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Long-Range Stereodirecting Participation across a Glycosidic Linkage in Glycosylation Reactions

Weizhun Yang, Jicheng Zhang, Chia-Wei Yang, Sherif Ramadan, Richard Staples, and Xuefei Huang*

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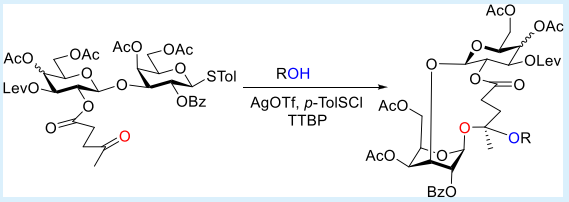
ABSTRACT: The formation of an unprecedented 12-membered macrocyclic ketal through the long-range participation of a levulinoyl group across a glycosidic linkage was observed in glycosylation reactions. This finding indicated that stereodirecting participation is not limited to groups within the glycan ring being activated, thus broadening the scope of remote group participation in glycosylation.

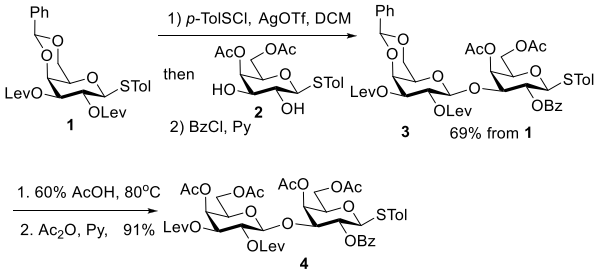


Stereochemical control is essential for a successful glycosylation reaction.[1,2] Neighboring group participation has been one of the most common strategies to direct the stereochemistry of the newly formed glycosidic bond.[3] A typical strategy involves the installation of a participatory group on the C-2 atom adjacent to the anomeric center of the glycosyl donor. Upon donor activation, the neighboring group assists in stabilizing the developing positive charge at the anomeric center, and stereoelectronically directs the formation of 1,2-*trans* glycosidic linkage. Other modes of participation have also been reported or proposed, which include intramolecular participation of a C-2 group on the donor ring to favor 1,2-*cis* glycosyl bond formation[4,5] and remote group participation from the C-3, C-4, or C-6 position respectively,[6] as supported by various spectroscopic[7−9] and trapping studies.[10−18] All current examples of remote group participation involve groups from the same glycan ring of the donor that is being activated during glycosylation, with the typical ring sizes invoked varying between five- to eight-membered rings. Herein, we report the observation that long-range intramolecular participation can occur across a glycosidic linkage by a participatory group from a remote glycan ring to form a 12-membered macrocyclic ketal, thus extending the scope of remote group participation.

Our work originated from the efforts toward the synthesis of heparan sulfate/chondroitin sulfate proteoglycan glycopeptides,[19−22] which contain a tetrasaccharide linker of glucuronic acid (GlcA)-β-1,3-galactose (Gal)-β-1,3-Gal-β-1,4-xylose (Xyl). To form this linkage region, we first synthesized the Gal-Gal disaccharide donor **3** bearing two levuniloyl (Lev) groups by the glycosylation of the bifunctional acceptor **2**[23] with thiogalactosyl donor **1**[19] followed by benzoylation (Scheme 1). Protective group manipulations led to the disaccharide donor **4**.

With disaccharide **3** in hand, the 2 + 1 glycosylation between **3** and the xylosyl serine **5**[19] was performed by premixing **3** and **5** followed by the addition of the promoter *p*-TolSCl/AgOTf[24]

Scheme 1. Preparation of Disaccharide Donors 3 and 4



in the presence of 2,4,6-tri-*tert*-butylpyrimidine (TTBP)[25] (Scheme 2). To our surprise, instead of the desired β-linked trisaccharide **7**, a major product **6** isomeric to **7** as determined by mass spectrometry (MS) was obtained in 71% yield. Structural analysis of **6** by NMR showed that, in its ^{13}C NMR spectrum, only one ketone carbonyl was present (δ = 205.9). Unlike in a typical Lev with its methyl moiety appearing around 2.1 ppm in ^{1}H NMR, the methyl moiety of what was Lev on the C-2′ of the nonreducing end Gal upfield shifted to 1.63 ppm. ^{1}H NMR of the reducing end Gal unit in **6** showed its H-2 appeared at 5.01 ppm as a singlet indicating a deviation of this glycan ring from the ideal $^{4}C_{1}$ conformation. The HMBC-NMR spectrum of **6** showed a strong correlation between H-1 and C-a. The evidence collectively suggested that the ketone carbonyl of the C-2′-*O*-Lev group participated in the glycosylation reaction, forming a macrocyclic ring. Although the formation of acetal and ketal glycosides has

