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Regio- and Stereoselective Organocatalyzed Relay Glycosylations To Synthesize 2-Amino-2-deoxy-1,3-dithioglycosides

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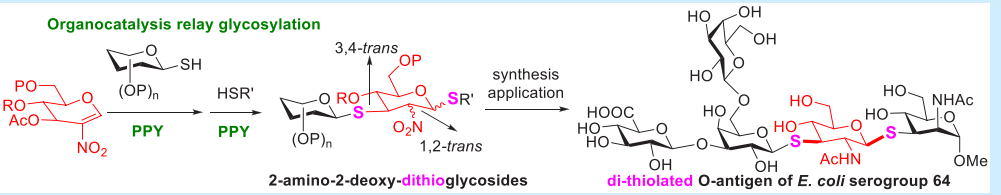

ABSTRACT: Herein, we describe a novel methodology for the regio- and stereoselective convergent synthesis of 2-amino-2-deoxy-dithioglycosides via one-pot relay glycosylation of 3-*O*-acetyl-2-nitroglucal donors. This unique organo-catalysis relay glycosylation features excellent site- and stereoselectivity, good to excellent yields, mild reaction conditions, and broad substrate scope. 2-Amino-2-deoxy-glucosides/mannosides bearing 1,3-dithio-linkages were efficiently obtained from 3-*O*-acetyl-2-nitroglucal donors in both stepwise and one-pot glycosylation protocols. The dithiolated O-antigen of *E. coli* serogroup 64 was successfully synthesized using this newly developed method.

Replacing the anomeric oxygen atom in sugars for a sulfur atom leads to thioglycosides, which have demonstrated enhanced stability under chemical and enzymatic hydrolysis conditions, while maintaining similar conformational behavior as their natural *O*-glycoside counterparts.[1] Naturally occurring and synthetic *S*-glycosides, such as S-KRN7000, lincomycin, clindamycin and iboxamycin, and ridaura, have shown attractive biological activities, ranging from antibacterial to antitumoral action (Figure 1).[2] Synthetic studies of *S*-glycosides have become a topical point in carbohydrate chemistry, leading to the establishment of various protocols, including base-mediated substitution reactions using glycosyl halides or glycosyl thiols,[3] acid-mediated thioglycosylation using glycosyl donors, such as glycosyl imidates,[4] reductive lithiation−thioglycosylation using 2-deoxyglycosyl phenylsulfides,[5] photocatalytic thioglycosylation using allyl glycosyl sulfones or glycal donors,[6] and metal catalyzed cross couplings.[7]

2-Nitroglycals have been recognized as important synthons in carbohydrate chemistry and used to synthesize various biologically relevant 2-amino-2-deoxy-glycosides.[8] Herein, we describe a novel convergent method for the regio- and stereoselective synthesis of 2-amino-2-deoxy-dithioglycosides from 3-*O*-acetyl-2-nitroglucal electrophiles via a mild organo-catalysis relay glycosylation using both stepwise and one-pot methods. Based on this protocol, a series of 2-amino-dithioglycoside containing oligosaccharides were obtained. Mechanistic studies have shed light on the reaction pathways followed, to account for the striking stereoselectivity observed.

Our exploratory studies started in a stepwise manner and began with C3-thio-glycosylation using 3-*O*-acetyl-2-nitro-glucal as a donor and per-*O*-acetyl-*β*-D-glucosyl thiol **2a** as an acceptor. Through serial optimization, we found that using 3-*O*-acetyl-2-nitroglucal **1a** bearing a bulky tri-isopropylsilyl (TIPS) protecting group on the C4-OH as a donor, the desired glycosylation product **3a** was obtained in 95% yield with excellent stereoselectivity (3,4-*trans*:3,4-*cis* = 16:1) catalyzed by 0.1 equiv organobase 4-pyrrolidinopyridine (PPY) (see Table SI-1). With the optimal conditions in hand, the substrate scope was then tested (Figure 2). We were pleased to find that per-*O*-acetyl-*β*-D-galactosyl thiol **2b**, 2-acetamido-3,4,6-tri-*O*-acetyl-*β*-D-glucosyl thiol **2c**, and disaccharide glycosyl thiol **2d** were coupled smoothly with electrophile **1a** to provide the products **3b**, **3c**, and **3d** in excellent yields (86%−95%) with excellent stereoselectivity (3,4-*trans*:3,4-*cis* > 20:1). Under identical conditions, the disaccharide 3-*O*-acetyl-2-nitroglucal **1b** reacted uneventfully with monosaccharide glycosyl thiol acceptors **2a**, **2b**, and **2c** to generate trisaccharide products **3e−g** (>82% yields). The tetrasaccharide **3h** was obtained in almost quantitative yield when the disaccharide donor **1b** and disaccharide thiol

