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Digest paper

Recent topics in β-stereoselective mannosylation

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ABSTRACT

The methods reported mainly since 2014 are discussed, since the latest review on 1,2-*cis*-glycosylation was published at that time. The updated mechanisms for S_N2-S_N1 borderlines in β-mannosylations are also discussed.

Contents

Introduction

Glycosidic linkages can be classified into four types based on the geometry of the oxygen substituents at C-1 and C-2 positions (Fig. 1). For 1,2-*trans* glycosidic linkages, regardless of whether they are α- or β-glycosides, neighboring group participation is the first and reliable choice for their construction, where the participating protective groups—typically acyl group at the O-2 position—are placed on the glycosyl donors (Fig. 2),[1] although care has to be taken for the disarming properties of the participating groups, orthoester formations, or anomeric equilibration of the products. On the other hand, efficient preparation of 1,2-*cis*-glycosidic linkages is quite puzzling, especially with regard to stereoselectivity. In general, glycosidic linkages are constructed by nucleophilic substitution reaction between glycosyl donors equipped with a leaving group and nucleophilic glycosyl acceptors. The developing cation at C-1 position is stabilized by electron donation from a lone pair of ring oxygen (O-5 in the case of pyranoses), facilitating the generation of oxocarbenium ion, the so-called glycosyl cation. Therefore, the reactions are liable to proceed *via* S_N1, which poses a challenge in stereoselectivity. The glycosyl cations have an intrinsic α-direction (Fig. 3), which is explained in the Woerpel model; that is, the postulated glycosyl cations mostly having $^4H_3$ half-chair conformation or as a more reactive form would be oriented at the lower $^4C_1$ transition state toward

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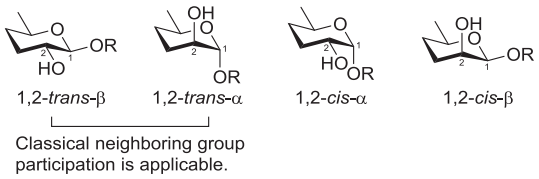

Fig. 1. Four categories of the glycosides in terms of C-1 and C-2 geometries. Extraneous oxygen functions are omitted in the drawings (the same hereinafter). This Digest focuses on 1,2-*cis*-β-glycosides.

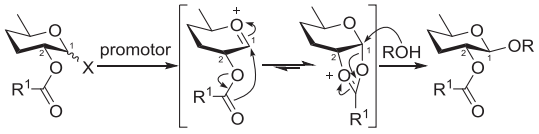

Fig. 2. Classical neighboring group participation. The participants, an acyl group in typical cases, located at O-2 shield on the same face, inducing a nucleophilic attack on the opposite face.

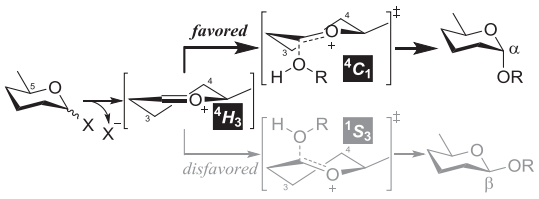

Fig. 3. Generally accepted mechanisms of α-directing S_N1-type glycosylations. When the reaction proceeds via a $^4H_3$ glycosyl cation, a $^4C_1$ transition state is preferred to $^1S_3$, resulting in α-glycoside formation. Nomenclature of the conformations are defined and summarized by Cremer and Pople.[4] X = leaving group.

the α-glycoside rather than the higher $^1S_3$ toward the β-glycosides.[2] Overall, the 1,2-*cis*-β-glycosidic linkages, typically called β-mannosidic linkages, poses an attention-drawing issue. This Digest covers the recent advances in the construction of β-mannosidic linkages, developed especially since 2014, as well as the recent discussions on mechanistic insight. Before 2014, we would like to refer to the reviews.[1a,3]

(Pseudo-) intramolecular aglycon delivery (IAD)

If nucleophiles could be delivered only at the upper face of the glycosyl cation, β-glycosides would form stereoselectively. The feasibility of such a concept has been proven by introducing a tether at the β-face-oriented O-2 position to support the nucleophiles before the activation of glycosyl donors, which is known as intramolecular aglycon delivery (IAD) (Fig. 4). Earlier and exquisite examples of this are isopropylidene tether by Hindsgaul et al.,[5] silylene by Stork et al.,[6] *p*-methoxybenzylidene by Ito and Ogawa,[7] and later, *m*-xylylene by Schmidt et al.[8] The IAD concept including these strategies are summarized in a review article,[9] including a very recent one.[10] Herein, we chose two of the very recent and novel systems: one utilizes *in situ*-generated boronate tethers

