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Perspective

Novel glycosylation methods and their application to natural products synthesis

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Dedicated to Professor K. C. Nicolaou on the occasion of his 60th birthday

Abstract—In this short review article, several glycosylation methods that were developed in our laboratories, including stereocontrolled glycosylation using 2,6-anhydro-2,6-dideoxy-2,6-dithio sugars for obtaining 2,6-dideoxy glycosides, C-glycosylation employing unprotected sugars, environmentally benign glycosylation utilizing heterogeneous solid acids and ionic liquids, are recounted. In addition, representative and significant applications of these methods to the synthesis of complex natural products are described.

Keywords: Carbohydrate; Glycosylation; Glycoside; Natural product; Glycomolecule

1. Introduction

Many carbohydrate-containing natural products are found in nature as important biological substances. A large number of recent studies on these glycomolecules, which possess mono- and oligosaccharides, such as proteoglycans, glycoproteins, glycolipids, and antibiotics have shed light on the significance of their carbohydrate parts (glycons) in molecular recognition for the transmission of biological information.[1] Therefore, it is now recognized that carbohydrates are at the heart of a multitude of biological events. With this stimulating biological background, the efficient synthesis of not only carbohydrates themselves, but also carbohydrate-containing complex natural products is becoming more and more important in the field of organic chemistry and chemical biology.[2] Consequently, efficient glycosylation methods, which are among the most fundamental and important reactions of carbohydrates, are of particular interest in the synthesis of biologically important glycosubstances.[3] In this short review article, several glycosylation methods that were developed in our laboratories, including stereocontrolled glycosylation using 2,6-anhydro-2,6-dideoxy-2,6-dithio sugars for obtaining 2,6-dideoxy glycosides, C-glycosylation employing unprotected sugars, environmentally benign glycosylation utilizing heterogeneous solid acids and ionic liquids, are discussed. In addition, representative and significant applications of these methods to the synthesis of complex natural products are also described.

2. Development of glycosylation methods and their applications to natural products synthesis

2.1. Glycosylations using 2,6-anhydro-2,6-dideoxy-2,6-dithio sugars and their applications to the synthesis of erythromycin A

In nature, many types of 2,6-dideoxy-α- and β-glycosides frequently appear in bioactive natural products, such as the macrolide antibiotics, aureolic acid antibiotics, anthracycline antibiotics, and cardiac glycosides, among others (Fig. 1). The stereocontrolled formation of 2,6-dideoxy glycosides, however, has been a formidable task and a long-standing problem in synthetic organic

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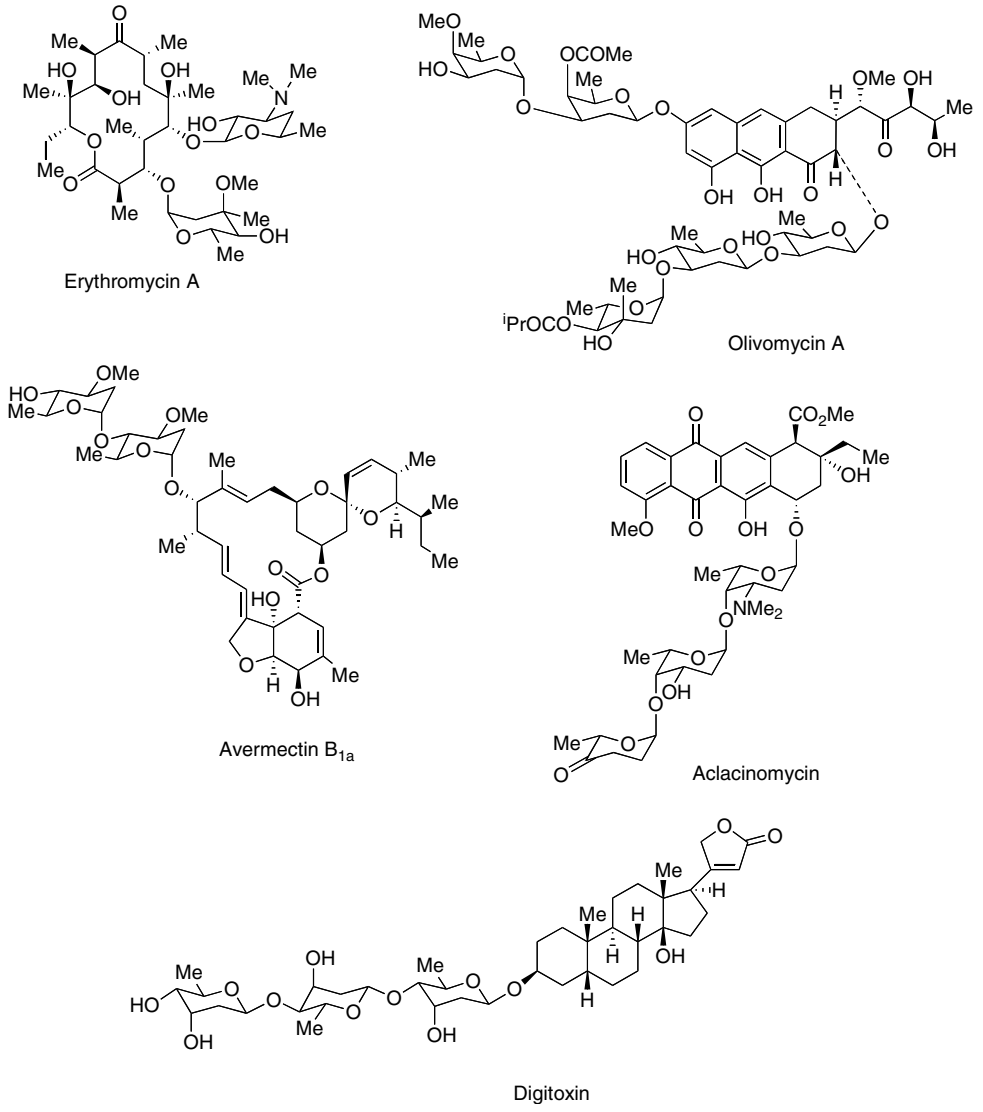


Figure 1. Some bioactive natural products possessing 2,6-dideoxy sugars.

chemistry. A representative study in this area is the elegant synthesis of the aureolic acid antibiotics reported by Roush's group.[4] In this context, we developed a highly stereocontrolled glycosylation method using 2,6-anhydro-2,6-dideoxy-2,6-dithio sugars as glycosyl donors for the efficient synthesis of both 2,6-dideoxy-α- and β-glycosides.[5] Furthermore, we successfully applied this glycosylation method to the synthesis of the clinically useful antibiotic, erythromycin A.[6]

The main reasons why the highly stereocontrolled glycosylation of the 2,6-dideoxy sugars is difficult are the lack of stereodirecting anchimeric assistance from both the C2 and C6 positions and the low stability of the glycosidic linkage due to the lack of an electron-withdrawing C2 substituent. To overcome these problems, we designed as novel glycosyl donors the conformationally rigid 2,6-anhydro-2,6-dideoxy-2,6-dithio sugars, which have a sulfur bridging the C2 and C6 positions. These

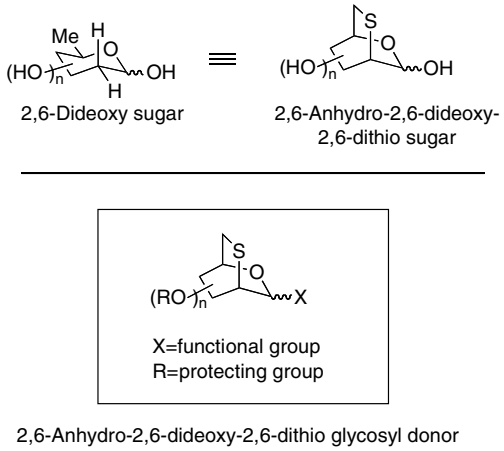


Figure 2. 2,6-Dideoxy and 2,6-anhydro-2,6-dideoxy-2,6-dithio sugars.

glycosyl donors have the following novel distinctive features as shown in Figure 2: (1) the donor has a very rigid

structure due to the bicyclic ring system; (2) the donor is a good precursor to 2,6-dideoxy glycoside; and (3) the stereoselectivity of the glycosylation is not affected by the anomeric effect in the same manner as the more usual chair conformers because of its unusual boat conformation.

