Anomeric Selectivity

Stereoselective Glycosylation Reactions with Chiral Auxiliaries**

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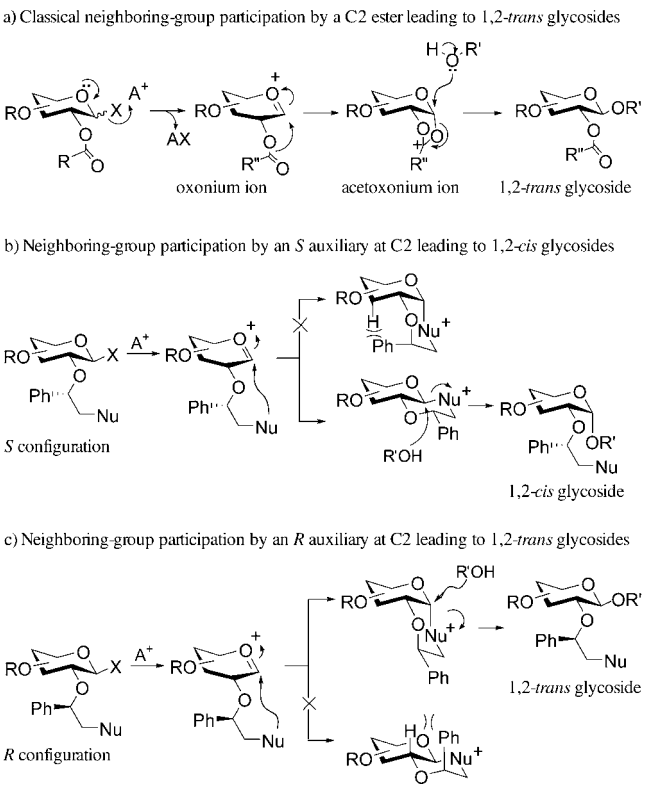
In memory of Professor Jacques van Boom

It is now well recognized that protein- and lipid-bound saccharides play essential roles in many molecular processes that have an impact on eukaryotic biology and disease.[1–3] Examples of such processes include fertilization, embryogenesis, neuronal development, hormone activities, and the proliferation of cells and their organization into specific tissues. The interactions of saccharides with proteins or lipids are also important in health science and are involved in the invasion and attachment of pathogens, inflammation, metastasis, blood-group immunology, and xenotransplantation. A major obstacle to advances in glycobiology is the lack of pure and structurally well-defined carbohydrates and glycoconjugates. These compounds are often found in low concentrations and in microheterogeneous forms, thus greatly complicating their isolation and characterization. In many cases, well-defined oligosaccharides can only be obtained by organic synthesis.[4]

Although much progress has been made in methods for oligosaccharide synthesis, the construction of complex carbohydrates remains time consuming.[5] One-pot multistep glycosylations[6,7] and polymer-supported syntheses[8–10] are two approaches being applied to streamline the preparation of complex oligosaccharides. The usefulness of these methods is, however, compromised by the fact that many glycosylations give mixtures of the two possible anomers. If these anomers are not separated after each glycosylation, complex mixtures of products are obtained that cannot be used for biological studies. Routine oligosaccharide synthesis will only be possible when robust stereoselective glycosylations become available.

The most reliable method for stereoselective glycosidic-bond formation is based on the neighboring-group participation of a 2-*O*-acyl functionality (Scheme 1a).[11] In these reactions, a promoter activates an anomeric leaving group, thereby resulting in its departure and the formation of an oxonium ion. Subsequent neighboring-group participation of a 2-*O*-acyl protecting group will give a more stable acetoxonium ion. An alcohol can attack the anomeric center of an acetoxonium ion from only one face, to provide a 1,2-*trans* glycoside. Thus, β-linked products will be obtained in the case of glucosyl-type donors, whereas mannosides will give α-glycosides. The introduction of 1,2-*cis* glycosidic linkages, such as α-glucosides and α-galactosides, requires glycosyl donors with a non-assisting functionality at the C2 position. Invariably, these glycosylations lead to mixtures of anomers.[12] In general, reasonable anomeric selectivities will only be obtained by extensive optimization of reaction conditions such as solvent, temperature, promoter, leaving group, and protecting-group pattern. Thus, the stereoselective formation of 1,2-*cis* glycosides is the principal challenge in complex oligosaccharide synthesis.



Scheme 1. Conventional and new approaches for stereoselective glycosylation. A = activating group, Nu = nucleophile, X = leaving group.