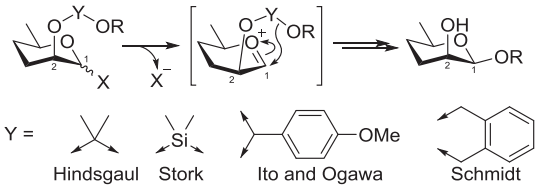

Fig. 4. Conceptual outline of intramolecular aglycon delivery. X = leaving group.

(section '*Hydrogen-bonding aglycon delivery*') and the other utilizes hydrogen bonding as pseudo-tethers (2.2).

Boron-mediated IAD with 1,2-anhydrosugars

Takahashi and Toshima et al. have recently reported a novel conceptual approach toward IAD, which starts with 1,2-anhydrosugar as a glycosyl donor (Fig. 5).[11] Their concept was first proved with 1,2-anhydro glucose.[12] As shown in Eqs. 1 and 2, the reaction of a 1α,2α-anhydro glycosyl donor with a diol-derived boronate acceptor proceeded to give a 1,2-*cis*-α-linked disaccharide smoothly with exclusive regio- and stereo-selectivities (Eq. 1).[12b] The reaction presumably proceeded *via* activation of the anhydrous sugar by Lewis acidity of the boronate to generate a boronate-tethered intermediate, followed by the rearrangement of the acceptor from the tethering boronate to glycosyl cation. The regioselectivity was rationalized by the sterics of the transition state. Further, univalent alcohol-derived borinate could be used as both an activator and acceptor for the same class of donors instead of the cyclic boronates (Eq. 2).[12a] Diarylborinic acid works as a catalyst. The borinate forms with an acceptor alcohol and brings the acceptor to the O-2 position simultaneously with the activation of the anhydro sugar. The tethered intermediate rearranges to the glycoside with perfect stereoselectivity along with the generation of a borinylated acceptor by an alcohol exchange reaction. They have extended these concepts to the preparation of 1,2-*cis*-β-glycosides (Eqs. 3 and 4). The borinates derived from a glycosyl acceptor presumably reacted with 1,2-anhydro mannose to generate the boron-tethered intermediate, which transformed into the glycoside with 1,2-*cis*-geometry *via* IAD (Eq. 3).[11b] Similarly, with 1,2-*cis*-α cases, they demonstrated regio- and stereo-selective glycosylation using the same anhydro sugar and cyclic boronate generated from the acceptor diols and a phenyl boronic acid (Eq. 4).[11a] Intriguingly, they proved that they could obviate the necessity for preformation of the cyclic boronic esters in this reaction. Mixing an anhydro sugar and a diol prior to the addition of a boronic acid provided a comparable result. The electrostatics of boronic acids seem to affect the stereoselectivity, and 4-nitrophenylboronic acid works efficiently in these cases. The regioselectivity was again rationalized by the sterics in the transition states (Fig. 6). It is noteworthy that the hindered hydroxy group is allowed to get glycosylated in the reaction. These reactions have been applied to the synthesis of naturally occurring, tetrasaccharide repeat of O-specific side-chains of LPS derived from *E. coli* O75, as shown in Fig. 7. Very recently, they have reviewed the methodologies in this line.[13]

Hydrogen-bonding aglycon delivery

Demchenko et al. have brilliantly proven that the tether for aglycon delivery is not necessarily a covalent bond. They first demonstrated that picolinyl and picoloyl groups placed on remote positions—O-3, O-4, or O-6 of the glucosyl donors—induced *syn* attack in respect to them *via* hydrogen bonding, resulting in highly stereoselective 1,2-*cis*-α-glycosylation (Fig. 8, Eq. 1),[14] whereas the same protective groups at O-2 position induced *anti* attack.[15] They carried out reactions in conditions where hydrogen bondings are disrupted as a survey to determine whether the effects of hydrogen bonding are evident. Addition of DMSO to the reaction media diminished the stereoselectivity, presumably by disarranging the key hydrogen bondings. Replacing the acceptor alcohol to the corresponding silyl ether, or excessive addition of electrophilic reagents such as DMTST or TfOH also resulted in reduced stereoselectivity. They suggested that these results indicate the intermediacy of the hydrogen bonding between picoline and the