provided equimolar mixture of C5-glycosylated product **8i** along with the hemiacetalized C3 product **8j**. The use of catalyst (*R*)-**6f** resulted in a highly selective formation of the corresponding C3 product **8g** (91:9 r.r., 1:99 = α : β , 93% yield). Using our prior findings, the formation of the C5-glycosylated product **8i** was accomplished with catalyst (*R*)-**5d** (71:29 r.r., 1.8:1 = α : β , 82% yield). Additionally, we demonstrated that, in analogy to 6-dEB, **7** could also be glycosylated at the C11 position to provide compound **8h** (99:1 r.r., 99:1 α : β , 48%, 89% brsm) yield) using traceless *in situ* protection with methylboronic acid prior to glycosylation (conditions VII). Finally, to assess the effect of sugar chirality, the reactions of **7** with enantiomeric *L*-fucose derivative **C** were investigated. The control experiments with **C** where TMSOTf was used as the catalyst resulted in essentially the same outcome as the *D*-fucose derivative **B** (*cf.* SI-Table 3). Similarly, the (*R*)-**6f**-catalyzed reaction of **7** and **C** proceeded with high levels of regioselectivity and provided the corresponding C3 glycoside **8k** (88:12 r.r., 1:2 α : β , 76% yield). In summary, while the change in the macrolactone structure may require reevaluation of a preselected group of catalysts (*i.e.* (*R*)- and (*S*)-enantiomers of **4d**, **5d** and **6f**), the overall regioselectivity trends hold for a given macrocycle and are not affected by minor changes in the donor structure.

To rule out the possibility of deglycosylation pathways that may affect the observed selectivities, NMR studies of the reaction was employed to monitor the reaction of **7** and **B** leading to selective formation of the C3-glycoside **8g** at different conversions (*cf.* SI), and no changes in the product composition were observed. In addition, the overnight exposure of the C5-glycoside **8i** to catalyst (*R*)-**6f** did not lead to any isomerization products or formation of hemiacetal **8j** (*cf.* SI). However, the overnight treatment of the C3-glycoside **8g** with TMSOTf at -20°C led to the slow formation of hemiacetalization product **8j**. These observations suggest that the selectivities observed in Tables 1 and 2 are due to the catalyst control and are not due to the decomposition/isomerization reactions.

In order to further understand the mechanism and stereoselectivity of the aforementioned reactions, a combined experimental and computational mechanistic investigation was undertaken (Figure 2 and SI). Based on a similar system,⁹ we hypothesized an oxocarbenium intermediate could be formed by Brønsted acid activation and departure of the trichloroacetimidate moiety. In this scenario, the chiral environment of the CPA/oxocarbenium ion pair would provide stereocontrol. To probe this mechanism a simplified model system was developed (Figure 2A) and modern reaction path searching algorithms were used.²⁰ This assessment surprisingly found the formation of β -anomeric phosphate **9B** via a S_N2 -like displacement of the α -trichloroacetimidate **9A** (**TS**₁, Figure 2B) was facile, at a 12.1 kcal/mol barrier. Following an exchange with 2,4-pentadiol (**9C**), a second, rate-determining (**TS**₂, 20.7 kcal/mol), S_N2 -like reaction affords the α -glycoside **9D**. Interestingly, the *syn*-1,3 diol moiety plays a role in the glycosylation step, as it is more geometrically suited to do an inversion on the anomeric center. This step involves a proton shuttle mechanism akin to enzymatic reactions,^{1–3} where one hydroxyl group protonates the leaving phosphate and simultaneously deprotonates the proximal attacking hydroxyl group.