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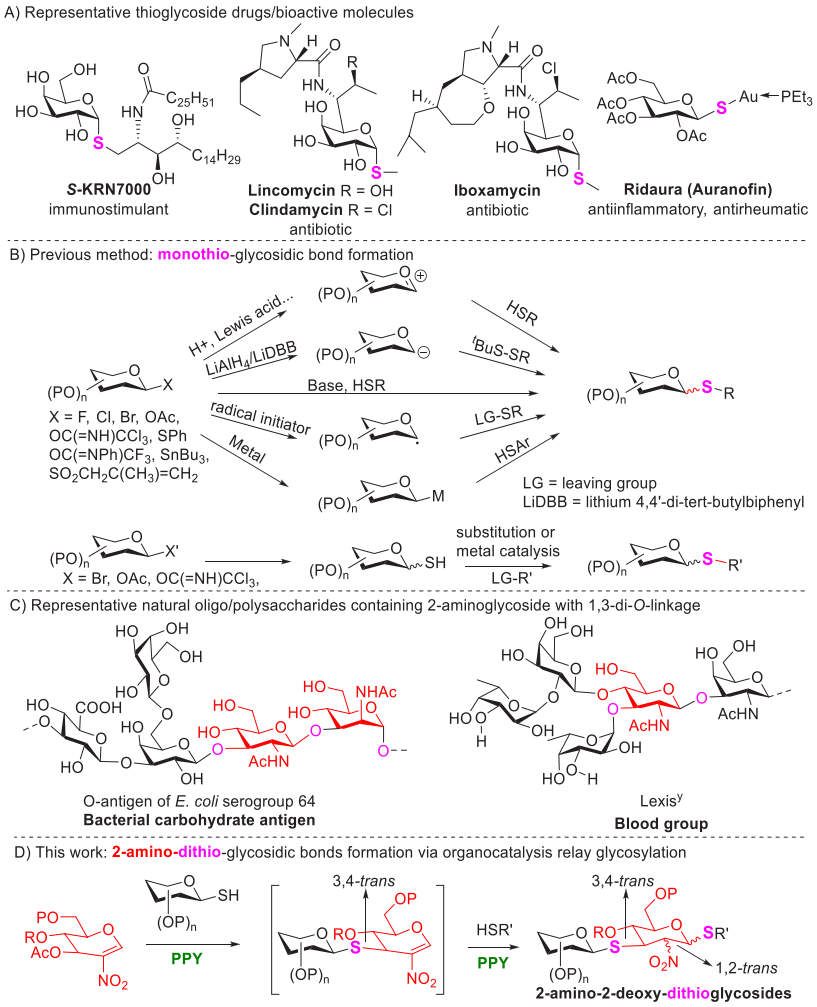

Figure 1. (A) Representative thioglycoside drugs/bioactive molecules; (B) previous methods for monothioglycosidic bond formation; (C) representative natural oligo/polysaccharides containing 2-amino-2-deoxy-glycosides with 1,3-di-*O*-linkages; (D) this work.

acceptor **2d** were condensed (Figure 1). The site-selectivity can be explained with the HSAB principle, since C-1 is hard and C-3 is soft, while the thiols are soft nucleophiles.[8d,9] It is worth noting that the conformation of the 2-nitroglucal residue was inverted when bulky groups on the C3 and C4 positions were present,[10] while the structures of the products were clarified by NMR data and further transformations (see Supporting Information).

With 3-*thio*-glycosyl-2-nitroglucals **3** in hand, we set out to optimize the conditions for the second *thio*-glycosylation with the coupling between disaccharide 2-nitroglucal **3a** and butanethiol **4a** as a model reaction (see Table SI-2). Under the optimized conditions, the reaction generated a mixture of the glucose- and mannose-configured products **5a** and **5a′** in 61% yield (**5a**:**5a′** = 2.1:1, Table 1, entry 1). Also, cyclopentanethiol **4b** provided a mixture of glucose- and manno-type products, **5b** and **5b′** (64% yield, **5b**:**5b′** = 3.4:1, entry 2). When glucose thiols **4c** and **4d** were used as acceptors, products **5c**/**5c′** and **5d**/**5d′** were obtained (**5c**:**5c′** = 1.6:1, 56%, entry 3; **5d**:**5d′** = 2.7:1, 41%, entry 4), while the bulky secondary glucose-C4-thiol **4e** furnished the glucose-configured product **5e** predominantly (**5e**/**5e′** = 11:1, 37%, entry 5). When secondary thiol **4e** was coupled with **3b**, the glucose configured product **5f** was predominantly formed (entry 6). Surprisingly, single mannose-type products **5g′** and **5h′** were obtained by using thiolated amino acids **4f** and **4g** as acceptors to couple with donor **3a**, respectively (74% and 76% yields, entries 7−8). Even when the more elaborate thiolated dipeptide **4h** was chosen as an acceptor to react with donor **3a**, the reaction also furnished the manno-type product **5i′** exclusively (56%, entry 9). Disaccharide 2-nitroglucal donor **3b** and trisaccharide 2-nitroglucal donors **3e**−**f** were coupled with thiolated amino acid acceptors including **4f**−**h** under the standard condition, to generate manno-type products **5j′**−**5n′** exclusively in moderate to good yields (above 54% yields, entries 10−14).