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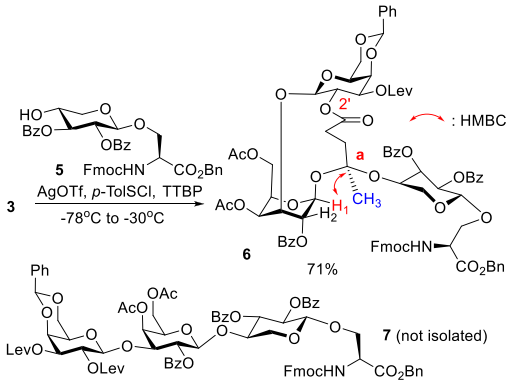
Scheme 2. Formation of Macrocyclic Ketal 6



been reported,[26−31] this 12-membered cyclic ketal ring is unprecedented. To support the structure of **6**, its crystal structure (CCDC: 1971865) was determined, which confirmed its macrocyclic ketal feature. The reducing end Gal unit adopted a $^1C_4$ conformation, and the absolute configuration of the newly formed ketal center was *S* (Figure 1).

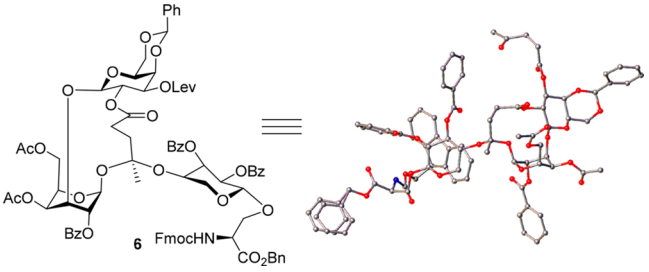


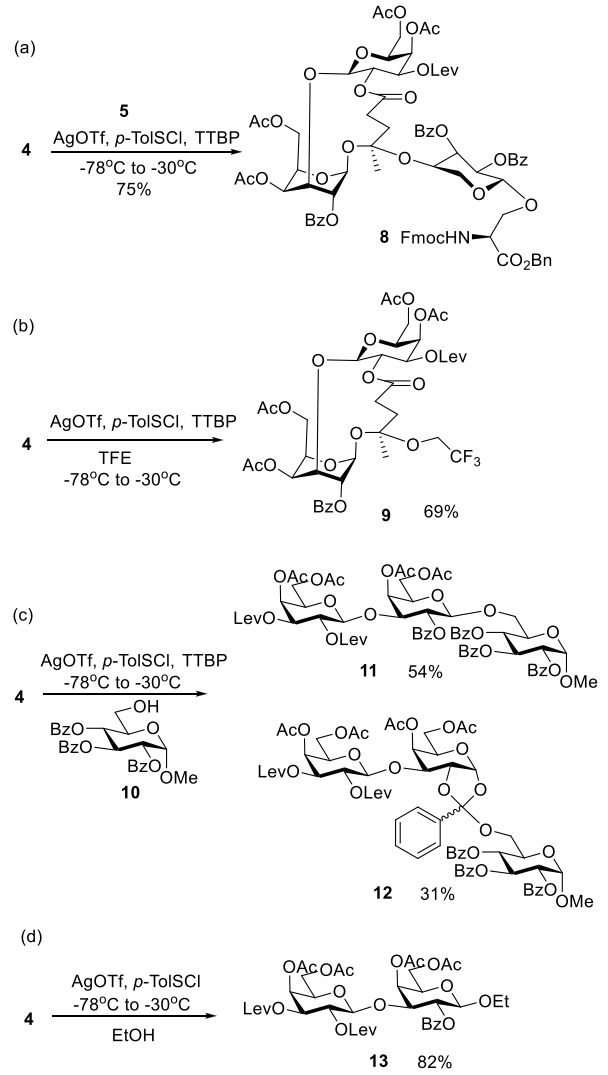
Figure 1. ORTEP plots of compound **6** with 30% probability ellipsoids.