While these steps are labeled S_N2 -like, the first step has a much earlier TS (**TS**₁: C-O_{formed} 2.63 Å vs C-O_{broken} 2.23 Å) compared to the second (**TS**₂: C-O_{formed} 2.09 Å vs C-O_{broken} 2.62 Å), which indicates that the latter is more dissociative in nature.^{21,22} In comparison, reactions in which the phosphate departed to form an intermediate oxocarbenium were found to be less favorable (> 26 kcal/mol). Finally, in order to discount the possibility of an uncatalyzed background reaction, an analogous S_N2 -like displacement of α -trichloroacetimidate by the diol was modeled but found to be implausible (**TS**₃ in SI, 34.8 kcal/mol). Finally, it should be noted that trichloroacetamide (CCl₃CONH₂) released throughout the reaction might serve as an inhibitor by forming a hydrogen bond complex with chiral phosphoric acid or phosphate intermediate.²³ Therefore further optimization of the glycosyl donor leaving group might lead to improved catalyst loading often observed for the other acetalization reactions.

As the proposed mechanism is fundamentally different to proposals on similar systems,^{20,22,24} experimental support was sought. Since the phosphate intermediate was predicted to be relatively stable, efforts were directed to detect the formation of **9B**. Indeed, when monosaccharide **A** is combined with (**R**)-**6f**, anomeric phosphate β -**10** was observed by NMR (Figure 3). When combined with CD₃OD, β -**10** underwent a facile S_N2 -like displacement forming product α -**11**. Likewise, when a similar investigation was carried on sugar derivative **C** (Figure 3), the formation of an α -phosphate (α -**12**) was observed. This intermediate underwent stereoselective S_N2 -like reaction with CD₃OD to provide the corresponding β -fucose derivative (β -**13**). In line with these experiments, the reaction between sugar **B** and (**R**)-**6f** produced anomeric phosphate α -**14** that was observed by NMR. When combined with **7**, phosphate α -**14** produced C3-glycosylation product **8g** (67% yield, 73:27 r.r., 99:1 α : β). Although the formation of the C3-glycoside **8g** for this control experiment was less selective than what was observed under condition V (Table 2), we believe that this result is nonetheless consistent with the mechanistic proposal outlined in Figure 2 as some discrepancy in selectivity is expected based on the absence of molecular sieves as well as difference in concentration, and presence of larger quantities of

trichloroacetimidate that may inhibit hydrogen bonding between α -**14** and **7**. Finally, a reaction of β **B** and **7** lead to the formation of **8g** in the same selectivity as for the α -trichloroacetimidate **B** (Eq. 2), which is consistent with the formation of the same reaction intermediate such as anomeric phosphate from both α and β donors **B**. Altogether, these results along with the computational studies and precedents by the Schmidt group^{25,26} suggest that the mechanisms for the formation of the anomeric phosphates from trichloroacetimidates may vary and are not always S_N2 -like, especially with axial alkoxy substituents in the C3 position. In addition, these results strongly imply that the α : β selectivity for the final glycosylation step is determined by the stereoselectivity for the anomeric phosphate formation step (*cf.* Eq. 2). It also should be noted that the proposed involvement of the covalently linked catalyst intermediates is consistent with the mechanistic proposals made by our group for the CPA-catalyzed reactions of acetals²⁷ and for the related transformation by Toste,²⁸ List,²⁹ Luo³⁰ and Ta-kasu³¹ groups.

CONCLUSION

In summary, this work describes the first example of chiral catalyst-controlled regioselective glycosylation of complex chiral polyols. These transformations were found to be particularly useful for the preparation of isomeric glycosides of 6-dEB and oleandomycin B derivative **7** with 6-deoxysugars, a task that cannot be readily accomplished with existing achiral catalyst-based or enzymatic methods. Chiral phosphoric acids and sulfonimides were used to promote regiodivergent introduction of the sugars at both the C5 or C3 positions of 6-dEB and **7** in a complementary manner. In addition, the conditions based on temporarily *in situ* masking of the C3/C5 diol as a cyclic boronate with a subsequent glycosylation of the C11 position followed by unmasking the diol upon work up have been developed and applied to directly form C11 glycosides **8a** and **8h** in excellent regioselectivities. While the change in the macrolactone structure required reoptimization of the catalyst, the methods developed for specific macrolactone tolerated changes in donor structure. Mechanistic and theoretical studies have been performed to elucidate the mechanism by which phosphoric acids promote these transformations. These studies lend support to a mechanism with the formation of covalently linked anomeric phosphate intermediates, and more detailed mechanistic studies directed to understand the observed selectivity are currently underway. This work represents the first example of chiral catalyst-controlled regioselective glycosylation, and the methods developed in this study hold great potential for the non-enzymatic generation of glycosylated isoforms of complex natural polyols.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Sources