Considering the same PPY catalyst was used for C3- and C1-thio-glycosylations with 3-*O*-acetyl-2-nitroglycals, we wondered whether the stepwise procedure could be developed into a streamlined one-pot protocol without isolation of the C3-thio-glycoside intermediate. To this end, the coupling reaction between 2-nitroglucal **1a**, glucose thiol **2a**, and glucose thiols **4e** was attempted via a consecutive one-pot relay glycosylation. Gratifyingly, after the glycosylation of **1a** and **2a**, catalyzed by PPY (0.1 equiv) in dichloromethane, the second glycosylation step with **3a** could be affected, after a solvent change to toluene and using an extra portion of PPY (0.1 equiv) and adding di-CF_3PhCOOH, TBAI, and **4e** to furnish **5e** in 36% yield with good stereoselectivity. Following an identical procedure, 2-nitroglucal **1a**, glucose thiol **2a**, and

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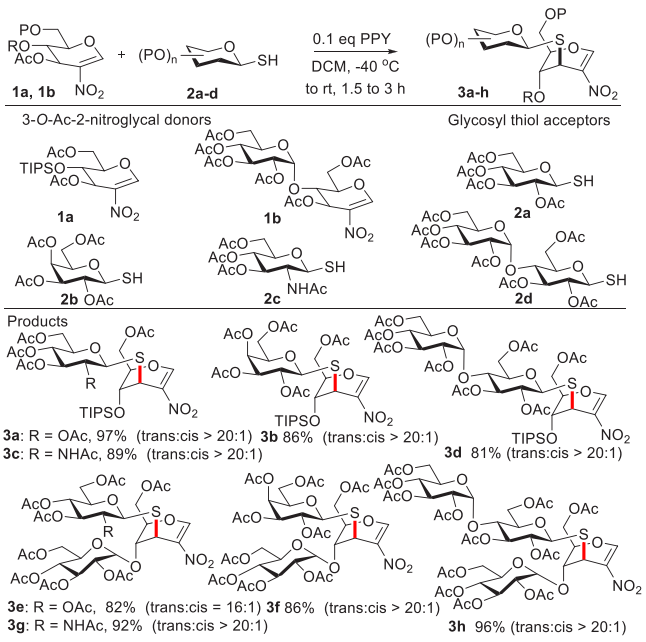


Figure 2. First step C3-thio-Glycosylation of 3-*O*-acetyl-2-nitroglycal via organo-catalysis C3-Ferrier rearrangement. The ratio is 3,4-*trans*:3,4-*cis* (2-nitroglycal residue), and the ratio was determined by ^{1}H NMR analysis.

amino acid thiol **4f** were smoothly transformed into desired mannose-type product **5g′** in 71% yield with excellent regio- and stereoselectivity, while this reaction worked well on gram scale. It was worth noting that when the more elaborate thiolated dipeptide **4h** and disaccharide 2-nitroglucal donor **1b** were used in relay glycosylation, the desired products **5i′−5n′** were obtained uneventfully (Figure 3).