This remote participation from the distal Lev group across the glycosidic linkage was operative in the di-Gal donor **4** as well (Scheme 3a). Following the same protocol as the formation of **6**, glycosylation of **4** with the xylosyl serine **5** produced the macrocyclic ketal **8** in 75% yield with the stereochemistry of the ketal center assigned analogously to **6**. Besides acceptor **5**, trifluoroethanol (TFE), glucoside **10**, and ethanol were investigated as the acceptor. Macrocyclic ketal **9** was generated with TFE acceptor in 69% yield (Scheme 3b). Interestingly, acceptor **10** did not give the macrocyclic ketal product. Rather, the *β*-linked trisaccharide **11** and orthoester **12** were isolated from the reaction of the glucosyl acceptor **10** in 54% and 31% yields, respectively (Scheme 3c). The ethanol acceptor behaved similarly to **10**, generating the *β*-linked ethyl glycoside **13** as the major product (Scheme 3d).

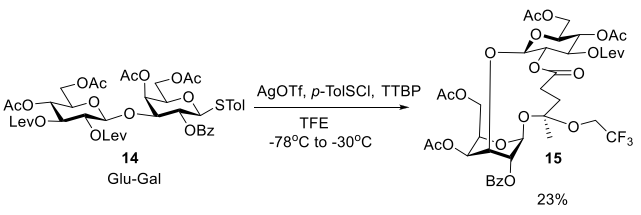
Besides the di-Gal donors, another disaccharide donor, glucose (Glu)-Gal **14**, was tested. Glycosylation between **14** and TFE provided the macrocyclic ketal **15** (Scheme 4). This result revealed that the remote participation is not restricted to Gal-Gal donors.

Several possible intermediates for the reaction of donor **4** with various acceptors are depicted in Figure 2. Activation of **4** should generate the glycosyl oxocarbenium ion **A** first, which can evolve into dioxalenium ion **B** through the classic neighboring group participation of the Bz group on C-2, oxocarbenium ion **C** by the participation of ketone carbonyl of the Lev moiety on C-2′, and the covalent glycosyl triflate **D**.[32]

Scheme 3. Glycosylation Reactions between Donor 4 and (a) 5, (b) TFE, (c) 10, and (d) Ethanol, Respectively



Scheme 4. Formation of Macrocyclic Ketal 15 from Glu-Gal Disaccharide Donor 14



Nucleophilic attack of **B** by an acceptor would lead to either the 1,2-*trans* glycoside or an orthoester. Alternatively, nucleophilic attack of **C** and **D** by an acceptor would generate 12-membered macrocyclic ketal and 1,2-*trans* glycoside, respectively.

One possible explanation for the differential product profile with various acceptors is that the intermediate **B** or **D** may be generated faster than the intermediate **C** upon donor activation. Acceptors such as ethanol or primary acceptor **10** should have higher nucleophilicities than TFE and **5** due to the reduced steric hindrance (primary vs secondary hydroxyl

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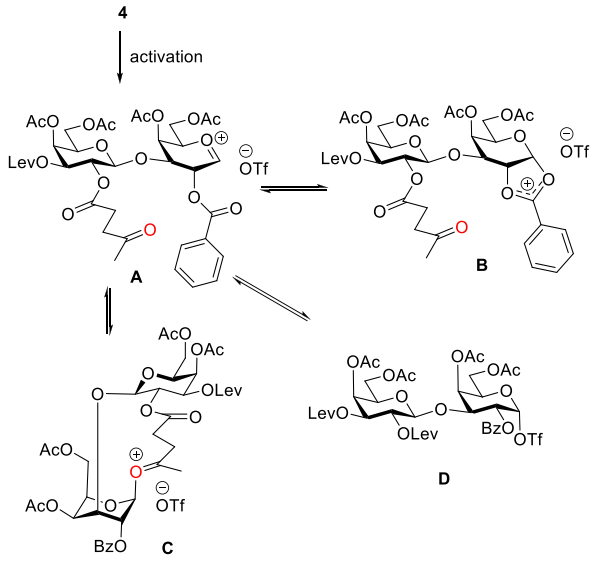


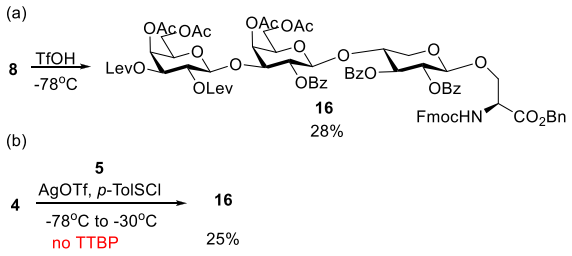
Figure 2. Possible structures of reactive intermediates upon activation of **4**.

group) or the absence of strongly electron-withdrawing groups (ethanol vs TFE), thus preferentially reacting with the intermediate **B** or **D** formed first. To test this possibility, donor **4** was preactivated with *p*-TolSCl and AgOTf in the absence of the acceptor, which would presumably enable the formation of all intermediates **B**, **C**, and **D**. Upon completion of donor preactivation, the acceptor ethanol or TFE was added. Compared with the premix glycosylation protocol, no significant changes in the amounts or the types of products formed were observed with either TFE or ethanol in preactivation. Therefore, the preferences over specific product most likely cannot be explained by different rates of intermediate formation.

It is known that the intermediates formed upon donor activation can transform to other reactive structures along the reaction pathway influencing product distribution. A classic example is the *in situ* anomerization of glycosyl bromide, where the isomerization of α-glycosyl bromide to the more reactive β-glycosyl bromide during the reaction is invoked to rationalize the preferential formation of the α-glycoside product.[33] Glycosyl triflate and dioxalenium ion have also been shown to be able to interconvert.[32] Thus, a probable rationale for the differential outcome of the reactions from donor **4** (Scheme 3) is the operation of a Curtin−Hammett scenario,[34] where the product distribution is determined by the relative potential energy barriers for the acceptor to approach various potential reactive intermediates. An acceptor can significantly impact glycosylation in terms of both chemical yield and stereoselectivity,[35] which can be due to a combination of steric, conformational, and electronic factors.

We next investigated whether the macrocyclic ketal can be transformed into a glycoside product. Compound **8** was treated with triflic acid (Scheme 5a). The 1,2-*trans* linked trisaccharide **16** was obtained in 28% yield along with the monosaccharide and disaccharide resulting from hydrolysis of the ketal. When the glycosylation reaction between **4** and **5** was carried out without TTBP, trisaccharide **16** was obtained in addition to the hydrolyzed donor and unreacted acceptor (Scheme 5b). These results suggest that the macrocyclic ketal

Scheme 5. Macrocyclic Ketal Can Be Transformed to 1,2-*trans* Glycoside



can be converted to the glycoside product under an acidic condition, albeit in moderate yields.

In conclusion, we report a new remote participation phenomenon during glycosylation, where the ketone of the Lev group participated across a glycosidic linkage to generate an unprecedented 12-membered macrocyclic ketal. This remote participation was observed with either Gal-Gal or Glu-Gal disaccharide donors. These interesting phenomena broaden the range of stereodirecting participation observed in glycosylation reactions and can serve as a caution to aid in future synthetic design and troubleshooting.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03394.

Detailed experimental procedures, preparation and characterization of the products (PDF)

Accession Codes

CCDC 1971865 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Xuefei Huang − *Department of Chemistry, Institute for Quantitative Health Science and Engineering, and Department of Biomedical Engineering, Michigan State University, East Lansing, Michigan 48824, United States;* orcid.org/0000-0002-6468-5526; Email: huangxu2@msu.edu

Authors

Weizhun Yang − *Department of Chemistry, Michigan State University, East Lansing, Michigan 48824, United States*

Jicheng Zhang − *Department of Chemistry, Michigan State University, East Lansing, Michigan 48824, United States*

Chia-Wei Yang − *Department of Chemistry, Michigan State University, East Lansing, Michigan 48824, United States*

Sherif Ramadan − *Department of Chemistry, Michigan State University, East Lansing, Michigan 48824, United States; Chemistry Department, Faculty of Science, Benha University, Benha, Qaliobiya 13518, Egypt;* orcid.org/0000-0002-8639-4105

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Richard Staples − *Department of Chemistry, Michigan State University, East Lansing, Michigan 48824, United States;* orcid.org/0000-0003-2760-769X

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c03394

Notes

The authors declare no competing financial interest.

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