This work was supported by NIH grant R01 GM11476 (P.N.) and NIH grant R35 GM118101 (D.H.S.). PN is the Sloan Foundation and Amgen Young Investigator Fellow. We thank Prof. John Montgomery for the useful discussions and David Braun for computational support during the preparation of this manuscript.

References

1. (a) Huang G, Lv M, Huang K, Xu H. *Mini Rev Med Chem*. 2016; 16:1013. [PubMed: 27499190]
(b) Huang G, Mei X. *Curr Drug Targets*. 2014; 15:780. [PubMed: 24942665]
2. (a) Blixt O, Razi N. *Glycoscience*. 2008;1361.(b) Koeller KM, Wong C-H. *Chem Rev*. 2000; 100:4465. [PubMed: 11749355]
3. Liang D-M, Liu J-H, Wu H, Wang B-B, Zhu H-J, Qiao J-J. *Chem Soc Rev*. 2015; 44:8350. [PubMed: 26330279]
4. Selected examples of chiral catalyst-controlled regioselective protection of chiral polyols:
Sculimbrene BR, Miller SJ. *J Am Chem Soc*. 2001; 123:10125. [PubMed: 11592903] Hu G, Vasella A. *Helv Chim Acta*. 2002; 85:4369. Sculimbrene BR, Morgan AJ, Miller SJ. *J Am Chem Soc*. 2002; 124:11653. [PubMed: 12296730] Sculimbrene BR, Xu Y, Miller SJ. *J Am Chem Soc*. 2004; 126:13182. [PubMed: 15479046] Morgan AJ, Wang YK, Roberts MF, Miller SJ. *J Am Chem Soc*. 2004;15370. [PubMed: 15563150] Kawabata T, Muramatsu W, Nishio T, Shibata T, Schedel HJ. *Am Chem Soc*. 2007; 129:12890–12895. Muramatsu W, Mishihiro K, Ueda Y, Furuta T, Kawabata T. *Eur J Org Chem*. 2010; 5:827–831. Jordan PA, Kayser-Bricker KJ, Miller SJ. *Proc Nat Acad Sci USA*. 2010; 107:20620–20624. [PubMed: 20439750] Longo CM, Wei Y, Roberts MF, Miller SJ. *Angew Chem Int Ed*. 2009; 48:4158–4161. Fiori KW, Puchlopek ALA, Miller SJ. *Nature Chem*. 2009; 1:630–634. [PubMed: 20161563] Zhao Y, Rodrigo J, Hoveyda AH, Snapper ML. *Nature*. 2006; 443:67. [PubMed: 16957727] Zhao Y, Mitra AW, Hoveyda AH, Snapper ML. *Angew Chem Int Ed*. 2007; 46:8741. Worthy AD, Sun X, Tan KL. *J Am Chem Soc*. 2012; 134:7321. [PubMed: 22515351] Ueda Y, Furuta T, Kawabata T. *Angew Chem Int Ed*. 2015; 54:11966. Sun X, Lee H, Lee S, Tan KL. *Nature Chem*. 2013; 5:790. [PubMed: 23965682] Allen CL, Miller SJ. *Org Lett*. 2013; 15:6178. [PubMed: 24274325] Kim JH, Coric I, Palumbo C, List B. *J Am Chem Soc*. 2015; 137:1778. [PubMed: 25636054] Chandler BD, Burkhardt AL, Foley K, Cullis C, Driscoll D, D'Amore NR, Miller SJ. *J Am Chem Soc*. 2014; 136:412. [PubMed: 24344932] Chen IH, Kou KGM, Le DN, Rathbun CM, Dong VM. *Chem Eur J*. 2014; 20:5013. [PubMed: 24623522] Xiao G, Clintron-Rosado DA, Glazier DA, Xi B, Liu C, Liu P, Tang W. *J Am Che Soc*. 2017; 139:4346. Yang H, Cao KS, Zheng WH. *Chem Commun*. 2017; 53:3737.
5. Chiral catalyst-controlled site-selective derivatization of erythromycin A: Lewis CA, Miller SJ. *Angew Chem Int Ed*. 2006; 118:5744–5747. Lewis CA, Merkel J, Miller SJ. *Bioorg Med Chem Lett*. 2008; 18:6007–6011. [PubMed: 18819795] . Chiral catalyst-controlled site-selective derivatization of vancomycin and teicoplanin: Pathak TP, Miller SJ. *J Am Chem Soc*. 2012; 134:6120. [PubMed: 22462775] Folwer BS, Laemmerhold KM, Miller SJ. *J Am Chem Soc*. 2012; 134:9755. [PubMed: 22621706] Pathak TP, Miller SJ. *J Am Chem Soc*. 2013; 135:8415. [PubMed: 23692563] Han S, Miller SJ. *J Am Chem Soc*. 2013; 135:12414. [PubMed: 23924210] . Chiral catalyst-controlled site-selective diversification of apoptolidine A: Lewis CA, Longcore KE, Miller SJ, Wender PA. *J Nat Prod*. 2009; 72:1864. [PubMed: 19769383] . Chiral catalyst-controlled site-selective derivatization of cardiotonic steroid glycosides: Yoshida K, Furuta T, Kawabata T. *Tetrahedron Lett*. 2010; 51:4830. Ueda Y, Mishihiro K, Yoshida K, Furuta T, Kawabata T. *J Org Chem*. 2012; 77:7850. [PubMed: 22870937] Tong ML, Huber F, Kaptouom EST, Cellnik T, Kirsch SF. *Chem Commun*. 2017; 53:3086.