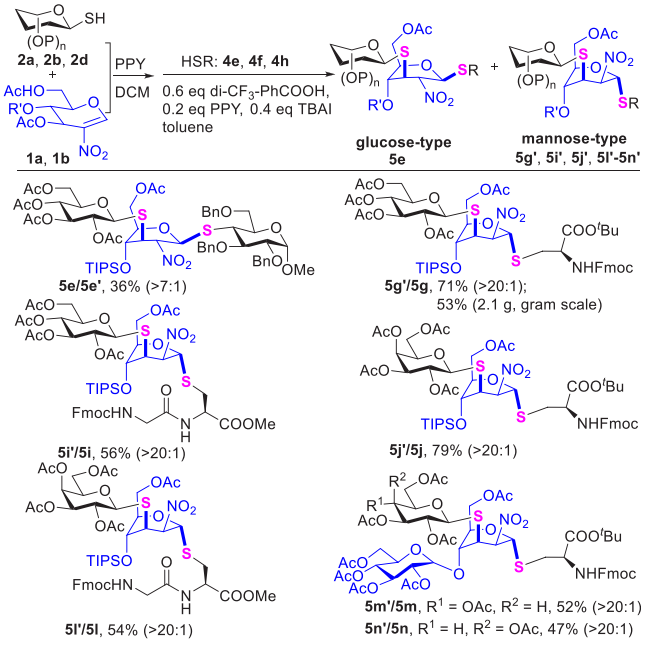
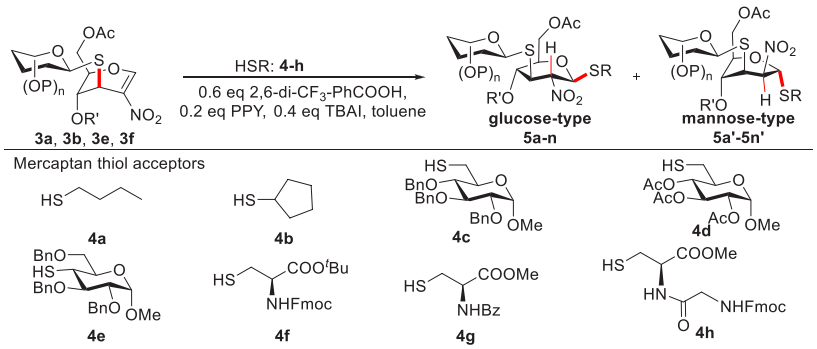


Figure 3. Synthesis of 1,3-di-*thio*-2-nitro-2-deoxy-glycosides via consecutive relay glycosylation. [a] The overall yield for stepwise synthesis.

Table 1. Substrate Scope for Stereoselective C1-Thioglycosylation with 3-*thio*-Glycosyl-2-deoxy-2-nitroglucals



Entry	Donor	Acceptor	Product	Yield	Ratio[a]
1	**3a**	**4a**	**5a/5a′**	61%	2.1:1
2	**3a**	**4b**	**5b/5b′**	64%	3.4:1
3	**3a**	**4c**	**5c/5c′**	56%	1.6:1
4	**3a**	**4d**	**5d/5d′**	41%	2.7:1
5	**3a**	**4e**	**5e/5e′**	37%	11:1
6	**3b**	**4e**	**5f/5f′**	40%	8:1
7	**3a**	**4f**	**5g/5g′**	74%	<1:20
8	**3a**	**4g**	**5h/5h′**	76%	<1:20
9	**3a**	**4h**	**5i/5i′**	42%	<1:20
10	**3b**	**4f**	**5j/5j′**	76%	<1:20
11	**3b**	**4g**	**5k/5k′**	72%	<1:20
12	**3b**	**4h**	**5l/5l′**	54%	<1:20
13	**3e**	**4f**	**5m/5m′**	63%	<1:20
14	**3f**	**4f**	**5n/5n′**	92%	<1:20

[a] $5_{glu}/5'_{mann}$.

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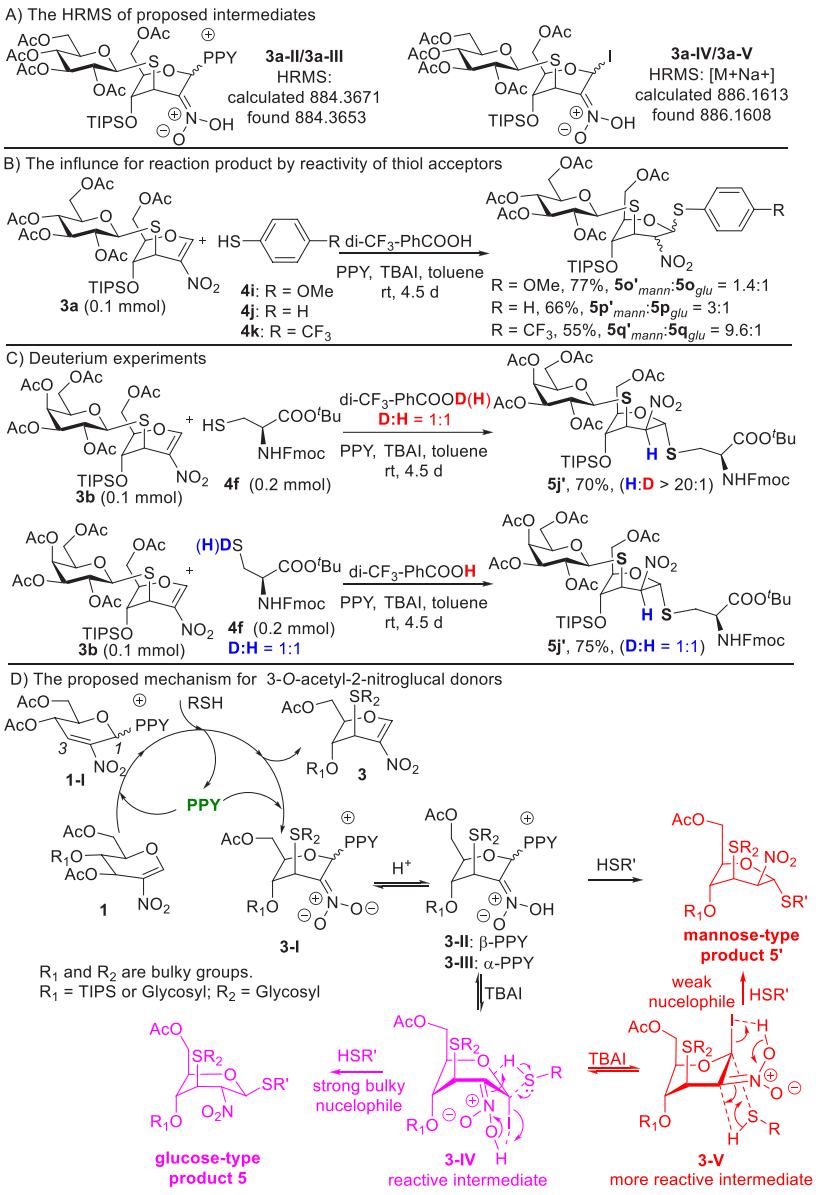