We synthesized the 2,6-anhydro-2,6-dideoxy-2,6-dithio glycosyl donors **1**, **2**, and **3** from the corresponding known methyl glycosides and tested them in glycosylation reactions. We first found that the glycosylations of the phenylthio glycoside **1** with several alcohols promoted by NBS (or CH_3OTf) showed some excellent features (Fig. 3). Thus, it was found that the glycosylations of **1** with alcohols including primary, secondary and tertiary alcohols in several solvents, such as dichloromethane, 1,2-dichloroethane, diethyl ether, tetrahydrofuran, acetonitrile, and toluene, proceeded very rapidly at low temperature to give the corresponding 2,6-anhydro-2,6-dideoxy-2,6-dithio α-glycosides in excellent yields. Remarkably, the stereoselectivity of the glycosylations was highly α-selective in all cases. It was also demonstrated that the stereoselectivity of the glycosylations was independent of both the solvent and the configuration of the anomeric center of the donor. Furthermore, we found that the glycosylations of fluoride **2** and several alcohols with many kinds of activators, such as $SnCl_2/AgClO_4$, $SnCl_2$, TMSOTf, $Cp_2ZrCl_2/AgClO_4$, $Cp_2HfCl_2/AgClO_4$, or $AgBF_4$, proceeded under mild conditions to afford the corresponding α-glycosides with high stereocontrol in excellent yields (Fig. 4). Again, the stereoselectivity was independent of the glycosylation conditions including the activator and solvent. In drastic contrast, the 2,6-anhydro-2,6-dideoxy-2,6-dithio β-glycosides were exclusively obtained for glycosylations of alcohols in dichloromethane using glycosyl acetate **3** and these alcohols (Fig. 5). Thus, we found that the glycosylations of **3** with several Lewis acids, such as $SnCl_4$, Tf_2O, TMSOTf, and $TrClO_4$, proceeded smoothly at low temperature to give the corresponding 2,6-anhydro-2,6-dideoxy-2,6-dithio β-glycosides with high stereocontrol in excellent yields. The stereoselectivity of the glycosylations was independent of the Lewis acid activator. We next examined for solvent effect of the unexpected and high β-stereoselective glycosylation reactions. Therefore, the glycosylations of **3** using TMSOTf in solvents, such as 1,2-dichloroethane, diethyl ether, tetrahydrofuran, acetonitrile, and toluene, were tested. It was interesting to note that the α-glycosides were exclusively produced in diethyl ether and tetrahydrofuran, while the β-anomers were predominantly obtained in acetonitrile and toluene and 1,2-dichloroethane as well as in dichloromethane. Also, it was found that the ratio of the β-anomer was increased by long reaction times, even in the case of diethyl ether and tetrahydrofuran and the β-glycoside was produced in reasonable yield by treatment of the corresponding α-glycoside with only the Lewis acids in dichloromethane, acetonitrile, and toluene and 1,2-dichloroethane. These results indicate that although these Lewis acids are considerably deactivated in diethyl ether and tetrahydrofuran, they are strong enough in dichloromethane, acetonitrile, toluene, and 1,2-dichlo-

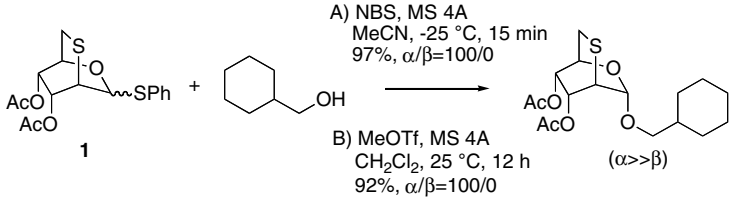


Figure 3. Glycosylations of **1** using NBS or MeOTf.

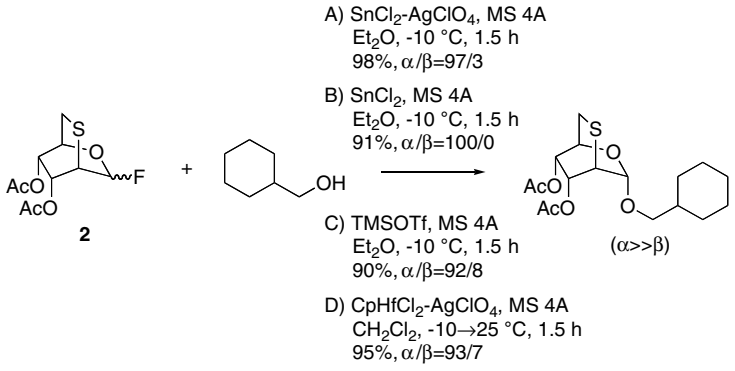


Figure 4. Glycosylations of **2** under several conditions.

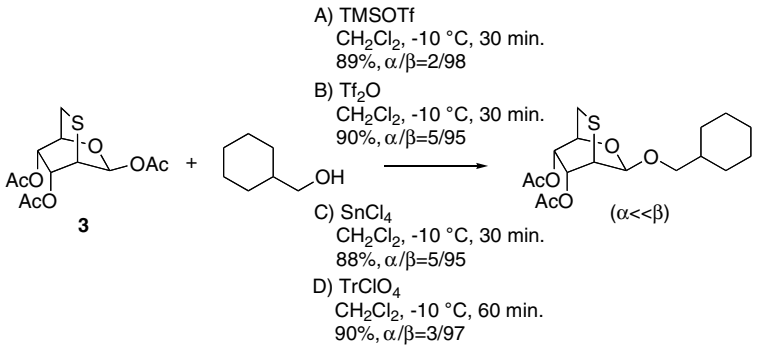


Figure 5. Glycosylations of **3** under several conditions.

roethane to reverse the glycosylation reaction and that thermodynamic control is responsible for the high β-stereoselectivity.

With both the 2,6-anhydro-2,6-dideoxy-2,6-dithio α- and β-glycosides in hand, they were efficiently converted to the desired 2,6-dideoxy sugar derivatives using two methods (Fig. 6). The first was standard hydrogenolysis, using Raney-Ni (W4) as a catalyst in ethanol at 40 °C, of the corresponding 3,4-deprotected derivatives, which were obtained by the prior hydrolyses of the 3,4-di-*O*-acetyl-2,6-anhydro-2,6-dideoxy-2,6-dithio glycosides. The second procedure was the reductive desulfurization of the protected glycosides using freshly prepared Bu_3SnH and AIBN in toluene at reflux. The latter method is useful for the chemoselective desulfurization in the presence of other functional groups affected by hydrogenolysis, such as double bonds.

We confirmed that the high reactivity of the 2,6-anhydro-2,6-dideoxy-2,6-dithio sugars under a variety of glycosylation conditions resulted from the electron donating nature of the sulfur at the C2 position, and that the rate of the glycosylation reaction was strongly affected by the oxidation state of the sulfur. Thus, glycosidations of both the sulfinyl fluorides **4** and **5** as well as sulfonyl fluoride **6** with alcohols under similar conditions as those used for fluoride **2α** did not proceed at all (Fig. 7).

The remarkably high stereoselectivity of glycosylations with these donors could be explained as follows.

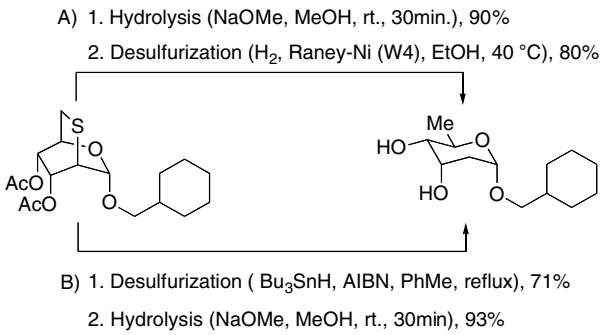


Figure 6. Conversion of 2,6-anhydro-2,6-dideoxy-2,6-dithio glycosides into 2,6-dideoxy glycosides.

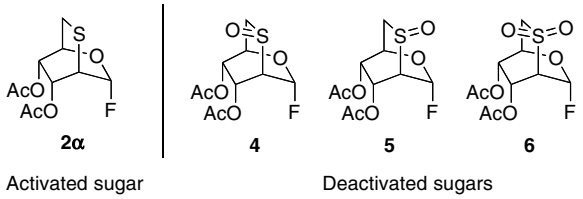


Figure 7. Activated (armed)-sugar and deactivated (disarmed)-sugars.

Because the configuration of the newly forming glycoside bond is completely independent of the configuration of the anomeric position of the donor, these reactions must proceed via a S_N1 type reaction pathway, and the oxocarbenium ion intermediate formed in these reactions is **A** (Fig. 8). Two major interactions must be considered when evaluating the face to which the alcohol will approach **A**. One is the repulsive electronic interaction between the bridging sulfur atom and the alcohol with it approaches the anomeric center from the β-face. The other is the 1,3-diaxial repulsion between the C3 substituent and the alcohol when it approaches from the α-face. When the glycosylation proceeds under kinetic conditions, the repulsive electronic interaction strongly impedes the reaction. Consequently, the alcohol predominantly attacks the α-face of **A**, and the configuration of the formed glycoside bond is maintained during the reaction (Fig. 8, path a). Indeed, no isomerization was observed when either the 2,6-anhydro-2,6-dideoxy-2,6-dithio α- or β-glycosides were exposed to the glycosylation conditions used for **1** and **2**. Alternatively, a sulfonium-ion intermediate **B** resulting from the participation of the sulfur was considered for the induction of the α-stereoselectivity. In contrast, under thermodynamic conditions, even if the α-bond formation preferentially occurs, the α-glycoside bond is cleaved and then the thermodynamically stable β-glycoside bond, which arises from the 1,3-diaxial interaction, finally forms (Fig. 8, path b). Interestingly, both effects strongly influence the stereoselectivity of the glycosylation of the 2,6-anhydro-2,6-dideoxy-2,6-dithio glycosyl donors under all glycosylation conditions due to the very rigid conformation of the donor.

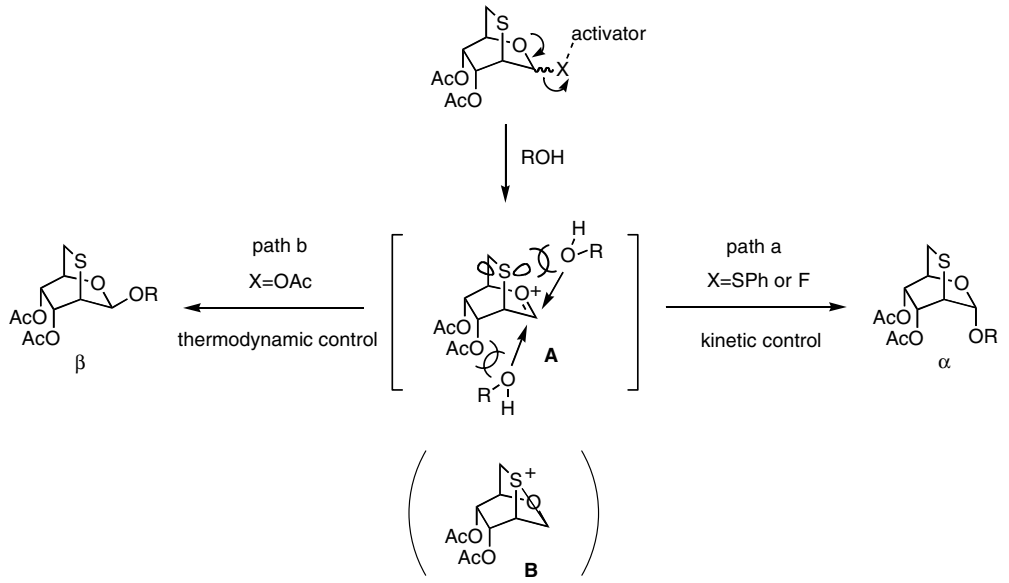


Figure 8. Presumed mechanism of the glycosylation of 2,6-anhydro-2,6-dideoxy-2,6-dithio sugars.

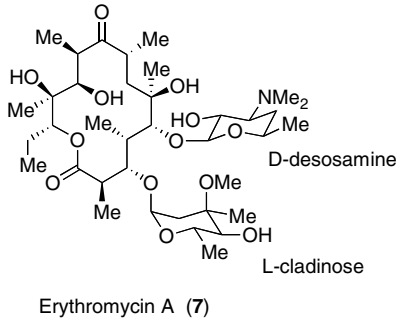
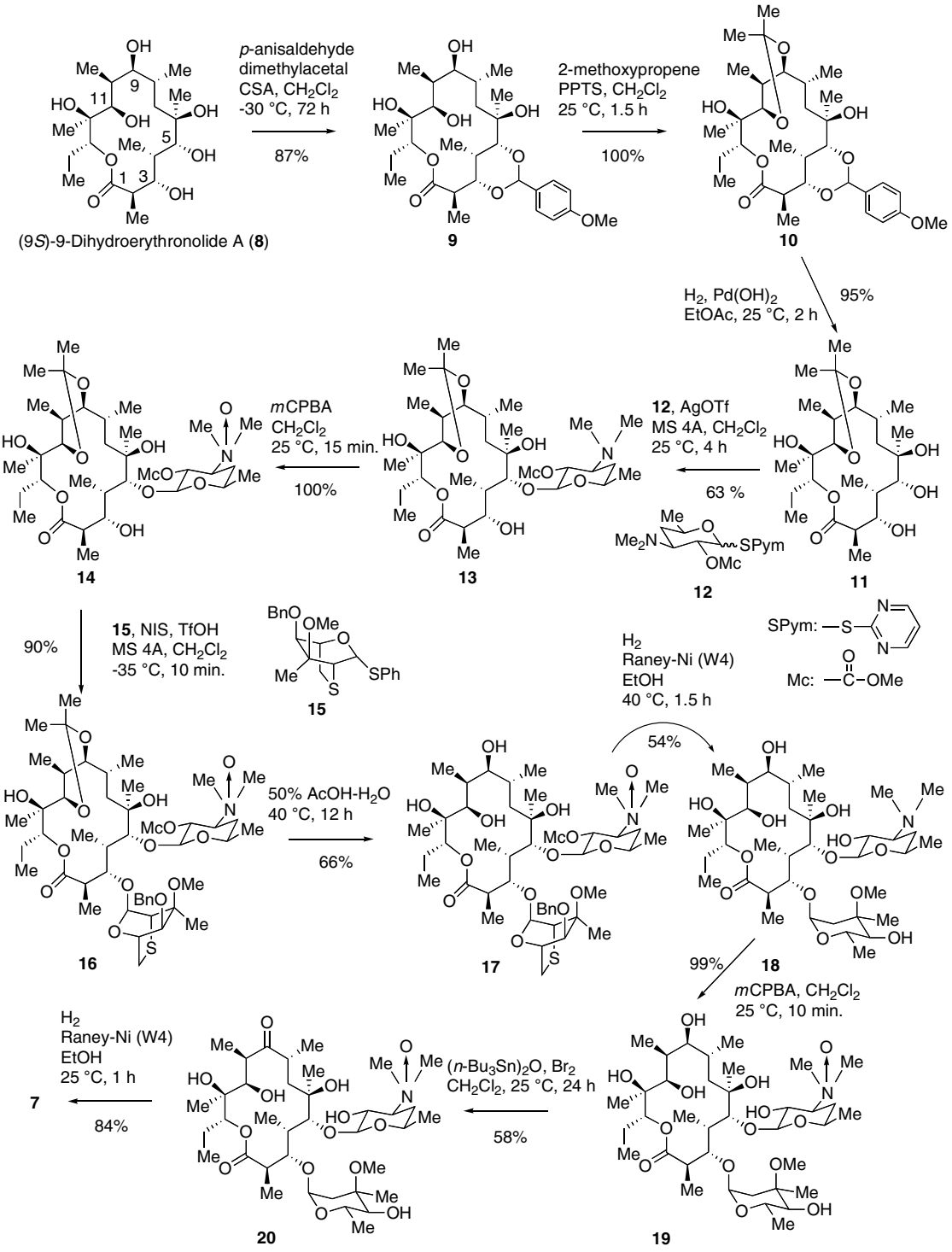


Figure 9. Structure of erythromycin A (**7**).

Based on these results, we applied this glycosylation method to the synthesis of several natural products. Among them is a typical and medicinally important macrolide antibiotic, erythromycin A (**7**, Fig. 9). Woodward's classic total synthesis of erythromycin A made it clear that the most difficult task after the aglycon synthesis was the stereoselective introduction of the acid-sensitive 2,6-dideoxy sugar, L-cladinose, to the very poorly reactive C3 hydroxyl group.[7] Our method overcame this problem. Our approach for the synthesis of **7** from its aglycon, (9*S*)-9-dihydroerythronolide A (**8**), began with the selective conversion of **8** into the C9 and C11 protected aglycon **11** in three steps (Scheme 1). Treatment of **8** with *p*-anisaldehyde dimethylacetal and a catalytic amount of camphorsulfonic acid afforded **9** with high regioselectivity. The isopropylidenation of **9** using 2-methoxypropene and PPTS also regioselectively proceeded to give the C9 and C11 *O*-isopropylidene product **10**. Subsequent reductive deprotection of the *p*-methoxybenzylidene group of **10** by hydrogenolysis using $Pd(OH)_2$ gave the first key aglycon **11**. The glycosylation of **11** with the thioglycoside **12** using the modified Woodward procedure with AgOTf and 4 Å molecular sieves in dichloromethane/toluene at 0→25 °C for 4 h proceeded regio- and stereoselectively to afford the desired C5 glycosylated β-glycoside **13** as the sole anomer in 63% yield. Glycosylation of lactone **13** with the phenylthio glycoside precursor to L-cladinose (**15**) using several activators, such as NBS or NIS, was next examined. However, it was found that only undesired products including N-formylated compounds were isolated as major components. Therefore, the *N*,*N*-dimethyl group of **13** was oxidized by *m*-CPBA to give the corresponding N-oxide **14**. At this stage, the glycosylation of **14** with glycosyl donor **15** in the presence of NIS, TfOH, and 4 Å molecular sieves in degassed dichloromethane under argon at −35 °C proceeded very rapidly to give the desired α-glycoside **16** as the sole isolated product in 90% yield. Removal of the isopropylidene acetal of **16** under mild acidic conditions using 50% $AcOH/H_2O$ afforded **17** with minimal cleavage of the glycoside bond of the 2,6-anhydro-2,6-dideoxy-2,6-dithio moiety in **16**. Subsequent treatment of **17** with H_2 in the presence of catalytic amounts of Raney-Ni (W4) caused the simultaneous desulfurization of the 2,6-anhydro-2,6-dideoxy-2,6-dithio sugar, the reduction of the N-oxide and removal of the benzyl and carbomethoxy groups to produce (9*S*)-9-dihydroerythromycin A (**18**). To selectively oxidize the C9 hydroxyl group of **18**, the *N*,*N*-dimethyl group of **18** was again oxidized by *m*-CPBA to afford the corresponding N-oxide **19**. Selective oxidation was eventually achieved under Saigo-Mukaiyama conditions using $(n\text{-}Bu_3Sn)_2O$ and Br_2 to give the desired C9 keto-compound **20**. Finally, the N-oxide of **20** was reduced by



Scheme 1. Synthesis of erythromycin A (**7**) by the glycosylation using 2,6-anhydro-2,6-dideoxy-2,6-dithio sugars.

standard hydrogenolysis using Raney-Ni (W4) as a catalyst to give erythromycin A. Thus, this novel O-glycosylation method, when used with several types of 2,6-anhydro-2,6-dideoxy-2,6-dithio glycosyl donors, allows the stereocontrolled synthesis of the 2,6-dideoxy glycosides that frequently occur in clinically useful antibiotics.

2.2. C-Glycosylations of unprotected sugars and their applications to the synthesis of urdamycinone B

Many biologically interesting C-glycosides, such as aryl C-glycoside antibiotics, are found in nature, and several types of C-glycosides, such as alkyl and allyl C-glycosides, are useful chiral building blocks for the synthesis

of optically active natural products. Although remarkable progress has been made in C-glycoside synthesis,[8] the development of simple and practical C-glycosylation methods remains one of the central problems in synthetic organic chemistry. The use of unprotected sugars as glycosyl donors in glycosylation reactions undoubtedly has considerable advantages. The main reasons why glycosylations of unprotected sugars are difficult are the undesirable generation of self-coupling products of the glycosyl donor and the deactivation of a glycosylation reagent by the free hydroxyl groups of the glycosyl donor. However, we have succeeded in developing aryl[9] and allyl[10] C-glycosylations utilizing unprotected sugars and we achieved the total synthesis of urdamycinone B,[11] a prototypical member of the *C*-glycosyl angucycline antibiotics.

Over the past several years, aryl C-glycoside antibiotics such as the angucyclin and pluramycin families have attracted considerable attention due to their significant biological properties and architecturally interesting structures (Fig. 10).[12] 2-Deoxy sugars are the most common and important class of the sugar residues in these molecules. In this context, we were challenged to develop aryl C-glycosylation methods employing unprotected sugars. For this purpose, we developed a new approach, which was based on the difference in the stability between the *C*-glycosidic and *O*-glycosidic bond. Thus, if we could find a reaction that cleaves any O-glycoside bond and then forms a C-glycoside bond, C-glycosylation using an unprotected sugar as the glycosyl donor would be achieved (Fig. 11).

During our initial attempts in searching for such a reaction, we examined the aryl C-glycosylation of a glycosyl donor possessing a methyl glycoside because it is one of the most stable *O*-glycosidic bonds. If a methyl glycoside is converted into a C-glycoside, then any *O*-glycosidic bond could be cleaved and converted to a *C*-glycosidic bond. We found that the C-glycosylation of the methyl glycoside **21** with 2-naphthol using 20 mol % of TMSOTf/$AgClO_4$ (1:1) proceeded smoothly to give the corresponding aryl β-C-glycoside

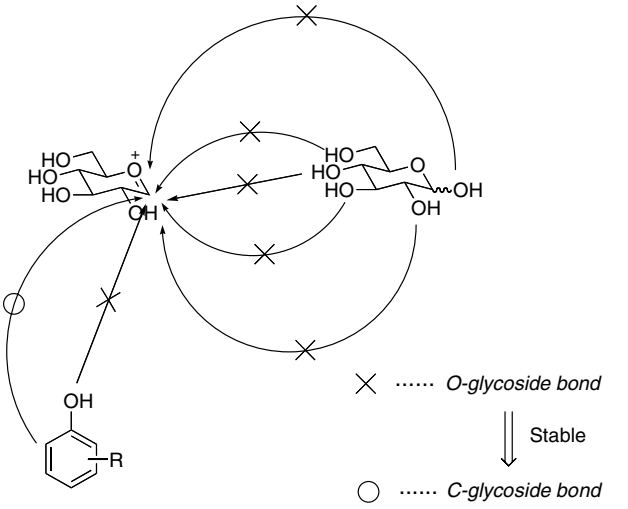
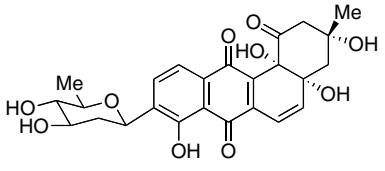


Figure 11. Concept of aryl C-glycosylation using an unprotected sugar.

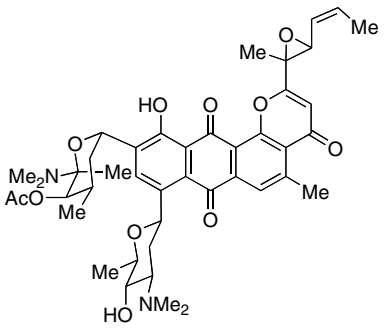
in 99% yield (Fig. 12). In addition, we confirmed that this reaction process involved the O→C-glycoside rearrangement, which was similar to the Lewis acid-catalyzed C-glycosylation mechanism proposed by Komentani[13] and Suzuki.[14]

With this favorable result in hand, we found after further study that the TMSOTf/$AgClO_4$ activator system was not deactivated by the hydroxyl groups and could effectively activate the anomeric oxygen of the glycosyl donor leading to the aryl C-glycosylation of a totally unprotected sugar. Thus, we found that the aryl C-glycosylations of the unprotected methyl glycoside **22** and reducing sugar **23** with several phenol and naphthol derivatives using TMSOTf/$AgClO_4$ proceeded smoothly under mild conditions to afford the corresponding unprotected *o*-hydroxyaryl β-C-glycosides in high yields (Fig. 13).

In subsequent studies on this project, we investigated a more practical method not employing $AgClO_4$, which is an undesired reagent, especially in large-scale experiments and industrial processes, due to its hazardous



Aquayamycin (a angucyclin)



Pluramycin A (a pluramycin)

Figure 10. Molecular structures of the representative aryl C-glycoside antibiotics.

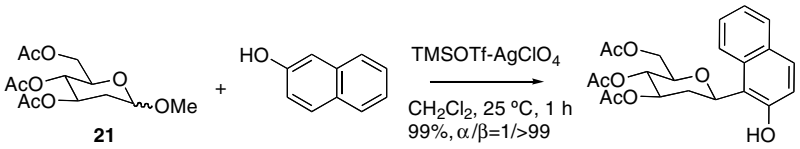


Figure 12. Aryl C-glycosylation of **21** using TMSOTf/$AgClO_4$.

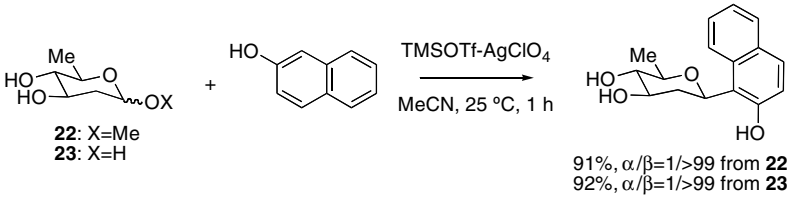


Figure 13. Aryl C-glycosylations of **22** and **23** using TMSOTf/$AgClO_4$.

and explosive properties. After many attempts to identify an activator with no hazardous or explosive properties, we found that although an acyl-protected glycosyl donor (e.g., **21**) was not suitable in glycosylations using TMSOTf, the reactions of the **22** and **23** with several phenol and naphthol derivatives in the presence of TMSOTf proceeded efficiently to afford the corresponding unprotected *o*-hydroxyaryl β-C-glycosides in high yields. These results clearly indicated that unprotected sugars can be very versatile glycosyl donors in the aryl C-glycosylation reaction when promoted by TMSOTf (Fig. 14). At this stage, we confirmed that, in the case of **23**, the combined use of TMSOTf/$AgClO_4$ sometimes gave better results than the use of TMSOTf. When the TMSOTf/$AgClO_4$ promoter system is used, the true activating species for the glycosyl donor is presumably $TMSClO_4$ and/or $HClO_4$, which is generated due to the presence of the free hydroxyl groups on the glycosyl acceptor and donor, while TMSOTf and/or TfOH is the activating species when TMSOTf is used.

Another approach for developing the C-glycosylations using unprotected sugars was based on the difference in the formation rate between the C-glycoside bond and O-glycoside bond. Thus, if we could find a reaction in which *C*-glycosidic bond formation is faster than *O*-glycosidic bond formation, C-glycosylation using unprotected sugars could be achieved (Fig. 15). This approach was investigated and realized in the allyl C-glycosylations of unprotected glycals and allyltrimethylsilane. These glycosylations gave exclusively the corresponding unprotected and 2,3-unsaturated allyl α-C-glycosides, which are very versatile synthetic intermediates for natural products syntheses.[15]

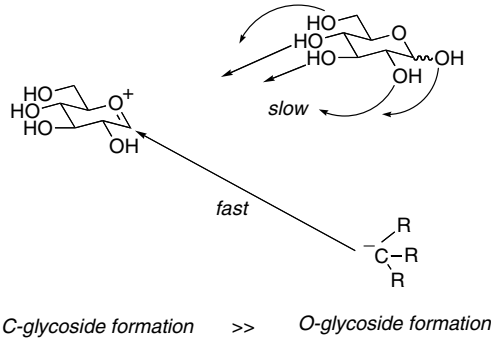


Figure 15. Concept of allyl C-glycosylation using an unprotected sugar.

We found that the unprotected glycal **24** was coupled smoothly with allyltrimethylsilane using 100 mol % of TMSOTf in dichloromethane at −78 °C for 0.5 h to afford only the unprotected and 2,3-unsaturated allyl α-C-glycoside in 94% yield (Fig. 16). Self-coupling products, resulting from the O-glycosylation of **24**, were not detected at any stage of the reaction. Furthermore, it was confirmed that the low temperature (−78 °C) was important for the selective formation of the C-glycoside bond. In addition, we found that the allyl

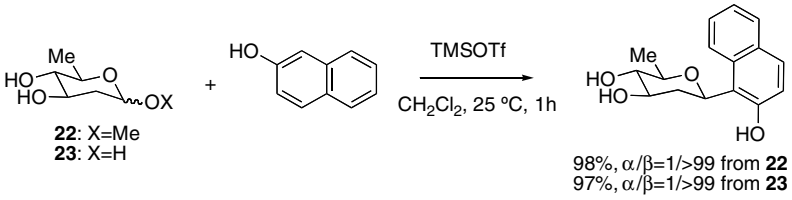


Figure 14. Aryl C-glycosylations of **22** and **23** using TMSOTf.

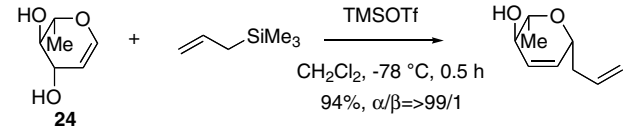


Figure 16. Allyl C-glycosylation of **24** with allyltrimethylsilane.

C-glycosylations of several other unprotected glycals, for example, D-glucal, D-galactal, and D-fucal, with allyltrimethylsilane proceeded under similar conditions to give the corresponding allyl α-C-glycosides in good to high yields. Remarkably, the stereoselectivity of these glycosylations was α-selective in all cases. For the glycosylations of D-glucal, D-galactal, and D-fucal, the use of acetonitrile as a co-solvent and the low glycal concentration were crucial factors in obtaining high yields of the desired allyl C-glycosides, due to their low solubility in dichloromethane at −78 °C. Furthermore, we found that the unprotected glycosyl donors were of higher reactivity compared to the acyl-protected derivatives.

With these results in hand, we successfully applied this method to the synthesis of the angucycline antibiotics. The angucyclines with a unique benz[*a*]anthraquinone as a common structure are a rapidly growing new class of antibiotics. They show a variety of biological activities including antitumor activity and enzyme inhibition. Among them is urdamycinone B (**25**), a prototypical member of the *C*-glycosyl angucyclines, which is obtained from the antibiotic urdamycin B by careful cleavage of the two O-glycoside moieties, which also exhibits antitumor activity (Fig. 17). Elegant total syntheses of (−)-urdamycinone B, the enantiomer of the natural urdamycinone B, and urdamycinone B have been reported by Yamaguchi[16] and Sulikowski,[17] respectively. We used the method described above to carry out a highly effective total synthesis of urdamycinone B (**25**).

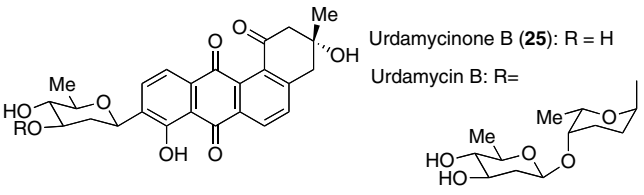


Figure 17. Structures of urdamycinone B and urdamycin B.

The retrosynthetic analysis of **25** is shown in Figure 18 along with our synthetic plan based on a key Diels–Alder reaction between the diene **27** and the dienophile **28**. Therefore, our synthetic approach began with the synthesis of the unprotected *C*-glycosyl juglone **27** using unprotected D-olivose (**23**). We first tried the direct aryl C-glycosylation of juglone with **23**. However, this reaction did not proceed using either TMSOTf or TMSOTf/$AgClO_4$ as activators. At this stage, it was considered that these unfavorable results came from the extremely low reactivity of the glycosyl acceptor, juglone, due to the quinone skeleton. Therefore, we investigated other syntheses of the unprotected *C*-glycosyl juglone **27**. After many attempts to develop such a synthesis, we finally developed the novel two-step synthesis of the unprotected *C*-glycosyl juglone **27** from the unprotected D-olivose (**23**) as shown in Scheme 2. We found that the C-glycosylation of 1,5-naphthalenediol (**30**) and **23** using TMSOTf in acetonitrile at 25 °C for 1 h proceeded smoothly to give the unprotected aryl β-C-glycoside **31** in 65% yield as a single isomer. Furthermore, it was found that the unprotected methyl D-olivoside (**22**) also coupled with **30** under similar conditions to afford **31** in comparable yield. Furthermore, it was found that the photo-oxygenation of **31** was best effected by irradiation with sunlight in *t*-BuOH/$CHCl_3$ under an oxygen atmosphere, which gave the desired unprotected *C*-glycosyl juglone **27** in 57% yield along with a 13% yield of **32**.

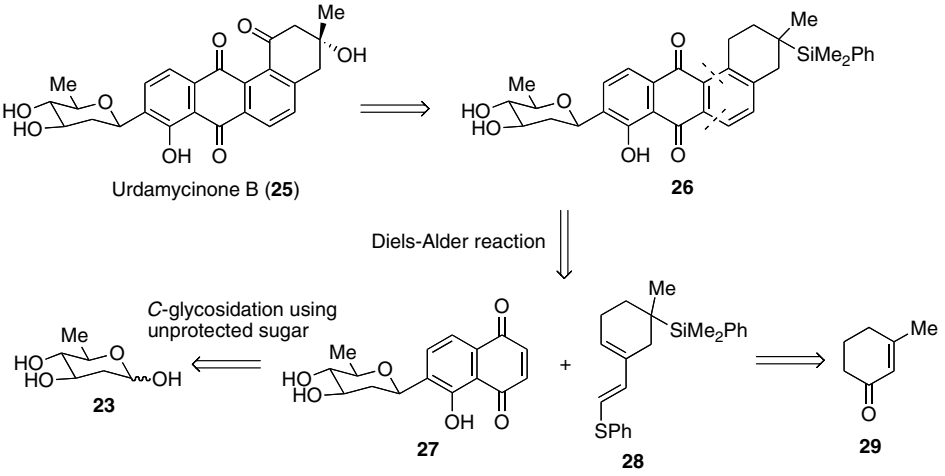
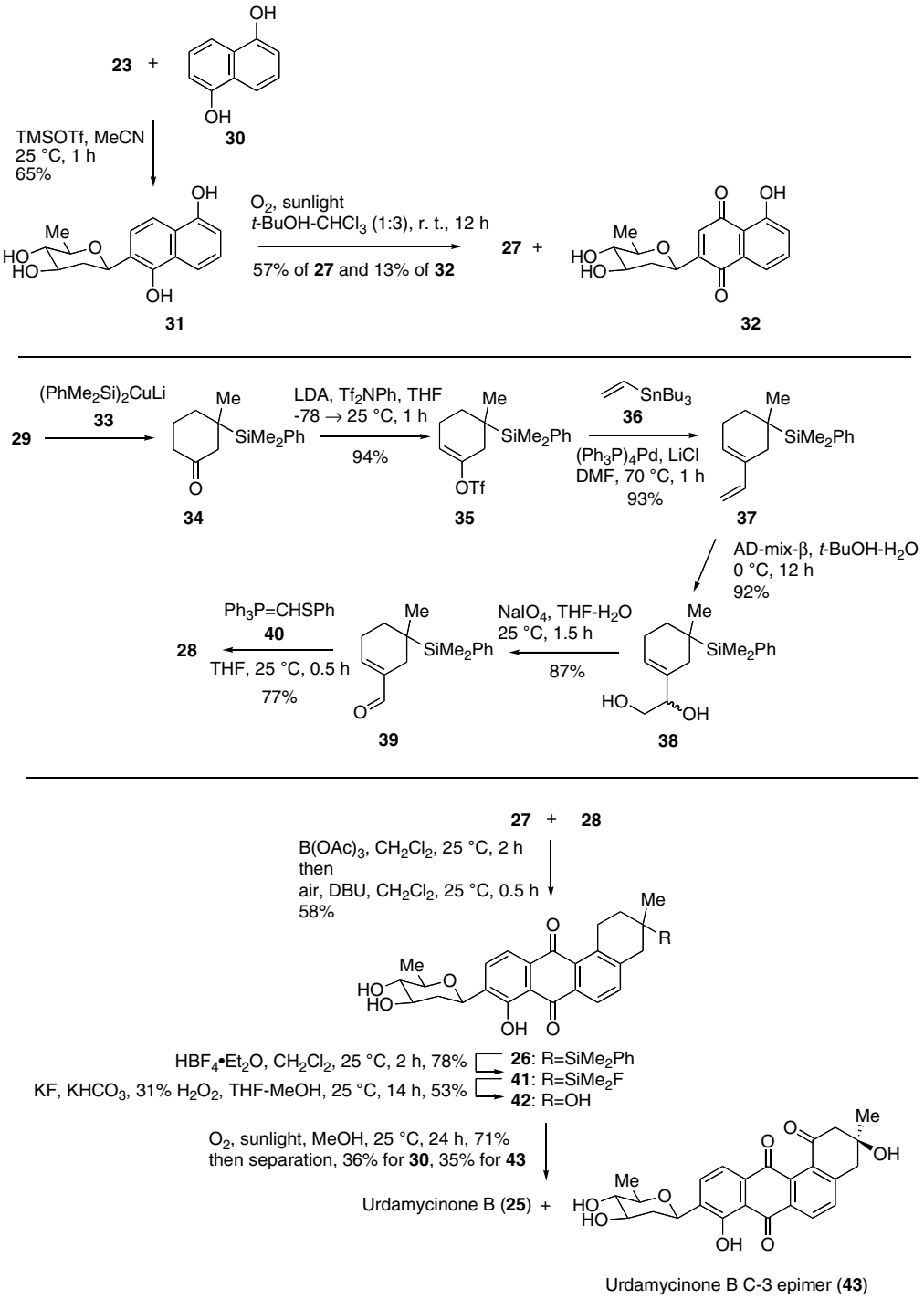


Figure 18. Retrosynthetic analysis of urdamycinone B (**25**).



Scheme 2. Synthesis of urdamycinone B (**25**) by the glycosylation of an unprotected sugar.

With the unprotected *C*-glycosyl juglone **27** as a dienophile for the Diels–Alder reaction in hand, our attention next turned to the preparation of an appropriate diene. For this purpose, cyclohexanone **34**, which was obtained using 3-methyl-2-cyclohexen-1-one (**29**) and silylcuprate **33**, was selected as the starting material. Cyclohexanone **34** has a phenyldimethylsilyl group as a masked hydroxyl group. Regioselective enolate formation of **34** with LDA and trapping of the intermediate enolate with Tf_2NPh afforded only the desired regioisomer of the vinyl triflate **35**. The cross-coupling reaction of vinyl triflate **35** and vinyltributyltin (**36**) using a catalytic amount of $(Ph_3P)_4Pd$ and LiCl in DMF yielded diene **37**. At this stage, we found that the dihydroxylation of **37** by the Sharpless reaction using the bulky AD-mix-β proceeded with good regioselectivity to afford

the desired diol **38**. Oxidative cleavage of **38** using $NaIO_4$ gave the α,β-unsaturated aldehyde **39**. Finally, Wittig reaction of **39** with triphenyl(phenylthiomethylene)phosphine (**40**) gave only the desired *E*,*E*-diene **28**.

The Diels–Alder cycloaddition between the unprotected *C*-glycosyl juglone **27** and the diene **28** using $B(OAc)_3$ followed by treatment of the resulting Diels–Alder product with 1,8-diazabicyclo[5.4.0]undec-8-ene (DBU) in air afforded the cycloadduct **26** in 58% overall yield. The high regioselectivity came from the coordination of $B(OAc)_3$ between the C5 hydroxyl group and the C4 carbonyl oxygen in **27** and the electron donating nature of the thiophenyl group in **28**. Next, **26** was treated with $HBF_4{\cdot}Et_2O$ to afford fluoride **41**, which was then treated with KF, $KHCO_3$, and 31% H_2O_2 to give tertiary alcohol **42**. Finally, regioselective oxygenation of **42** was successfully carried out by mild photo-oxygenation, in which a solution of **54** in methanol was exposed to sunlight, thus furnishing urdamycinone B (**25**) and its C3 epimer **43**.

The present novel aryl and allyl C-glycosylations using unprotected sugars as simple glycosyl donors offered promising new entries to practical and effective syntheses of the totally unprotected aryl and allyl C-glycosides. Furthermore, the total synthesis of the *C*-glycosyl angucycline, urdamycinone B, by a novel strategy including the highly stereoselective aryl C-glycosylation of an unprotected sugar, was also achieved.

2.3. Environmentally benign glycosylations using reusable heterogeneous solid acids and ionic liquids

The greening of chemical glycosylations may include the use of reusable catalysts and solvents. Before we started this project, only Florent and Monneret had reported chemical glycosylations using montmorillonite K-10 as a solid-supported acid.[18] Unfortunately, however, the method did not reach a practical level and the reusability of the solid acid was not mentioned. In this context, we developed several glycosylation methods using reusable heterogeneous solid acids, for example, glycosylations with glycals,[19] glycosyl fluorides,[20] glycosyl sulfoxides,[21] and glycosyl phosphites[22] as the donors and montmorillonite K-10, sulfated zirconia (SO_4/ZrO_2), and Nafion-H as environmentally friendly heterogeneous solid activators. Montmorillonite K-10, Nafion-H, and SO_4/ZrO_2 work well as Brønsted and/or Lewis acid(s). These heterogeneous solid acids are well known as environmentally benign catalysts in organic synthesis because they can be easily recovered from the reaction mixture by filtration and then reused. Moreover, neutralization of the reaction mixture is not required after the reaction is completed. Consequently, extraction of the product from the reaction mixture using an organic solvent is not needed in the work-up process. In addition, we recently realized the stereoselective glycosylations using acidic ionic liquids, ionic liquids containing a protic acid, as reusable and dual catalyst/solvent systems.[23]

The most representative method using a heterogeneous solid acid is the stereocontrolled glycosylations of glycosyl fluorides using SO_4/ZrO_2 as the activator. Because the proton is a hard acid and fluoride is a hard base by the HSAB rule, we expected that these solid acids would be effective activators of glycosyl fluorides. As we expected, it was found that the glycosylations of the totally benzylated α-mannopyranosyl fluoride **44** and cyclohexylmethanol using the solid acids, Montmorillonite K-10, Nafion-H, and SO_4/ZrO_2, proceeded smoothly to afford the corresponding mannopyranoside in high yields. Furthermore, SO_4/ZrO_2 was shown to be superior to the other catalysts with respect to both the chemical yield and α-stereoselectivity. We next tested glycosylations of **44** and cyclohexylmethanol using SO_4/ZrO_2 in various solvents such as acetonitrile, dichloromethane, toluene, tetrahydrofuran, and diethyl ether. These studies revealed that acetonitrile was the best solvent to selectively obtain the α-mannopyranoside, and the use of 5 wt % activator was sufficient to perform this reaction at 40 °C with quite satisfactory chemical yield and α-stereoselectivity. Moreover, interestingly, the stereoselectivity of the glycosylation was dramatically changed by the solvent, and predominately β-stereoselectivity was observed when diethylether was used as the solvent. Finally, we found that the use of 5 Å molecular sieves as an additive in the glycosylation in diethyl ether led to not only a high chemical yield, but also to a good stereoselectivity for the β-mannopyranoside. Thus, the glycosylations of **44** with several alcohols using 5 wt % SO_4/ZrO_2 in acetonitrile at 40 °C for 15 h gave exclusively the corresponding α-mannopyranosides, while glycosylations employing 100 or 200 wt % of the same activator in the presence of equal amounts of 5 Å molecular sieves in diethylether at 25 °C for 15 h afforded the corresponding β-mannopyranosides in high yields with good stereoselectivities (Fig. 19).

Furthermore, based on the results of the stereocontrolled α- and β-mannosidations, we successfully applied this glycosylation method to the stereocontrolled synthesis of 2-deoxy glycosides. Thus, the glycosylations of the benzylated 2-deoxy-α-glucopyranosyl fluoride **45** and several alcohols using 5 wt % SO_4/ZrO_2 in acetonitrile at 25 °C for 1 h predominantly gave the corresponding 2-deoxy-α-glucopyranosides, while the glycosylation employing 100 wt % of the same activator in the presence of five times the amount of 5 Å molecular sieves in diethyl ether at 0 °C for 1 h afforded the corresponding 2-deoxy-β-glucopyranosides in high yields with good stereoselectivities (Fig. 20). These optimized conditions for selectively obtaining either the 2-deoxy α- or β-glycosides (e.g., the reaction temperature and

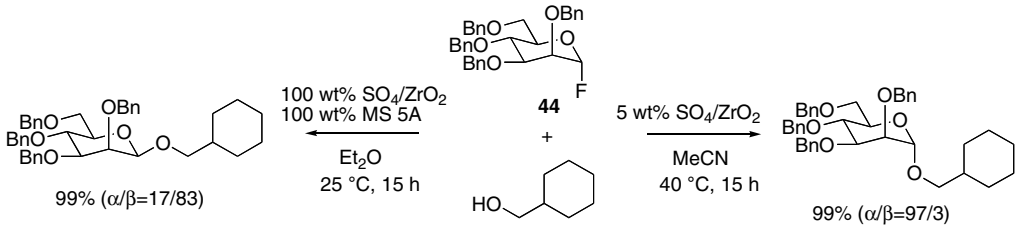


Figure 19. Glycosylations of **44** using SO_4/ZrO_2.

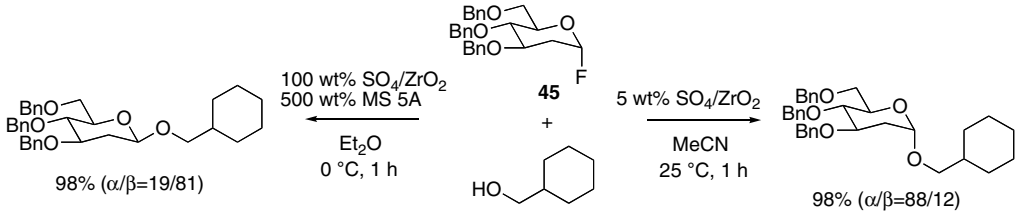


Figure 20. Glycosylations of **45** using SO_4/ZrO_2.

time, and the ratio of SO_4/ZrO_2 and 5 Å molecular sieves) differed significantly from those used for the stereocontrolled mannosylations. This is due to the higher reactivity of the 2-deoxyglycosyl donor **45** compared to that of the mannosyl donor **44**.

To investigate the mechanism of the present unusual stereocontrolled glycosylations, we examined the effect of the leaving group of the glycosyl donor and its stereochemistry. For this purpose, we prepared another glycosyl donor, the corresponding β-mannopyranosyl sulfoxide **46** possessing a β-stereochemistry at the C1 position, and then examined the glycosylation with cyclohexylmethanol under conditions similar to those employed for the glycosyl donor **44**. It was found that when the glycosylation was performed using SO_4/ZrO_2 in acetonitrile, the α-mannopyranoside was selectively obtained, while that with the same activator in the presence of 5 Å molecular sieves in diethyl ether, the reaction predominantly afforded the β-mannopyranoside (Fig. 21). These results showed exactly the same tendency as observed in the glycosylations using α-mannopyranosyl fluoride **44**. From these results, it was clear that the α- and β-stereoselectivities of the present glycosylations are independent of both the leaving group at the anomeric position of the glycosyl donor and its configuration. Therefore, these glycosylations proceed via an S_N1 type reaction and involve the oxocarbenium ion intermediate **C** as shown in Figure 22. When acetonitrile is used as a solvent, the alcohol attacks the α-face of the anomeric center of **C**, due to the steric interaction of the axial β-hydroxy group at the C2 position and the anomeric effect, to generate the α-glycosidic bond (Fig. 22, path a). It is known that, in some cases, acetonitrile is coordinated with the α-face of the anomeric center of oxocarbenium ion intermediates, and then the alcohol attacks the β-face. However, in the present case, acetonitrile is probably coordinated to Zr on SO_4/ZrO_2 rather than **C**. Therefore, the solvent effect of acetonitrile leading to β-stereoselectivity was not observed. On the other hand, when diethyl ether was used as the solvent, the solvent can coordinate with both Zr on SO_4/ZrO_2 and the α-face of intermediate **C** due to the bidentate coordinating nature of diethyl ether. Therefore, SO_4/ZrO_2 coordinates with the α-face of the intermediate **C** through the solvent like the triflate formation proven by Crich and Sun.[24] Consequently, the alcohol attacks the less hindered β-face of the oxocarbenium intermediate **C** to form the β-glycosidic bond (Fig. 22, path a). In this case, the 5 Å molecular sieves would play the important role of replacing the water

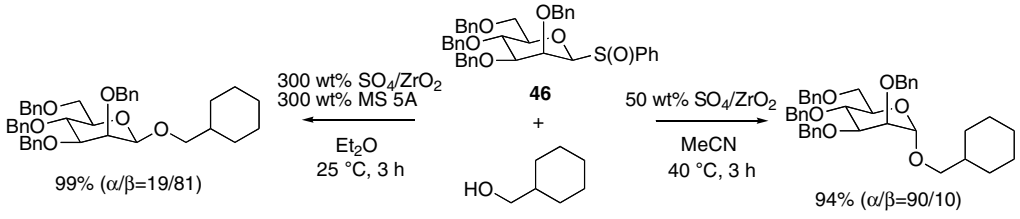


Figure 21. Glycosylations of **46** using SO_4/ZrO_2.

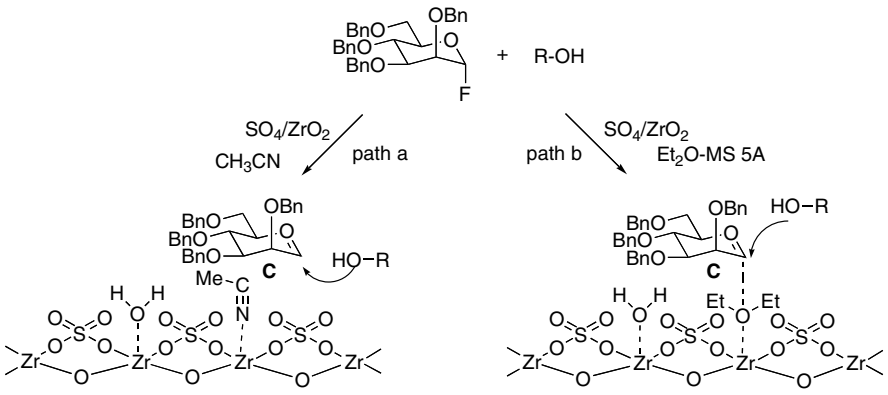
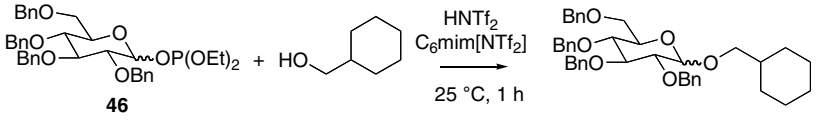


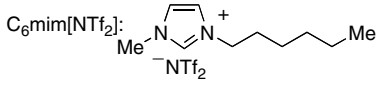
Figure 22. Presumed mechanism of the glycosylations using SO_4/ZrO_2.

originally coordinated with the Zr in SO_4/ZrO_2, with diethyl ether, which will increase the diethyl ether coordinated points on the surface of SO_4/ZrO_2.

Recently, ionic liquids have been described as some of the most promising environmentally benign reaction media. They have several benefits compared to conventional organic solvents. For example, they are nonvolatile, immiscible with some organic solvents, reusable and can be designed. In this context, we developed a glycosylation method using an ionic liquid as an environmentally benign reaction solvent. In addition to our work, Yadav,[25] Poletti[26] and Pakulski[27] also independently reported glycosylations using ionic liquids.

In these studies, we used an acidic ionic liquid, that is, an ionic liquid containing a protic acid possessing a common anion with the ionic liquid as a dual catalyst/solvent system. We found that the glycosylations of the diethyl phosphite **46** and several alcohols using $HNTf_2$ (1 mol % to $C_6mim[NTf_2]$) in $C_6mim[NTf_2]$ at 25 °C for 1 h smoothly proceeded to give the corresponding glycosides in good to high yields (Fig. 23). This result clearly indicated, for the first time, that an acidic ionic liquid was effective as a solvent/catalyst system for chemical glycosylation. Furthermore, we confirmed that the use of the ionic liquid, $C_6mim[NTf_2]$, is equal or more effective than those of the conventional organic solvents in terms of yield and stereoselectivity. In addition, we confirmed the ionic liquid recycling. After the extraction of the products with a mixture of 5:1 hexane/ethyl acetate, drying at 25 °C/1 mmHg for 12 h, the recovered $C_6mim[NTf_2]$ containing $HNTf_2$ was reused many times without any loss in efficiency. We noted that the homogeneous protic acid, $HNTf_2$, was recovered in the ionic liquid, $C_6mim[NTf_2]$, and no further addition of $HNTf_2$ was needed to repeatedly perform the glycosylation. Overall, the present glycosylation method using an acidic ionic liquid has some environmentally benign features. Distillation of the solvent with a drying agent is not needed to provide anhydrous conditions for chemical glycosylation, because a nonvolatile ionic liquid can be dried under reduced pressure. Furthermore, neutralization of the reaction mixture using aqueous media is not required after the reaction is complete; extraction of the products with an organic





reaction cycle	yield/%	α/β ratio
0	91	18/82
1	87	18/82
2	89	19/81
3	89	18/82
4	90	18/82
5	89	17/83

Figure 23. Glycosylations of **46** using an acidic ionic liquid.

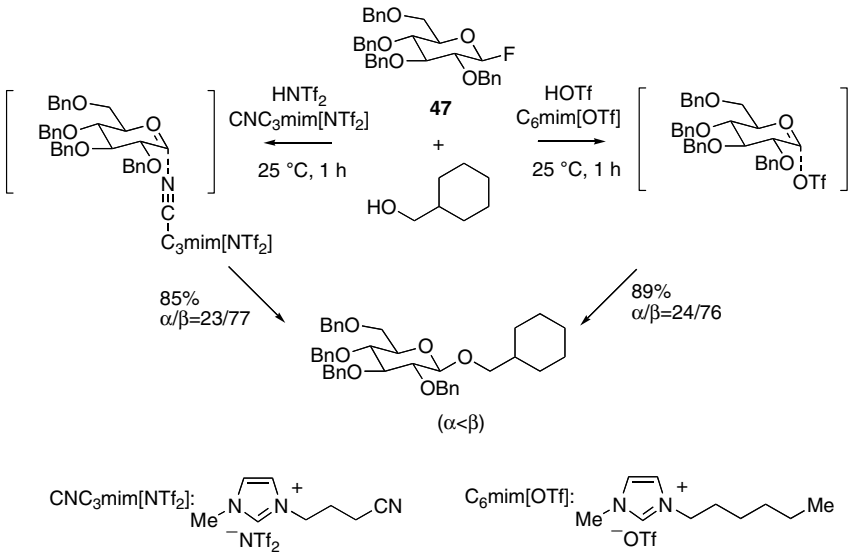


Figure 24. β-Stereoselective gycosidations of **47** induced by an acidic ionic liquid.

solvent is sufficient. In addition, both the catalyst and the solvent can be recovered and reused many times.

Another promising feature of ionic liquid is their ability to be designed. In our previous studies, we expected that the stereoselectivity of the glycosylation would be strongly influenced by the ionic liquid as a solvent. Many glycosylation reactions involve an oxocarbenium ion intermediate, which could interact with an anionic species. Therefore, if an oxocarbenium ion intermediate could interact with an anionic species contained in ionic liquid, a stereoselective glycosylation induced by the ionic liquid would be achieved.

To confirm our hypothesis, we examined the glycosylations of the glucopyranosyl fluoride **47** and alcohols using several ionic liquids containing a protic acid. We found that the stereoselectivity of the glycosylation was highly dependent on the catalyst-solvent system. Thus, C_6mim[NTf_2] containing $HNTf_2$ provided the α-stereoselectivity with good yield, while C_6mim[OTf] with HOTf afforded the highest β-stereoselectivity with high yield. It was confirmed that the stereoselectivity of the glycosylation using **47** was quite similar to that using the corresponding α-anomer, thus showing that the stereoselectivity of the glycosylation is independent of the configuration at the anomeric center of the glycosyl donor, and that this reaction proceeds via an S_N1 type pathway and involves an oxocarbenium ion intermediate. Furthermore, it was also confirmed that the stereoselectivity of the glycosylation was dependent on the ionic liquid, not the protic acid. Based on these results, we found that the α-stereoselectivity observed using C_6mim[NTf_2] containing $HNTf_2$ resulted from the anomeric effect, while the β-stereoselectivity shown using C_6mim[OTf] with HOTf was due to the α-oriented coordination of the trifluoromethanesulfonate anion from the ionic liquid with the oxocarbenium ion intermediate (Fig. 24). Furthermore, we designed and synthesized 1-(3-cyanopropyl)-3-methylimidazolium trifluoromethanesulfonimidide (CNC_3mim[NTf_2]) containing a cyano group, and examined glycosylations using a protic acid, $HNTf_2$, in the ionic liquid. We found that β-stereoselectivity was induced. These results strongly suggest that the cyano group in the side chain of the imidazolium cation coordinates with the oxocarbenium intermediate and significantly affects the stereoselectivity of the glycosylation (Fig. 24).

Thus, we demonstrated a novel and stereocontrolled strategy for the direct syntheses of both the α- and β-manno- and 2-deoxyglucopyranosides using a heterogeneous solid acid. These results, including a simple protocol and high stereoselectivity, should be instructive for further research that employs heterogeneous solid acids in glycosylation reactions. In addition, we presented novel glycosylations using an acidic ionic liquid, that is, an ionic liquid containing a protic acid, as a novel and reusable dual catalyst/solvent system. Furthermore, the effect of the ionic liquids on the stereoselectivity of the glycosylation was clearly demonstrated. These results should also be instructive for further research that uses ionic liquids for stereoselective and environmentally benign glycosylation reactions.

3. Conclusion

We have developed several novel glycosylation methods, including the stereocontrolled glycosylations using 2,6-anhydro-2,6-dideoxy-2,6-dithio sugars for obtaining 2,6-dideoxy glycosides, C-glycosylations employing unprotected sugars, environmentally benign glycosylations utilizing heterogeneous solid acids and ionic liquids, and applied them to the synthesis of natural

products. However, a general chemical method for glycosylation has still not been realized. Furthermore, general aspects for the synthesis of glycomolecules have not yet been ascertained from the point of view of yield and stereoselectivity. A major breakthrough will be needed before any given glycomolecule can be synthesized by fully controlled chemistry. In addition, environmentally benign chemistry on carbohydrates, 'green carbohydrate chemistry', must be established in this century. Because carbohydrates are indispensable biosubstances in our life activities, the study of carbohydrate chemistry has a prosperous future.

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