6. (a) Giuliano MW, Miller SJ. *Top Curr Chem.* 2016; 372:157. [PubMed: 26307403] (b) Ueda Y, Kawabata T. *Top Curr Chem.* 2016; 372:303. (c) Lee D, Taylor MS. *Synthesis.* 2012; 44:3421. (d) Lawandi J, Rocheleau S, Moitessier N. *Tetrahedron.* 2016; 72:6283.
7. (a) Walk JT, Buchan ZA, Montgomery J. *Chem Sci.* 2015; 6:3448. [PubMed: 26000163] (b) Gouliaras C, Lee D, Chan L, Taylor MS. *J Am Chem Soc.* 2011; 133:13926. [PubMed: 21838223] (c) Beale TM, Taylor MS. *Org Lett.* 2013; 15:1358. [PubMed: 23465047] (d) Nakagawa A, Tanaka M, Hanamura S, Takahashi D, Toshima K. *Angew Chem Int Ed.* 2015; 54:10935. (e) Pelletier G, Zwickler A, Allen L, Schepartz A, Miller SJ. *J Am Chem Soc.* 2016; 138:3175. [PubMed: 26859619] (f) Park Y, Harper KC, Kuhl N, Kwan EE, Liu RY, Jacobsen EN. *Science.* 2017; 355:162. [PubMed: 28082586]
8. Mensah E, Camasso N, Kaplan N, Nagorny P. *Angew Chem Int Ed.* 2013; 52:12932.
9. For the examples of chiral phosphoric acids employed as the catalysts to enhance the selectivity for the S_N2-like formation of the anomeric linkage refer to the following publications: Cox DJ, Smith MD, Fairbanks AJ. *Org Lett.* 2010; 12:1452. [PubMed: 20199058] Kimura T, Sekine M, Takahashi D, Toshima K. *Angew Chem Int Ed.* 2013; 52:12131. Liu D, Sarrafpour S, Guo W, Goulart B, Bennett CS. *J Carbohydr Chem.* 2014; 33:423. Palo-Nieto C, Sau A, Williams R, Galan MC. *J Org Chem.* 2017; 82:407. [PubMed: 28004941]
10. (a) Cortes J, Haydock SF, Roberts GA, Bevirt DJ, Leadlay PF. *Nature.* 1990; 348:176. [PubMed: 2234082] (b) Donadio S, Staver MJ, McAlpine JB, Swanson SJ, Katz L. *Science.* 1991; 252:675. [PubMed: 2024119]
11. (a) Pfeifer BA, Admiraal SJ, Gramajo H, Cane DE, Khosla C. *Science.* 2001; 291:1790. [PubMed: 11230695] (b) Zhang H, Boghigian BA, Pfeifer BA. *Biotechnol Bioeng.* 2010; 105:567. [PubMed: 19806677]
12. (a) Borisova S, Kim HJ, Pu X, Liu H. *ChemBioChem.* 2008; 8:547. (b) Tang L, McDaniel R. *Chemistry & Biology.* 2001; 8:547. [PubMed: 11410374]
13. (a) Akiyama T, Itoh J, Yokota K, Fuchibe K. *Angew Chem Int Ed.* 2004; 43:1566. (b) Uraguchi D, Terada M. *J Am Chem Soc.* 2004; 126:5356. [PubMed: 15113196]