Figure 4. Mechanistic study and the proposed mechanism.

To better understand the stereochemical course of the reaction, we focused our attention on understanding the mechanism of the new relay glycosylations. In the first step of the reaction, 3-*O*-acetyl-2-nitroglycal donors **1** react with glycosyl thiol **2a**−**d** to generate 3-*thio*-glycosyl-2-nitroglycals **3** with excellent site-selectivity and stereoselectivity. The site-selectivity can be explained by the HSAB principle,[8d,9] and the stereoselectivity can be explained by the steric hindrance effect of the groups on C4 of 3-*O*-acetyl-2-nitroglucal donors. Several experiments were carried out to probe the reaction mechanism of the second glycosylation step (see Figure 4A−C). To identify potential reactive intermediates, the reaction was followed using HRMS, which showed that products were formed having a mass that correspond to the PPY-intermediates (**3a-II**, and/or **3a-III**) as well those having a mass corresponding to the glycosyl iodides (**3a-IV** and/or **3a-V**, Figure 4A). Next, we used a set of thiols of gradually changing nucleophilicity to probe how the stereoselectivity in the addition to glucal **3a** depends on the nucleophilicity of the thiol (Figure 4B) to reveal that the more acidic, less nucleophilic thiols provided more of the manno-configured products. Interestingly, deuterium labeling experiments showed that the proton at the C2 position in the products (the position α to the NO_2 group) originated from the thiol acceptor, indicating that the addition of the thiol at C1 and protonation of the C2 position occurs on the same face of the molecule and thus likely happens in coordinated processes (Figure 4C). This can explain the formation of the 1,2-*trans*-glycosides in all cases as well. A putative mechanism for the reactions of 3-*O*-acetyl-2-nitroglucal **1** is shown in Figure 4D. Attack of PPY to 2-nitroglucal **1** generates intermediate **1-I**, which then reacts with the soft thiol nucleophile at the soft and sterically most accessible C-3 to stereo- and regioselectively generate 3-thio-glycosyl-2-nitroglucal **3**. Then, the regenerated PPY attacks the C1 position of the newly formed 3-thio-glycosyl-2-nitroglucal donor **3** to form intermediate **3-I** which can be protonated by 2,6-di-CF_3-PhCOOH to generate intermediate **3-II** or **3-III**. Without the acid or when using a too weak acid, intermediate **3-I** undergoes an elimination to regenerate the glycosyl thiol and intermediate **1-I** which then

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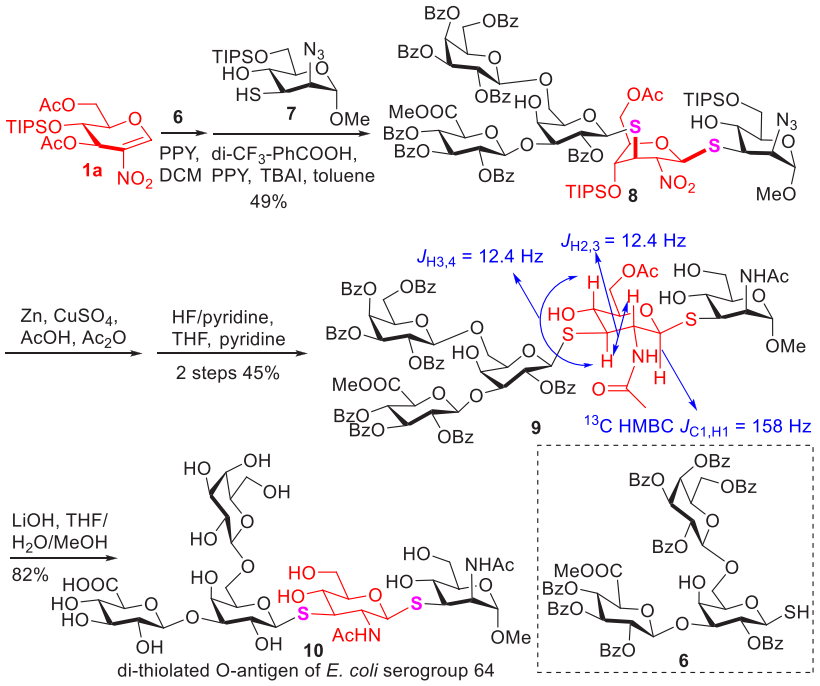
Scheme 1. Application of the Relay Glycosylation Method: Synthesis of the Di-thiolated O-Antigen of *E. coli* Serogroup 64



reacts with the thiol acceptor to yield C3-thiolated byproduct. Intermediate **3-II** is attacked by the second thiol nucleophile from the α side to stereoselectively afford mannose-type product **5′**. The TBAI additive can speed up this glycosylation, probably by forming the iodide-intermediate **3-IV**/**3-V**, which is a softer nucleophile that is readily attacked by the thiol nucleophile. The intermediate **3-V** is more reactive because it experiences a strong 1,3-diaxial interaction between the iodine and sulfur atoms. In addition, the substitution of the axial iodide in **3-V** is favored because this places the σ^*_{C-I} orbital parallel to the $\pi^*_{C2=N}$ orbital.[11] The more nucleophilic sulfur nucleophiles can displace the more stable α-iodides, while the less nucleophilic thiols need a stronger electrophile, *i.e.* the -iodide, to engage in an effective reaction.[12]

Finally, to illustrate the utility of the established method, the applications of the synthetic protocol were evaluated with the synthesis of the dithiolated O-antigen of *E. coli* serogroup 64. *E. coli* belongs to *Enterobacteriaceae*, one of "critical priority" antibiotic resistance pathogens listed by the World Health Organization (WHO).[13] Owing to their antibiotic resistance, the developing of anti-*E. coli* vaccines is receiving significant attention. The O-antigen is an important component of the lipopolysaccharide, and an attractive antigen for vaccine development.[14] The O-antigen of *E. coli* serotype 64 is built up from a →3)-D-GlcA-(β1 → 3)-[D-Gal*p*-(β1 → 6)-D-Gal*p*-(β1 → 3)]-D-Glc*p*NAc-(β1 → 3)-D-Man*p*NAc-(α1→ pentasaccharide repeating unit.[15] We designed a synthetic route to yield a dithiolated O-antigen of *E. coli* serogroup 64, using our newly developed one-pot relay glycosylation method as shown in Scheme 1. The synthesis required three key building blocks, including trisaccharide glycosyl thiol **6**, 3,6-di-*O*-acetyl-2-nitroglucal **1a**, and mannosyl acceptor **7** (synthesis of **6** and **7**, see the Supporting Information for details). To our delight, trisaccharide thiol **6** was reacted smoothly with 3-*O*-acetyl-2-nitroglucal **1a** to generate the tetrasaccharide intermediate which was further coupled with the second thiol acceptor **7** to furnish the desired pentasaccharide **8** in 49% yield with excellent stereoselectivity. The stereochemistry of the newly formed chiral centers in **8** was substantiated by transformation of this compound into **9** by conversion of the nitro group into the corresponding acetamide and removal of the bulky TIPS groups. Pentasaccharide **9** adopts a regular $^4C_1$ conformation, and the value of the one-bond coupling constant of C1−H1 (^{13}C HMBC $J_{C1,H1}$= 158 Hz) and the three bond H−H coupling constant of the triplet corresponding to H3 ($J_{2,3} = J_{3,4}$ = 12.4 Hz) proved the formation of the β-glucose configured product. Finally, all benzoyl groups and the methyl ester in **9** were removed under base conditions to provide the target compound **10**, the dithiolated *O*-antigen of *E. coli* serogroup 64.

In summary, we have developed a highly efficient method for the regio- and stereoselective synthesis of 2-amino-2-deoxy-dithioglycosides via the 4-pyrrolidinopyridine-mediated relay glycosylation of 2-nitroglycals. 3-Thio-glycosyl-2-amino-2-deoxy-1-thio- manno/glucosides were successfully obtained from 3-*O*-acetyl-2-nitroglucals. The installation of the C-3 and C-1 thio-linkages could be afforded in a one-pot manner. The organocatalyzed relay glycosylation protocol proceeds under very mild reaction conditions and proceeds with excellent regio- and stereoselectivity in good to excellent yields. It has a broad substrate scope as well. Initial mechanistic experiments revealed that the 1,2-*trans*-products were formed by the simultaneous addition of the C-1 thiol and the C-2 proton to the same face of the electrophile. The method was successfully applied in the synthesis of a dithiolated O-antigen of *E. coli* serogroup 64, which can be used as a stabilized antigen.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

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Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c00859.

Detailed experimental procedures, characterization, and copies of ^{1}H, ^{13}C NMR and 2D NMR spectra of new compounds. (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Pachamuthu, K.; Schmidt, R. R. Synthetic Routes to Thiooligosaccharides and Thioglycopeptides. *Chem. Rev.* **2006**, *106*, 160−187. (b) Melo, A. M.; Zhang, L.; Dockry, E. F.; Petrasca, A.; Ghnewa, Y. G.; Breen, E. P.; Morrissey, M. E.; O'Reilly, C.; Bruen, R.; O'Meara, A.; Lysaght, J.; Zhu, X.; Doherty, D. G. Novel thioglycoside analogs of alpha-galactosylceramide stimulate cytotoxicity and preferential Th1 cytokine production by human invariant natural killer T cells. *Glycobiology* **2018**, *28*, 512−521.

(2) (a) Witczak, Z. J.; Culhane, J. M. Thiosugars: new perspectives regarding availability and potential biochemical and medicinal applications. *Appl. Microbiol. Biotechnol.* **2005**, *69*, 237−244. (b) Feng, M.; Tang, B.; Liang, S. H.; Jiang, X. Sulfur Containing Scaffolds in Drugs Synthesis and Application. *Curr. Top. Med. Chem.* **2016**, *16*, 1200−1216. (c) Mitcheltree, M. J.; Pisipati, A.; Syroegin, E. A.; Silvestre, K. J.; Klepacki, D.; Mason, J. D.; Terwilliger, D. W.; Testolin, G.; Pote, A. R.; Wu, K. J. Y.; Ladley, R. P.; Chatman, K.; Mankin, A. S.; Polikanov, Y. S.; Myers, A. G. A synthetic antibiotic class overcoming bacterial multidrug resistance. *Nature* **2021**, *599*, 507−512.

(3) (a) Gerz, B. M.; Matter, H.; Kessler, H. S-Glycosylated Cyclic Peptide. *Angew. Chem., Int. Ed.* **1993**, *32*, 269−271. (b) Calce, E.; Digilio, G.; Menchise, V.; Saviano, M.; De Luca, S. Chemoselective Glycosylation of Peptides through S-Alkylation Reaction. *Chem.—Eur. J.* **2018**, *24*, 6231−6238.

(4) (a) Xiao, K.; Hu, Y.; Wan, Y.; Li, X.; Nie, Q.; Yan, H.; Wang, L.; Liao, J.; Liu, D.; Tu, Y.; Sun, J.; Codee, J. D. C.; Zhang, Q. Hydrogen bond activated glycosylation under mild conditions. *Chem. Sci.* **2022**, *13*, 1600−1607. (b) Escopy, S.; Singh, Y.; Demchenko, A. V. Triflic acid-mediated synthesis of thioglycosides. *Org. Biomol. Chem.* **2019**, *17*, 8379−8383. (c) Zhu, S.; Samala, G.; Sletten, E. T.; Stockdill, J. L.; Nguyen, H. M. Facile triflic acid-catalyzed alpha-1,2-*cis*-thio glycosylations: scope and application to the synthesis of S-linked oligosaccharides, glycolipids, sublancin glycopeptides, and TN/TF antigens. *Chem. Sci.* **2019**, *10*, 10475−10480.

(5) Baryal, K. N.; Zhu, J. Stereoselective Synthesis of S-Linked Hexasaccharide of Landomycin-A. *Org. Lett.* **2015**, *17*, 4530−4533.

(6) (a) Wan, L. Q.; Zhang, X.; Zou, Y.; Shi, R.; Cao, J. G.; Xu, S. Y.; Deng, L. F.; Zhou, L.; Gong, Y.; Shu, X.; Lee, G. Y.; Ren, H.; Dai, L.; Qi, S.; Houk, K. N.; Niu, D. Nonenzymatic Stereoselective S-Glycosylation of Polypeptides and Proteins. *J. Am. Chem. Soc.* **2021**, *143*, 11919−11926. (b) Ji, P.; Zhang, Y.; Gao, F.; Bi, F.; Wang, W. Direct, stereoselective thioglycosylation enabled by an organo-photoredox radical strategy. *Chem. Sci.* **2020**, *11*, 13079−13084.

(7) (a) Zhu, F.; Miller, E.; Zhang, S. Q.; Yi, D.; O'Neill, S.; Hong, X.; Walczak, M. A. Stereoretentive C(sp3)-S Cross-Coupling. *J. Am. Chem. Soc.* **2018**, *140*, 18140−18150. (b) Xiong, T.; Xie, R.; Huang, C.; Lan, X.; Huang, N.; Yao, H. Recent advances in the synthesis of thiosugars using glycal donors. *J. Carbohydr. Chem.* **2021**, *40*, 401−439.

(8) (a) Schmidt, R. R.; Vankar, Y. D. 2-Nitroglycals as Powerful Glycosyl Donors Application in the Synthesis of Biologically Important Molecules. *Acc. Chem. Res.* **2008**, *41*, 1059−1073. (b) Delaunay, T.; Poisson, T.; Jubault, P.; Pannecoucke, X. 2-Nitroglycals: Versatile Building Blocks for the Synthesis of 2-Aminoglycosides. *Eur. J. Org. Chem.* **2014**, *2014*, 7525−7546. (c) Liu, J. L.; Zhang, Y. T.; Liu, H. F.; Zhou, L.; Chen, J. *N*-Heterocyclic Carbene Catalyzed Stereoselective Glycosylation of 2-Nitrogalactals. *Org. Lett.* **2017**, *19*, 5272−5275. (d) Dharuman, S.; Gupta, P.; Kancharla, P. K.; Vankar, Y. D. Synthesis of 2-nitroglycals from glycals using the tetrabutylammonium nitrate-trifluoroacetic anhydride-triethylamine reagent system and base-catalyzed Ferrier rearrangement of acetylated 2-nitroglycals. *J. Org. Chem.* **2013**, *78*, 8442−50. (e) Hobson, C.; Chan, A. N.; Wright, G. D. The Antibiotic Resistome: A Guide for the Discovery of Natural Products as Antimicrobial Agents. *Chem. Rev.* **2021**, *121*, 3464−3494.

(9) (a) Dunkerton, L. V.; Adair, N. K.; Euske, J. M.; Brady, K. T.; Robinson, P. D. Regioselective Synthesis of Substituted l-Thiohex-2-enopyranosides. *J. Org. Chem.* **1988**, *53*, 845−850. (b) Chen, P.; Guo, S.; Zuo, J.; Chu, R.; He, X.; Zhu, G. Synthesis of 3-S- and 3-Se-glycals by using R-S-S-R and R-Se-Se-R as the nucleophile precursors promoted by $Hf(OTf)_4$ and the temperature-dependent formation of

the above-mentioned 3-S- and 3-Se products. *Tetrahedron Lett.* **2020**, *61*, 151648.
(10) Okada, Y.; Asakura, N.; Bando, M.; Ashikaga, Y.; Yamada, H. Completely beta-selective glycosylation using 3,6-O-(o-xylylene)-bridged axial-rich glucosyl fluoride. *J. Am. Chem. Soc.* **2012**, *134*, 6940−3.
(11) Haranosono, Y.; Ueoka, H.; Kito, G.; Nemoto, S.; Sakaki, M. K. a. H A reaction mechanism-based prediction of mutagenicity: α-halo carbonyl compounds adduct with DNA by SN2 reaction. *J. Toxicol. Sci.* **2018**, *43*, 203−211.
(12) Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. Halide Ion Catalyzed Glycosidation Reactions. Syntheses of α-Linked Disaccharides. *J. Am. Chem. Soc.* **1975**, *97*, 4056−4062.
(13) Tacconelli, E.; Magrini, N. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. *World Health Organization, Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics*, **2017**.
(14) (a) Micoli, F.; Del Bino, L.; Alfini, R.; Carboni, F.; Romano, M. R.; Adamo, R. Glycoconjugate vaccines: current approaches towards faster vaccine design. *Expert Rev. Vaccines* **2019**, *18*, 881−895. (b) Li, W.-H.; Li, Y.-M. Chemical Strategies to Boost Cancer Vaccines. *Chem. Rev.* **2020**, *120*, 11420−11478. (c) Seeberger, P. H. Discovery of Semi- and Fully-Synthetic Carbohydrate Vaccines Against Bacterial Infections Using a Medicinal Chemistry Approach. *Chem. Rev.* **2021**, *121*, 3598−3626.
(15) Liu, B.; Furevi, A.; Perepelov, A. V.; Guo, X.; Cao, H.; Wang, Q.; Reeves, P. R.; Knirel, Y. A.; Wang, L.; Widmalm, G. Structure and genetics of Escherichia coli O antigens. *FEMS Microbiol. Rev.* **2020**, *44*, 655−683.

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