We describe herein a novel strategy for stereoselective glycosylations in which a chiral auxiliary at the 2-position of a glycosyl donor is used (Scheme 1b,c). The auxiliary is a substituted ethyl moiety that contains a nucleophilic group. Upon formation of an oxonium ion, participation of the nucleophilic moiety of the auxiliary should lead to the formation of either a *trans*- or a *cis*-decalin system. It was expected that the use of an auxiliary with *S* stereochemistry would lead only to the formation of the *trans* decalin, since the alternate *cis*-fused system would place the phenyl substituent in an axial position and induce unfavorable steric interactions (Scheme 1b). Subsequent displacement of the anomeric moiety of the *trans*-decalin intermediate would then lead to the formation of a 1,2-*cis* glycoside. Alternatively, the use of an auxiliary with *R* stereochemisty would lead to the formation of a 1,2-*trans* glycoside, because in this case the

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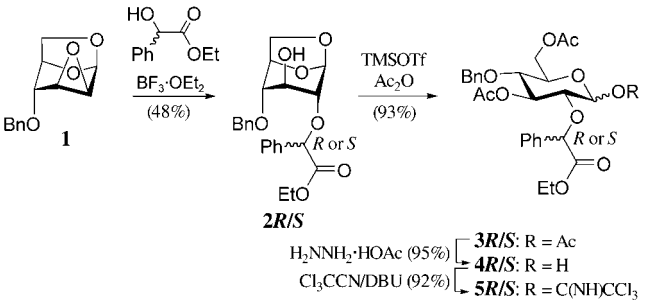
[**] This work was supported by the National Cancer Institute of the National Institutes of Health (Grant: RO1 CA88986).

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

 DOI: 10.1002/anie.200461745

trans-decalin system would experience unfavorable steric interactions, and therefore glycosylation would only take place from the *cis*-decalin intermediate (Scheme 1c).

Ethyl mandelate was explored as a first-generation chiral auxiliary (Scheme 2). This derivative was deemed attractive because both enantiomers are



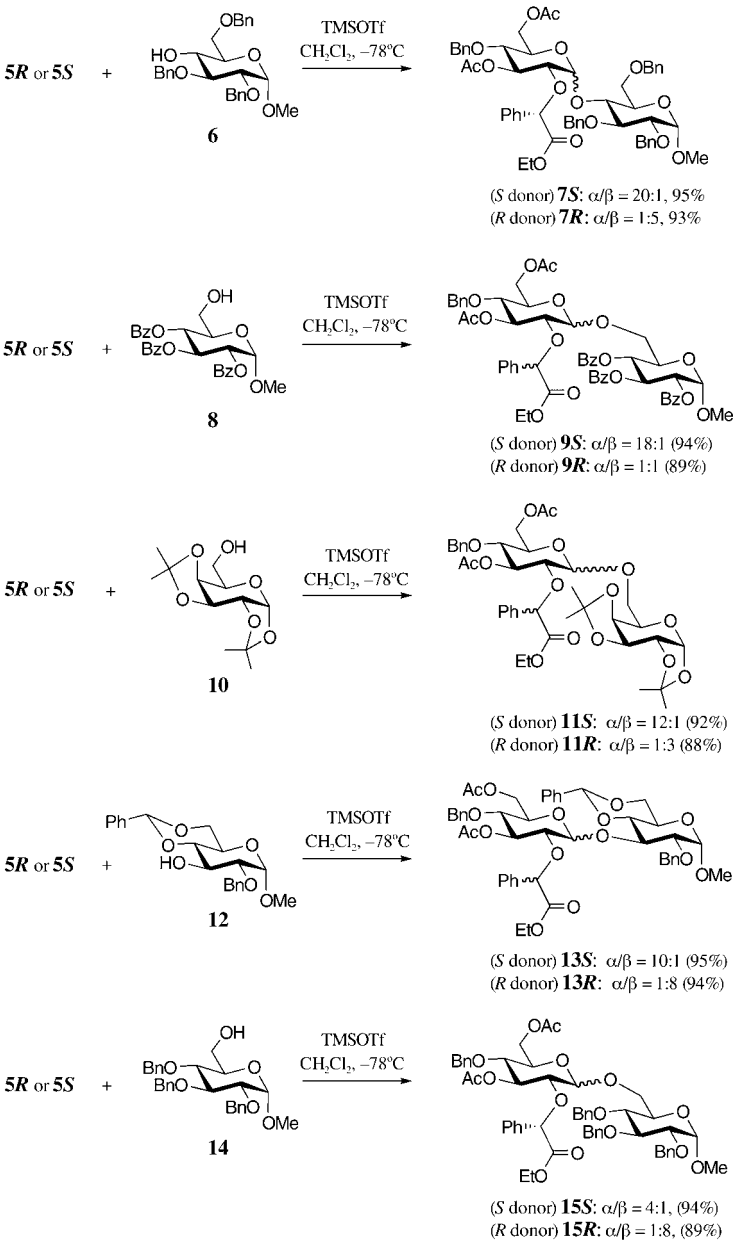
Scheme 2. Preparation of glycosyl donors **5*R*** and **5*S***. Bn = benzyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TMSOTf = trimethylsilyl trifluoromethanesulfonate.

readily available, esters are well established as appropriate participating functionalities in glycosylations, and the benzylic nature of the auxiliary should make its removal possible under reductive conditions.

Glycosyl donors **5*R*** and **5*S***, containing an (*R*)- or (*S*)-ethoxycarbonylbenzyl moiety, could be prepared by an efficient procedure from the readily available epoxide **1**.[13] Thus, the reaction of **1** with ethyl (*R*)-mandelate in the presence of $BF_3{\cdot}Et_2O$ led to a *trans*-diaxial opening of the epoxide to give **2*R*** in a yield of 48%. Next, acetolysis of the 1,6-anhydro bridge of **2*R*** with acetic anhydride and TMSOTf gave compound **3*R*** in an almost quantitative yield. The anomeric acetyl group of **3*R*** was selectively removed with hydrazine acetate to give hemiacetal **4*R***, which was converted into trichloroacetimidate **5*R*** by using standard conditions.[14] Glycosyl donor **5S** was prepared by a similar protocol with ethyl (*S*)-mandelate as the starting material.

With glycosyl donors **5*R*** and **5*S*** in hand, attention was focused on the glycosylation of a range of different glycosyl acceptors. Thus, coupling of **5*S*** with **6** by using a catalytic amount of TMSOTf in dichloromethane at −78 °C gave disaccharide **7*S***, mainly as the α-glycoside, in an almost quantitative yield (Scheme 3). At this low temperature, the reaction was completed within 15 minutes, which indicates that the glycosyl donor **5*S*** is highly reactive. Dilution of the reaction mixture led to a small increase in anomeric selectivity, whereas higher reaction temperatures led to decreases in selectivity. As expected, coupling of **1*R*** with **6** under similar reaction conditions gave **7*R*** mainly as the β anomer.

The fact that an inversion of configuration at the asymmetric center of the auxiliary led to a reversal of the stereochemical outcome of the glycosylation provides strong



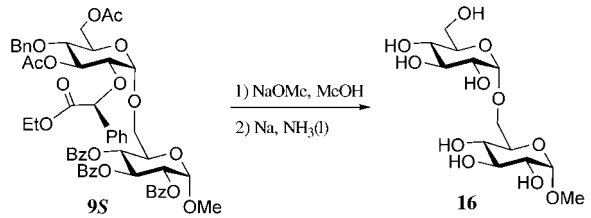
Scheme 3. Stereoselective glycosylation with glycosyl donors **5*R*** and **5*S***. Bz = benzoyl.

support for the proposed mode of participation as outlined in Scheme 1.

To demonstrate the generality of the approach, a range of glycosyl acceptors were glycosylated with **5*R*** and **5*S***. As can be seen in Scheme 3, glycosylations of **5*S*** with glycosyl acceptors that have either a primary or a secondary hydroxy group gave disaccharides with high α-anomeric selectivity. In each case, the use of glycosyl donor **5*R*** led to a reversal of anomeric selectivity and mainly β-linked disaccharides were isolated, albeit with somewhat lower selectivity than that observed with **5*S***.

The results of the glycosylations indicate that the use of ethyl mandelate as an auxiliary at the 2-position provides a reliable approach for the synthesis of α-linked glycosides. To

be useful for target synthesis, it is important that the auxiliary can be removed under mild conditions. The auxiliary was designed as a substituted benzyl ether, and thus should be removable by a catalytic hydrogenation over Pd or by Birch reduction. Indeed, saponification of the benzoyl and acetyl esters of **9*S*** by treatment with NaOMe in methanol followed by removal of the benzyl ethers and the auxiliary by using sodium in liquid ammonia led to the clean formation of the deprotected compound **16** (Scheme 4).



Scheme 4. Deprotection of disaccharide **9*S***.

Although the glycosylations with **5*S*** led to disaccharides with high α-anomeric selectivity, the ultimate goal is the development of an auxiliary that gives only one of the two possible anomers in each glycosylation. The small amount of unwanted anomer that is formed probably results from glycosylation of the oxonium ion. In this respect, participation by an ethoxycarbonylbenzyl moiety is probably slower than that of a conventional acyl functionality because the formation of the six-membered ring is slower than that of the five-membered ring. Thus, it is expected that a second-generation auxiliary could be obtained by improving the nucleophilicity of the auxiliary or reducing the flexibility of the rotatable bonds.

In summary, it has been shown for the first time that the anomeric selectivity of a glycosylation can be controlled by a chiral auxiliary. This new method for anomeric control is particularly suited for the introduction of α-glucosides. However, it is expected that other glycosides can easily be installed by a similar approach. For example, the use of the readily available 1,6:2,3-dianhydro-β-D-talopyranoside[15] as the starting material, instead of epoxide **1**, would lead to a galactosyl donor. Furthermore, preliminary studies have shown that the methodology is also compatible with other protecting-group patterns. It is to be expected that a systematic optimization of the structure of the auxiliary will lead to a stereospecific glycosylation protocol. Only such a method will make it possible for the potential of polymer-supported[8–10] and one-pot multistep oligosaccharide[6,7] syntheses to be realized, so that these methods can be used in a routine manner for a large number of oligosaccharide targets.

Received: August 20, 2004
Published online: January 3, 2005

Keywords: anomeric control · carbohydrates · chiral auxiliaries · glycosides · glycosylation

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