14. (a) Akiyama T. *Chem Rev.* 2007; 107:5744. [PubMed: 17983247] (b) Terada M. *Synthesis.* 2010; 12:1929. (c) Zamfir A, Schenker S, Freund M, Tsogoeva SB. *Org Biomol Chem.* 2010; 8:5262. [PubMed: 20820680] (d) Phipps RJ, Hamilton GL, Toste DF. *Nature Chem.* 2012; 4:603. [PubMed: 22824891] (e) Mahlau M, List B. *Angew Chem Int Ed.* 2012; 52:518. (f) Parmar D, Raja SS, Rueping M. *Chem Rev.* 2014; 114:9047. [PubMed: 25203602]
15. While other types of chiral catalysts, such as thiourea-based hydrogen bond donors (*cf.* Ref. 7f and 9d) could promote glycosylation, the current studies were limited to evaluation of chiral phosphoric acids. The full list of catalysts and conditions screened in this work could be found in SI-Table 1. It should be noted that more acidic phosphoric acids with fluorinated 3,3'-aryl substituents were superior promoters of glycosylation while the significantly slower reaction rates were observed for the CPAs lacking electronwithdrawing substitution at the 3,3'-aryl group. The catalysts do not decompose and could be recovered and recycled for larger scale experiments.
16. (a) Woodward RB, Logusch E, Nambiar KP, Sakan K, Ward DE, Au-Yeung BW, Balaran P, Browne LJ, Card PJ, Chen CH. *J Am Chem Soc.* 1981; 103:3215. (b) Toshima K, Nozaki Y, Mukaiyama S, Tamai T, Nakata M, Tatsuka K, Kinoshita M. *J Am Chem Soc.* 1995; 117:3717. (c) Tatsuta K, Kobayashi Y, Gunji H, Masuda H. *Tetrahedron Lett.* 1988; 29:3975. (d) Anzai Y, Li S, Chaulagain MR, Kinoshita K, Kato F, Montgomery J, Sherman DH. *Chemistry & Biology.* 2008; 15:950. [PubMed: 18804032]
17. Champagne PA, Houk KN. *J Am Chem Soc.* 2016; 138:12356. [PubMed: 27629045]
18. (a) Fenger TH, Madsen R. *Eur J Org Chem.* 2013; 26:5923. (b) Kaji E, Nishino T, Ishige K, Ohya Y, Shirai Y. *Tetrahedron Lett.* 2010; 51:1570. (c) Mancini RS, Lee JB, Taylor MS. *Org Biomol Chem.* 2017; 15:132.
19. (a) Tatsuta K, Kobayashi Y, Gunji H, Masuda H. *Tetrahedron Lett.* 1988; 29:3875. (b) Parker KA, Wang P. *Org Lett.* 2007; 9:4793. [PubMed: 17924640]
20. (a) Zimmerman PM. *J Comput Chem.* 2013; 34:1385. [PubMed: 23508333] (b) Zimmerman PM. *J Chem Phys.* 2013; 138:184102. [PubMed: 23676024] (c) Zimmerman PM. *J Chem Theory Comput.* 2013; 9:3043. [PubMed: 26583985] (d) Zimmerman PM. *J Comput Chem.* 2015; 36:601. [PubMed: 25581279] (e) Zimmerman PM. *Mol Simul.* 2015; 41:43.

21. Crich D, Sun S. *J Org Chem.* 1997; 62:1198.
22. Huang M, Garrett GE, Birlirakis N, Bohe L, Pratt DA, Crich D. *Nat Chem.* 2012; 4:663. [PubMed: 22824899]
23. (a) Monaco MR, Poladura B, Diaz de los Bernardos M, Leutzsch M, Goddard R, List B. *Angew Chem Int Ed.* 2014; 53:7063.(b) Monaco MR, Fazzi D, Tsuji N, Leutzsch M, Liao S, Thiel W, List B. *J Am Chem Soc.* 2016; 138:14740. [PubMed: 27779872]
24. Geng Y, Kumar A, Faidallah HM, Albar HA, Mhkalid IA, Schmidt RR. *Angew Chem Int Ed.* 2013; 52:10089.
25. Schmidt RR, Gaden H, Jatzke H. *Tetrahedron Lett.* 1990; 31:327.
26. (a) Schmidt RR, Stumpp M, Michel J. *Tetrahedron Lett.* 1982:405.(b) Schmidt RR, Wegmann B, Jung K-H. *Liebigs Ann Chem.* 1991; 2:121.
27. (a) Sun Z, Winschel GA, Zimmerman P, Nagorny P. *Angew Chem Int Ed.* 2014; 53:11194.(b) Nagorny P, Sun Z, Winschel GA. *Synlett.* 2013; 24:661.(c) Khomutnyk YY, Arguelles AJ, Winschel GA, Sun Z, Zimmerman PM, Nagorny P. *J Am Chem Soc.* 2016; 138:444. [PubMed: 26641317]
28. Shapiro ND, Rauniyar V, Hamilton GL, Wu J, Toste DF. *Nature.* 2011; 470:245. [PubMed: 21307938]
29. Liu L, Leutzsch M, Zheng Y, Alachraf WM, Thiel W, List B. *J Am Chem Soc.* 2015; 137:13268. [PubMed: 26448153]
30. Lv J, Zhang Q, Zong X, Luo S. *J Am Chem Soc.* 2015; 137:15576. [PubMed: 26594778]
31. Kuroda Y, Harada S, Oonishi A, Kiyama H, Yamaoka Y, Yamada K, Takasu K. *Angew Chem Int Ed.* 2016; 55:13137.

Figure 1.
Regioselective glycosylation of 6-dEB

Figure 2.
Theoretical studies of the reaction mechanism

Figure 3.
 Preparation and characterization by NMR of the covalently-linked phosphate intermediates
 10, 12 and 14

Scheme 1.

Single-pot traceless protection/glycosylation of the C11-position of 6-dEB

Table 1

Optimization of CPA-catalyzed glycosylation of 6-dEB^a

entry	activator (mol %)	solvent (conc.)	T (°C)	t (h)	yield	1	2	3
1	TMS-OTf (20)	PhMe (0.05 M)	-20	17	57%	0	88	12
2	PhO ₂ PO ₂ H (50)	CH ₂ Cl ₂ (0.05 M)	r.t.	26	30%	21	79	0
3	PhO ₂ PO ₂ H (50)	PhMe (0.05 M)	r.t.	26	35%	15	85	0
4	<i>p</i> -TsOH (20)	PhMe (0.05 M)	r.t.	26	<10%	17	83	0
5	BF ₃ ·OEt ₂ (20)	PhMe (0.05 M)	-20	24	59%	34	66 ^b	0
6	(R)-4a (20)	CH ₂ Cl ₂ (0.05 M)	r.t.	30	13%	13	87	0
7	(R)-4b (20)	CH ₂ Cl ₂ (0.05 M)	r.t.	30	13%	17	83	0
8	(R)-4c (20)	PhMe (0.10 M)	r.t.	24	57%	25	75	0
9	(R)-4d (20)	CH ₂ Cl ₂ (0.05 M)	r.t.	26	50%	50	50	0
10	(R)-4d (20)	PhMe (0.20 M)	r.t.	31	82%	35	65	0

entry	activator (mol%)	solvent (conc.)	T (°C)	t (h)	yield	1	2	3
11	(S)-4d (20)	PhMe (0.20 M)	rt.	30	98%	1	99	0
12	(R)-5d (20)	PhMe (0.10 M)	rt.	24	71%	1	99	0
13	(R)-4e (20)	PhMe (0.10 M)	rt.	24	80%	52	48	0
14	(R)-4f (20)	CH ₂ Cl ₂ (0.05 M)	rt.	48	51%	69	31	0
15	(R)-6f (20)	PhMe (0.10 M)	rt.	48	75%	7	93	0
16	(S)-6f (20)	PhMe (0.10 M)	rt.	48	54%	60	40	0
17	(S)-6f (20)	PhCF ₃ (0.10 M)	rt.	64	83%	63	37	0
18	(S)-6f (20)	CH ₂ Cl ₂ (0.10 M)	rt.	64	57%	71	29	0
19	(S)-6f (30)	CH ₂ Cl ₂ (0.10 M)	rt.	72	82%	73	27	0

^a Conditions: 6-dEB (1 equiv.), A (1.2 equiv.), 4 Å M.S., solvent (0.20–0.05 M). Reactions were run on 0.02 mmol scale.

^b Obtained as the 2.9:1 mixture of α:β diastereomers.

Table 2

Regiodivergent glycosylation of 6-dEB and oleandomycin derivative 7

Condition I: 6-dEB (1 equiv.), donor (1.2 equiv.), (S)-6f (30 mol%), 4 Å M.S., CH₂Cl₂ (0.10M), r.t.; **Condition II:** 6-dEB (1 equiv.), donor (1.2 equiv.), (S)-4d (20 mol%), 4 Å M.S., PhMe (0.20M), r.t.; **Condition III:** 6-dEB (1 equiv.), PhB(OH)₂ (1 equiv.), 4 Å M.S., PhMe, r.t.; then A (3 equiv.), TMS-OTf (0.2 equiv.); -20 °C, work-up with H₂O₂ and NaHCO₃; **Condition IV:** 7 (1 equiv.), donor (1.2 equiv.), TMSOTf (0.2 equiv.), 4 Å M.S., PhMe (0.05 M), -20 °C; **Condition V:** 7 (1 equiv.), donor (1.2 equiv.), (R)-6f (20 mol%), 4 Å M.S., PhMe (0.30M), r.t.; **Condition VI:** 7 (1 equiv.), donor (1.2 equiv.), (R)-5d (20 mol%), 4 Å M.S., PhMe (0.20 M), r.t.; **Condition VII:** 7 (1 equiv.), MeB(OH)₂ (1 equiv.), 4 Å M.S., PhMe, r.t.; then B (3 equiv.), TMS-OTf (0.5 equiv.), -20 °C; work-up MeOH. All reactions were carried on 0.02 mmol scale with the exception of 8g, which was formed on both 0.02 and 0.1 mmol scales without erosion in yield and selectivity.

^a Only C₃ and C₅ glycosides were observed.

^b The α : β selectivity for the major regioisomer

^c Isolated yield for the mixture of regioisomers

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript