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Article

Controllable 1,3-Bis-Functionalization of 2-Nitroglycals with High Regioselectivity and Stereoselectivity Enabled by a H-Bond Catalyst

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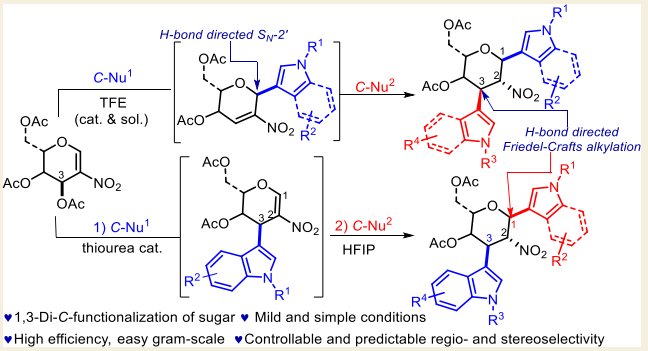
ABSTRACT: The selective modification of carbohydrates is significant for producing their unnatural analogues for drug discovery. C1-functionalization (glycosylation) and C1,C2-difunctionalization of carbohydrates have been well developed. In contrast, C3-functionalization or C1,C3-difunctionalization of carbohydrates remains rare. Herein, we report such processes that efficiently and stereoselectively modify carbohydrates. Specifically, we found that trifluoroethanol (TFE) could promote 1,3-bis-indolylation/pyrrolylation of 2-nitroglycals generated carbohydrate derivatives in up to 93% yield at room temperature; slightly reducing the temperature could install two different indoles at the C1- and C3-positions. Switching TFE to a bifunctional amino thiourea catalyst leads to the generation of C3 monosubstituted carbohydrates, which could also be used to construct 1,3-di-*C*-functionalized carbohydrates. This approach produced a range of challenging sugar derivatives (over 80 examples) with controllable and high stereoselectivity (single isomer for over 90% of the examples). The potential applications of the reaction were demonstrated by a set of transformations including the synthesis of bridged large-ring molecules and gram scale reactions. Biological activities evaluation demonstrated that three compounds exhibit a potent inhibitory effect on human cancer cells T24, HCT116, AGS, and MKN-45 with IC_{50} ranged from 0.695 to 3.548 μM.



KEYWORDS: *bis-indoles, 2-nitroglycals, fluorinated alcohols, carbohydrate, C-glycoside, selective modification*

INTRODUCTION

Carbohydrates are one of the four foundational biological macromolecules, playing key roles in diverse biological events, including cell differentiation and cell−cell and cell−extracellular matrix interactions. These interactions are related to a variety of physiological and pathological processes, such as fertilization, immune response, bacterial and viral infection, immune response, and tumor metastasis.[1] Sugars are also fundamental components of many natural products with a wide range of bioactivities.[2,3] Moreover, carbohydrates have long been established drugs for the treatment of various diseases, including diabetes, tuberculosis, cancer, and, especially, bacterial and viral infections.[3−6] Besides, the multifunctional and chiral properties of sugars have led to the development of carbohydrate-based stereoselective synthesis.[7] Indeed, with the rapid development of carbohydrate-based drugs, glycochemistry and glycobiology in recent decades, controllable and highly selective methods are urgently needed to precisely modify carbohydrates to enhance or alter their pharmaceutical properties and improve their biological functions.[8]

In this context, difunctionalization of carbohydrates can not only economically and efficiently synthesize unnatural sugar analogues in a single step but also convert inexpensive yet abundant feedstocks into a variety of structurally complex molecules. 1,2-Difunctionalization of sugars could be achieved by 1,2-C/N/S/Se[9−11] (Scheme 1A, eq 1) or radical migration[12,13] (Scheme 1A, eq 2). Glycals are another important building blocks utilized for 1,2- or 1,3-difunctionalization of sugars[9,14,15] through electrophilic activation nucleophilic capture protocols[14] or radical-triggered difunctionalization of double bonds to form 2-Br/2-I/2-S/2-Se/2-N/2-C or 2-P-substituted carbohydrate derivates (Scheme 1A, eq 3, left).[9,16] These strategies provided irreplaceable methodologies for the synthesis of 1,2-disubstituted unnatural sugars and established a robust platform for the exploration of new functions of such compounds. Despite these excellent achievements, the synchronous 1,3-difunctionalization (especially 1,3-di-C-functionaliza-

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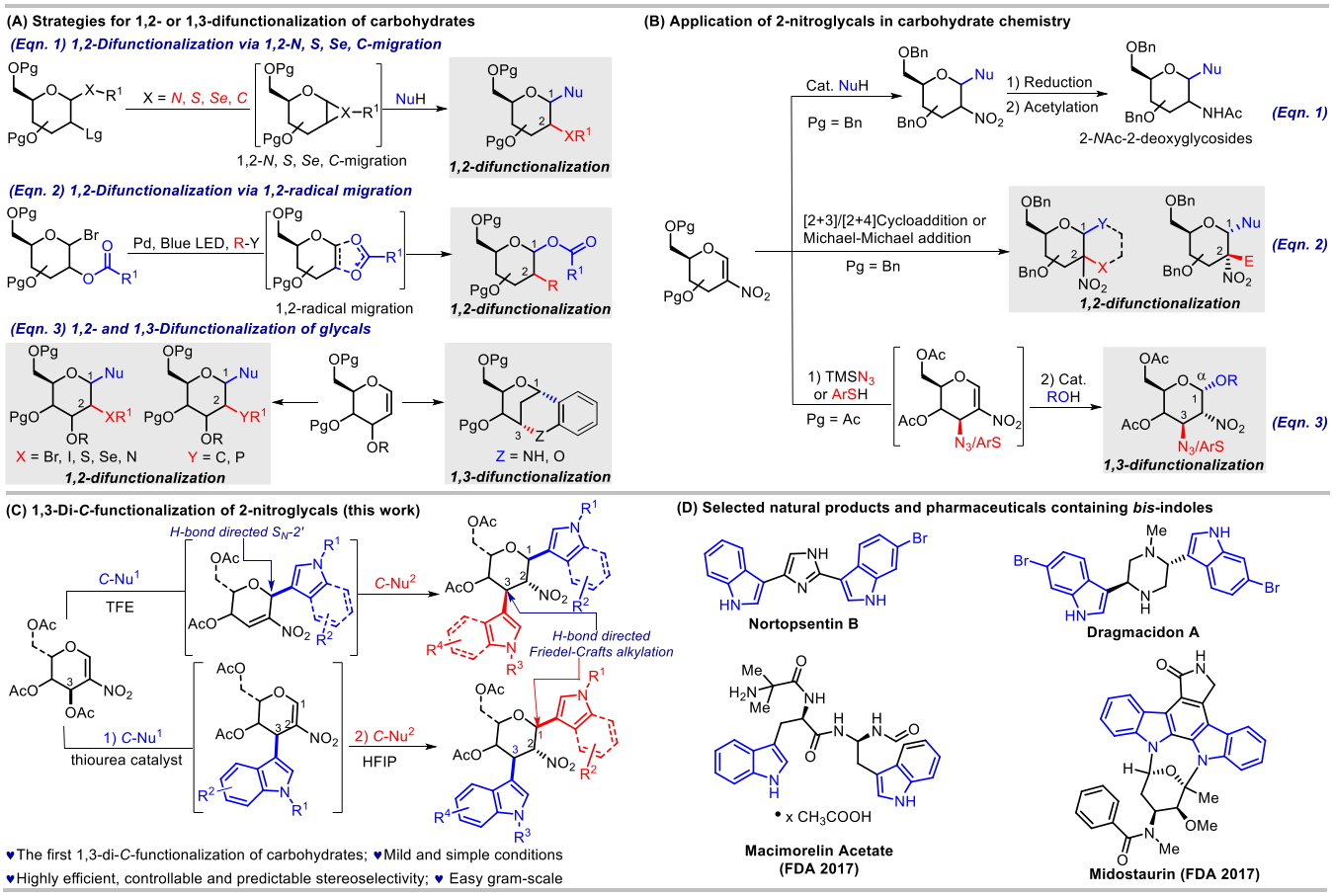
Scheme 1. Strategies for Difunctionalization of Sugars and Importance of Bis-indole Compounds



tion) of carbohydrates remains rare,[14] and the predominant protocols rely on the Ferrier rearrangement-intramolecular cyclization to access tetrahydroquinoline derivatives (Scheme 1A, eq 3, right),[17−24]

Because of the pioneering work from Schmidt's group, 2-nitroglycals,[9,25] especially benzylated 2-nitroglycals, have been extensively used for glycosylation under various catalytic conditions, such as noncovalent catalyzed glycosylations[26−32] (Scheme 1B, eq 1). The α,β-unsaturated double bond in benzylated 2-nitroglycals, under certain conditions, could also undergo [2 + 3]/[2 + 4] cycloaddition[33,34] or Michael−Michael addition[35,36] to achieve 1,2-difunctionalized products (Scheme 1B, eq 2). Compared with benzylated 2-nitroglycals, acetylated analogues are easier to prepare from corresponding oligosaccharides in two steps,[37,38] and the acetyl group, after the reaction, can be readily removed under mild conditions. However, due to its potentially high reactivity, especially the side reaction of Ferrier rearrangement under conventional glycosylation conditions,[14,37−44] the application of acetylated 2-nitroglycals in carbohydrate chemistry is much less developed. In 2013, by using DMAP as a catalyst, Vankar's group found that acetylated 2-nitroglycals can undergo selective functionalization at the C1- or C3-position based on the properties of nucleophiles. Harder O-type nucleophiles attack the C1-position, while softer azide and thiophenol prefer to add to the C3-position. The obtained C3-azidized (N_3) and C3-thiophenolated (SPh)-2-nitroglycals were further reacted with O-nucleophiles, realizing 1,3-difunctionalized 2,3-dideoxy sugar derivatives (Scheme 1B, eq 3).[37] This process was recently developed further by Zhang and co-workers to synthesize 2,3-diamino-2,3-dideoxy-glycosides,[39] or 1,3-dithioglycosides.[40] Despite the success in the construction of glycosides with a N_3 or SPh substituent at the C3 position, the great potential of acetylated 2-nitroglycals for the 1,3-difunctionalization of sugars by *C*-nucleophiles with controllable regioselectivity and stereoselectivity remains elusive.

Herein, we have developed a controllable, efficient, and highly stereoselective hydrogen bond-directed site-selective C3-functionalization and C1,C3-difunctionalization reaction of 2-nitroglycals (Scheme 1C). This reaction provides a range of challenging 3-indolyl-/pyrrolyl-, 1,3-bis-indolyl- and 1,3-bis-pyrrolyl-substituted carbohydrate derivatives with controllable and high levels of stereoselectivity. The significance of this reaction includes (i) represents the first example of 1,3-di-*C*-functionalization of sugars under very simple and mild reaction conditions, with high stereoselectivity and regioselectivity, and excellent scalability; (ii) the stereochemistry of the anomeric carbon center in the product can be precisely predicted by the employed 2-nitroglycals; and (iii) the products obtained from this protocol contain bis-indole subunits, which are prevalent in a wide array of natural products, as illustrated by nortopsentin B, Dragmacidon A, and FDA-approved drugs, such as macimorelin acetate and midostaurin[45−47] (Scheme 1D). (iv) Combined with the multifunctional features of sugars and the multiple reactivity of abundant indoles, a series of carbohydrate analogues would be constructed by late-stage diversification, which will in turn further benefit the synthesis of carbohydrate

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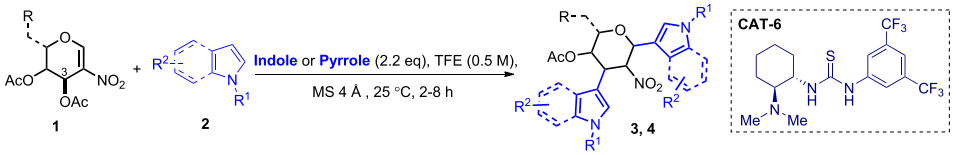
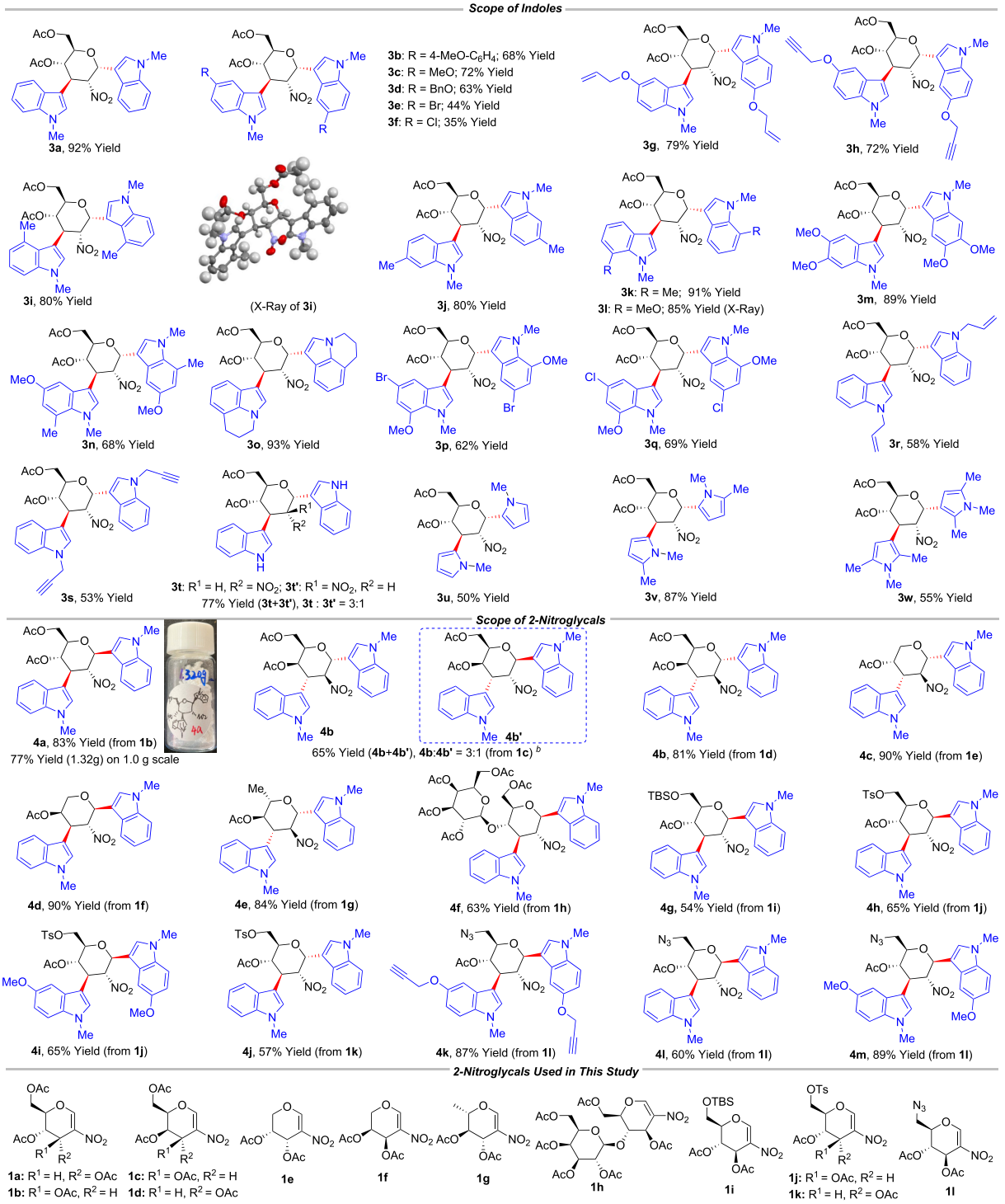
Table 1. Substrate Scope of the 1,3-Difunctionalization of 2-Nitroglycals[a]





[a]Standard conditions: **2** (2.20 equiv), **1** (1.00 equiv), MS 4 Å (100 mg), and TFE (0.5 M) at 25 °C for 2−8 h. [b]Using **CAT6** at 65 °C.

derivatives and the discovery of carbohydrate-based molecules.[48,49]

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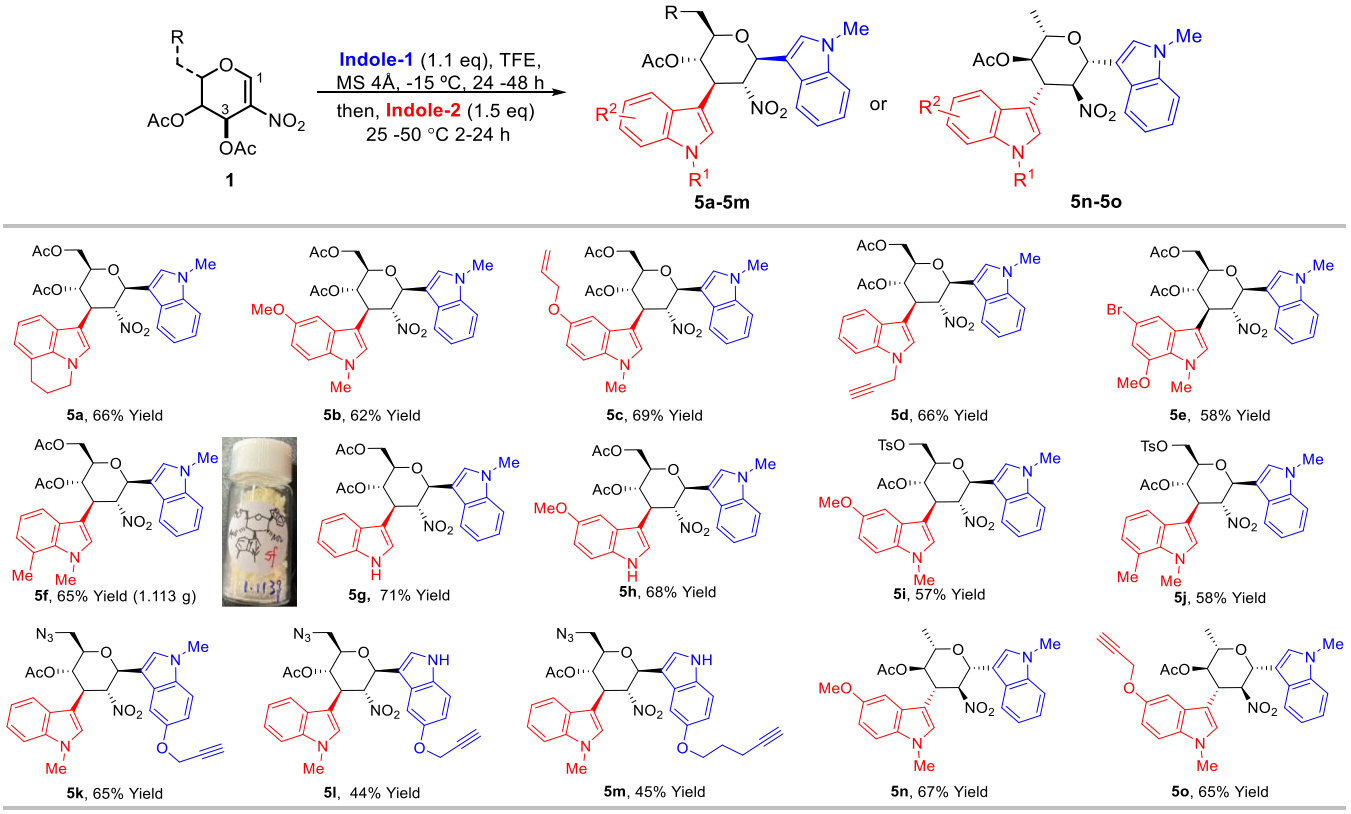
Table 2. Access to 1,3-Bis-Indolylated Sugars with Different Indoles at the C1- and C3-Positions



RESULTS AND DISCUSSION

Discovery and Optimization of 1,3-Bis-Indolylation of 2-Nitroglycals

We commenced our studies by evaluating a range of classical glycosylation conditions, including organic and Lewis acidic catalysts, using acetylated 2-nitroglycal (**1a**) and *N*-methyl-indole (**2a**) as model substrates (Table S1). Nitroglycal **1a** could be readily prepared in one step as a white solid on the gram scale from glucal, which facilitated optimization of the conditions.[50] Ultimately, the optimal conditions were obtained when molecular sieve (MS) was added to the reaction mixture using 2,2,2-trifluoroethanol (TFE) as the solvent and promoter, which delivered 1,3-bis-indolylation product[51−53] **3a** in 92% isolated yield as a single diastereomer. The dual role of TFE both as a catalyst and as a solvent is significant because it allows the reaction to be carried out without the need for expensive and/or toxic catalysts under very simple and mild conditions.[54−57]

Substrate Scope of 1,3-Bis-Indolylation of 2-Nitroglycals

The scope of indoles was initially investigated through the reaction of 2-nitroglycal (**1a**) under optimal reaction conditions (Table 1). Both *N*-methyl substituted indoles with a phenyl and alkoxy substitution can be used for this transformation, offering products (**3b**−**3d**) in 63−72% yields. 5-Br- and 5-Cl-indoles are also suitable substrates for this process, furnishing 1,3-bis-indolyl-substituted carbohydrate derivatives (**3e** and **3f**) in synthetically useful yields. The presence of Br and Cl substitutions in the products is useful for further functionalization by coupling reactions. Indoles with 5-allyloxy and 5-propargyloxy substituents are also smoothly coupled with 2-nitroglycal, providing 1,3-bifunctionalized products (**3g** and **3h**) in 79 and 72% yield, respectively. The substitutions at the 4-, 6-, and 7-positions of indoles generated **3i**−**3l** in excellent yields. Disubstituted indoles such as 5,6-dimethoxy- and 5-methoxy-7-methyl-substituted indoles gave the corresponding products in 89 and 68% yield, respectively. Tricyclic indole was also successfully added to 2-nitroglycal, delivering **3o** in excellent yield and stereoselectivity. The presence of an electron-donating group in the phenyl ring of indole could dramatically improve the yield, as shown by **3p** and **3q** (vs **3e** and **3f**). We also examined the potential substituted group on the N-atom. *N*-Allyl- and propargyl-substituted indoles were smoothly transformed to 1,3-bis-indolyl-substituted sugar derivatives **3r** and **3s** in approximately 55% yield, while the *N*-unprotected indole delivered product **3t** in 83% yield with 3:1 diastereoselectivity. The lower stereoselectivity of *N*-unprotected indole may due to the multiply H-bond interaction between TFE, C2-NO_2, and NH of indole.[58] Moreover, substituted pyrroles also worked well under the standard conditions, affording the desired 1,3-bis-pyrrolyl-substituted sugar derivatives (**3u**−**3w**) in 50 to 87% yields. It is worth mentioning that due to its higher electron density, pyrrole typically reacts at the 2-position; however, in the event that a substituent is present at the 2-position, the reaction will take place at the 3-position instead. Notably, in all of the tested cases, the three newly formed continuous chiral centers had the same configuration based on single-crystal X-ray diffraction (SC-XRD) and NMR analysis, and other isomers were not observed, except when *N*-unprotected indole was employed.

The generality of the reaction was further investigated by examining the reaction between *N*-methyl-indole and different 2-nitroglycals (**1b** to **1l**). When 2-nitroglucal (**1b**) was employed in the reaction, **4a** was formed in 83% yield with only one diastereomer, and the reaction can be performed on a

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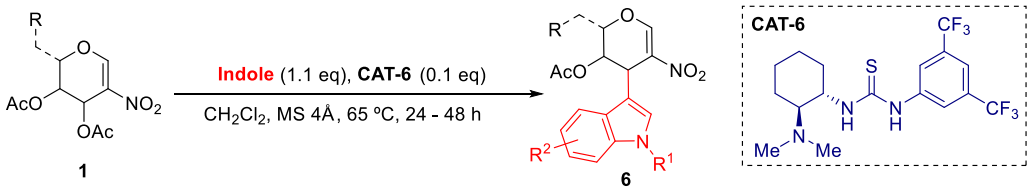
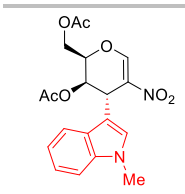
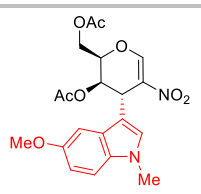
Table 3. Access to 3-Indolylated Sugars

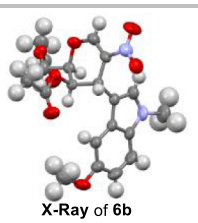




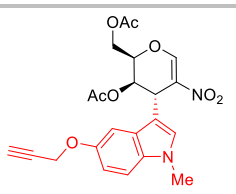
6a, 74% Yield



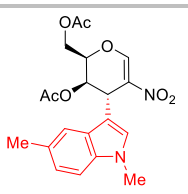
6b, 68% Yield (**X-Ray**)



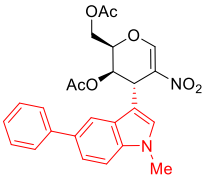
X-Ray of **6b**



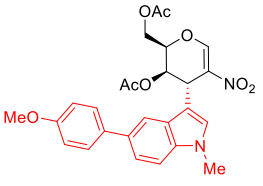
6c, 36% Yield



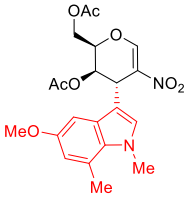
6d, 69% Yield



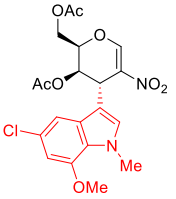
6e, 61% Yield



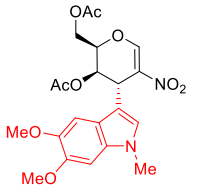
6f, 76% Yield



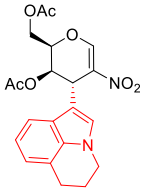
6g, 66% Yield



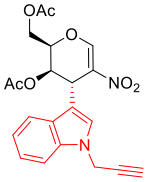
6h, 32% Yield



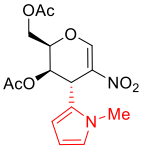
6i, 52% Yield



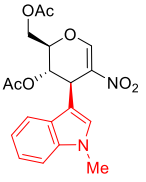
6j, 71% Yield



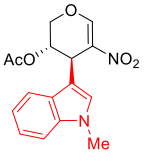
6k, 44% Yield



6l, 33% Yield



6m, 40% Yield



6n, 38% Yield

gram scale without a detrimental impact on the yield of **4a**. Interestingly, it was found that when the acetate (OAc) group at the C3-position was changed from an axial bond in **1a** to an equatorial bond in **1b**, the configuration of the anomeric carbon in product **4a** was also switched to the opposite configuration, while the stereochemistry at the C2 and C3 positions was not affected. For the reaction of 2-nitrogalactal (**1c**), it was found that under the standard conditions, an approximately 1:1 diastereoselective mixture was obtained in approximately 60% yield, and further optimization led to the formation of product **4b** in 65% yield with 3:1 diastereoselectivity catalyzed by a thiourea catalyst (**CAT-6**). The lower stereoselectivity might be attributed to 2-nitrogalactal tending to form 3-indolylated derivative as confirmed by ^{1}H NMR analysis of the crude mixture (see also Figure S3). Fortunately, by use of the C3 isomer (**1d**), **4b** was isolated in 81% yield as the single isomer under standard conditions. Starting from 2-nitro-D-arabinal (**1e**) and 2-nitro-L-arabinal (**1f**), a pair of enantiomers (**4c** and **4d**) could be produced in excellent yields and stereoselectivity. 2-Nitro-L-rhamnal (**1g**) could be used in this protocol, delivering the product (**4e**) in 84% yield with only one diastereomer. The protocol also extends to disaccharide 2-nitroglycal, generating **4e** in good yield with high stereoselectivity. In addition, different protecting groups at the 6-position, such as TBS, and functional groups, including OTs and N_3 of 2-nitroglycals, could also react with indoles offered products (**4f**−**4m**) in good to excellent yields with only one diastereomer. Notably, in all of the tested examples, the products were isolated as the only diastereomer in high yield, and the stereochemistry in the product could be precisely forecasted by the stereochemistry of the leaving group (OAc) at the C3 position of the corresponding 2-nitroglycals. For example, when the C3-OAc is at axial bond position, the product was obtained in the α-configuration (as in **3a**−**3w**, **4b**, **4c**, **4e**, and **4j**), whereas the 2-nitroglycals with an equatorial OAc group at the C3-position resulted in the formation of the product in the β-configuration (as in **4a, 4d**, **4f**−**4i**, and **4k**−**4l**). This phenomenon may be caused by stereoelectronic factor and the H-bond interaction between TFE, C3-OAc, and C2-NO_2.

During investigation of the generality with respect to both indoles and 2-nitroglycals (Table 1), it was found that by decreasing the reaction temperature and reducing the amount of indole, we could isolate C1-substituted indole *C*-glycoside,[59−61] which led us to try to place different indoles at the C1- and C3-positions of sugars (Table 2). Therefore, 2-nitroglycals **1** were reacted with the first indole (**Indole-1**) in TFE at −15 °C for 24 to 48 h, to which the secondary indole (**Indole-2**) was added and the mixture was slowly wormed to 25−50 °C for 2 to 24 h. By this protocol, we successfully installed two different indoles at the C1- and C3-positions of sugars in satisfactory yields and excellent stereoselectivity. For example, **1b** was first reacted with *N*-methylindole **2a**, which was followed by the reaction with tricyclic indole to achieve **5a** in 66% yield with excellent regioselectivity and stereoselectivity. Similarly, bis-indolylated sugars **5b**−**5f** were obtained in 58 to 69% yields with the same high level of regioselectivity and stereoselectivity. The N-unprotected indole could also be installed at the C-3 position of sugars by this protocol, as illustrated by **5g** and **5h**. The method proved to be useful for the 1,3-bis-indolylation of C6-functionalized 2-nitroglycals as well. For example, 6-OTs and 6-N_3 substituted 2-nitroglycals were smoothly transformed into

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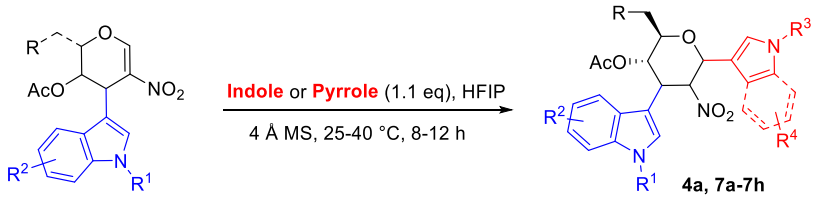
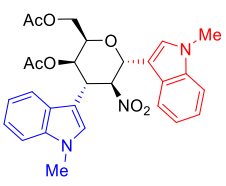
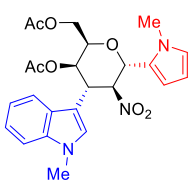
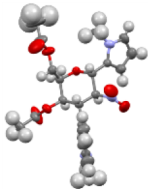
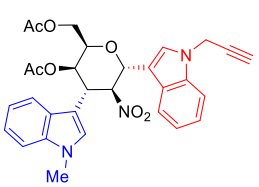
Table 4. Access to 1,3-Difunctionalized Sugars from 3-Indolylated Sugars

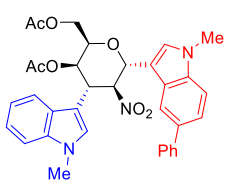


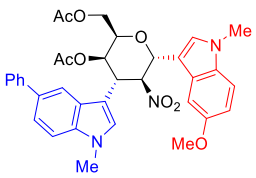

4b, 75% Yield, dr = 3.5:1

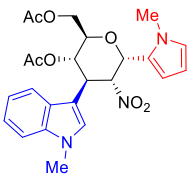

7a, 58% Yield, dr > 20:1

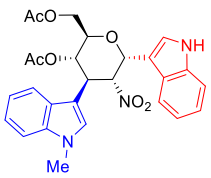

X-Ray of **7a**

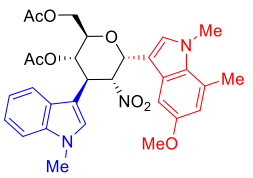

7b, 54% Yield, dr = 2:1

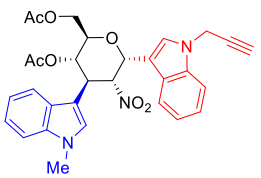

7c, 55% Yield, dr = 2.5:1


7d, 68% Yield, dr = 5:1


7e, 49% Yield, dr > 20:1


7f, 40% Yield, dr > 10:1


7g, 80% Yield, dr = 3:1


7h, 48% Yield, dr = 8:1

the corresponding products (**5i**−**5m**) in 45−65% yields. Moreover, the procedure was amenable to constructing 1,3-bis-indolylated rhamnose derivatives (**5n** and **5o**) in approximately 66% yield with a single diastereoisomer.

Again, a gram-scale experiment of 2-nitroglucal **1b** with 7-methyl-indole under the standard reaction conditions afforded **5f** in 65% yield, along with **4a** in 6% yield.

Substrate Scope of C3-Indolylation of 2-Nitroglycals

The one-pot stepwise installation of two different indoles at the C1- and C3-positions combined with the fact that the C1-indolylated product can be isolated in good yield with excellent anomeric selectivity made us further try C3-indolylation of 2-nitroglycals to produce C3 monoindole-substituted glycals. Indeed, during our optimization of the stereoselectivity of the 1,3-bis-indolyl-substituted sugar derivative from 2-nitrogalacal, we found that H-bond catalysts such thiourea and chiral phosphoric acids could deliver the C3-indolylated product in approximately 30% yield (see the Supporting Information for details). This promoted us to further examine other parameters of the reaction and eventually isolated the corresponding product in 74% yield by using thiourea (**CAT-6**) as the catalyst and DCM as the solvent in the presence of 4 Å MS. Under these conditions, a suite of C3 monoindolyl-substituted 2-nitroglycals were generated in good yields with a single diastereomer from 2-nitrogalacal. The stereochemistry at the C3-position was confirmed by SC-XRD analysis of **6b**. A range of indoles were then used to investigate the generality of this reaction, and the selected results are shown in Table 3. *N*-Methyl indole delivered C3-functionalized sugar **6a** in 74% yield. 5-Substituted indole produced the corresponding products (**6b**−**6f**) in synthetically useful yield (36−76%). Disubstituted indoles also generated the products (**6g**−**6i**) in good yields. The tricyclic indole derivative was smoothly integrated into 2-nitroglycal, affording the product (**6j**) in a 71% yield. *N*-Propargyl indole and *N*-methyl pyrrole were also successfully installed in the C3-position of 2-nitroglycal, giving the corresponding products (**6k** and **6l**) in approximately 40% yield. Other 2-nitroglycals were also investigated, and the C3 monoindolyl-substituted products (**6m** and **6n**) were formed in synthetically useful yields.

1,3-Bis-Indolylated Sugars from 3-Indolylated Sugars

Because 1,3-bis-indolylated galactoses with different indoles at the C1- and C3-positions from 2-nitrogalacal are inaccessible under the conditions of Table 2, the 3-indolyl-2-nitrogalacal was then successfully converted into 1,3-bis-indolylated galactose derivatives by using 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as the solvent and 4 Å MS as the additive. For comparison, we first reacted **6a** with *N*-methyl indole (**2a**), and 1,3-bis-indolylated product **4b** was obtained in 75% yield (Table 4) with a slightly higher diastereoselectivity than that of the one-pot protocol in Table 1. In the presence of pyrrole, 1-pyrrolyl-2-NO_2-3-indolyl galactose (**7a**) was isolated in 58% yield with a diastereoselectivity higher than 20:1, and the absolute configuration of **7a** was confirmed by SC-XRD analysis. The protocol was then used to synthesize other 1,3-difunctionalized galactose derivatives, and 1,3-bis-indolylated galactoses (**7b**−**7d**) were obtained in 49 to 68% yield. 3-Indolylated glucose was also smoothly converted into C1-indolyl/pyrrolyl-C3 indolyl-glucoses (**7e**−**7h**) in moderate yield with high diastereoselectivity. The stereochemistry of the major product, which is the same as that in Table 2, was confirmed by the NMR analysis of the products.

CONTROL EXPERIMENTS AND THE PROPOSED REACTION MODEL

A key property of the protocol described here is that the configuration of the leaving group (OAc) at the C3 position determined the stereochemistry of the anomeric carbon center. This made us try to understand the mechanism by control experiments (Scheme 2). The reaction with C3-deuterated indole (**2a-D**, 75%-D) and TFE-D_3 formed the corresponding products in approximately 85% yield with 5%-D and 50%-D at C2 of sugar, respectively, while a similar reaction with both **2a-D**

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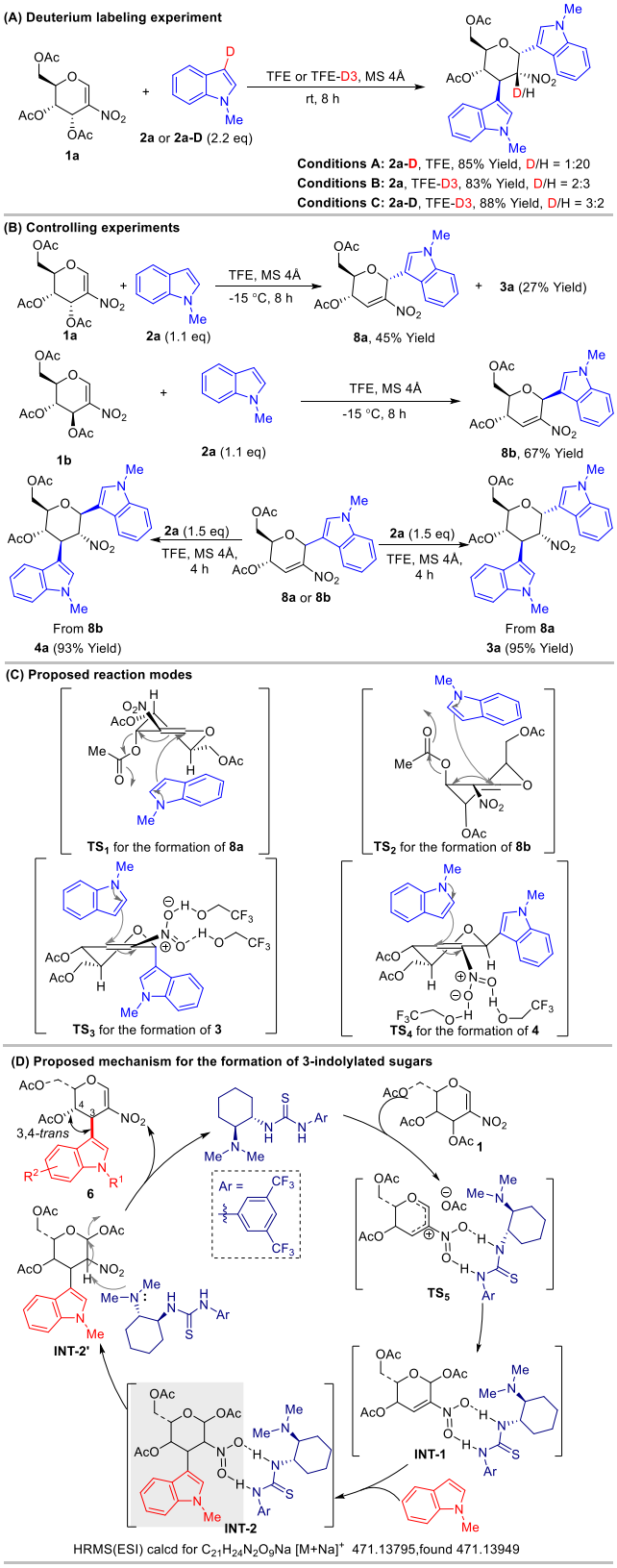
Scheme 2. Mechanistic Studies of 1,3-Bis-Indolylation of Acetylated 2-Nitroglycals



and TFE-D_3 resulted in **3a-D** in 88% yield with 75% D at C2 (Scheme 2A). These results indicate that trifluoroethanol and the indole may both provide hydrogen to the C2 position of the products (see Figure S2 for detail). Subjecting **1a** and **2a** (1.1 equiv) at a lower temperature (−15 °C) led to the formation of monoindolyl-substituted *C*-glycoside **8a** in 45% yield, accompanied by 1,3-difunctionalized product **3a** in 27% yield (Scheme 2B). Resubmission of **8a** under the standard reaction conditions in the presence of 1.5 equiv of indole furnished **3a** in 95% yield exclusively, and no other isomers were isolated. Similarly, the reaction between **1b** and **2a** (1.1 equiv) at −15 °C delivered **8b** in 67% yield as the only product. When **8b** was stirred with another equivalent of indole **2a** (1.5 equiv), **4a** was formed in 93% yield. The stereochemistry of the product from these stepwise manners is the same as the one-step process shown in Table 1. These observations allowed us to believe that in our case, the stereochemistry in the products is not because of isomerization after the reaction but from the reaction itself.

Based on the above observation and relevant reports,[43,44] the reaction modes for this transformation are proposed in Scheme 2C. The Friedel−Crafts alkylation of the first indole at C1 should occur preferably from the same-side of C3-OAc ($\mathbf{TS_1}$ and $\mathbf{TS_2}$) due to the stereoelectronic factor[25,29,37,38,62] to replace the allylic acetate via the S_N2'-type mechanism, producing intermediate **8**, which was attacked by the secondary indole from the up-face[63−65] ($\mathbf{TS_3}$ and $\mathbf{TS_4}$) through a Friedel−Crafts alkylation promoted by the H-bond from TFE, producing 1,3-bis-indolylated products (**3** and **4**). Although further studies may be warranted, according to DFT calculations, the influence of TFE is largely evident in a solvation effect during the first stage of the reaction. However, TFE may form hydrogen bonds with C2-NO_2 and C3-OAc during the addition of the second indole, thereby lowers the activation energy of the reaction (for details see the Supporting Information).

For the synthesis of 3-indolylated sugars catalyzed by a thiourea catalyst (**CAT-6**), we assumed that **CAT-6** might induce the acetate anion in 2-nitroglycals (**1**) to be eliminated, producing the allyl cation $\mathbf{TS_5}$, which was then trapped by the acetate anion forming **INT-1**. After that, indole attacked the C3 position through a Friedel−Crafts alkylation generated 3-indolylated sugar (**INT-2**), which was followed by base catalyzed elimination of acetic acid to give final product **6** and regenerated catalyst to re-enter the reaction process. The presence of **INT-1** was confirmed by HRMS analysis of the crude reaction mixture after 12 h.

Derivatization of the Products and Intermediates

The potential derivatization of the products is demonstrated in Scheme 3A. Treatment of **4a** with Raney-Ni in the presence of H_2 followed by the one-pot protection of the free amino-group into sulfamide led to the formation of 1,2,3-trideoxy-2-amino-carbohydrate derivative **9** in 53% yield. Deacetylation of **4a** under basic conditions resulted in free alcohol **10** in 88% yield. The presence of both azide and alkynyl groups in the same molecule in compounds **5k−5m** allows us to make bridged macrocyclic molecules **11−13** with up to 18-membered rings in 46−59% yields by Cu(I)-catalyzed azide−alkyne 1,3-dipolar cycloaddition.[66] Intermediates such as **8b** could also further react with pyrrole to obtain 1-indolyl-3-pyrrolyl-sugar derivatives **14** and **15** in approximately 60% yield.

Preliminary Evaluation of Biological Activities of the Products

Fascinated by the diverse therapeutic activity of indole,[67−70] we tested the bioactivity of the obtained products (Scheme 3B). In vitro cytotoxicity against 21 cells (A549, MKN-45, HCT 116, HeLa, K-562, 786-O, TE-1, 5637, GBC-SD, MCF7, HepG2, SF126, DU145, CAL-62, PATU8988T, HOS, A-375, A-673,

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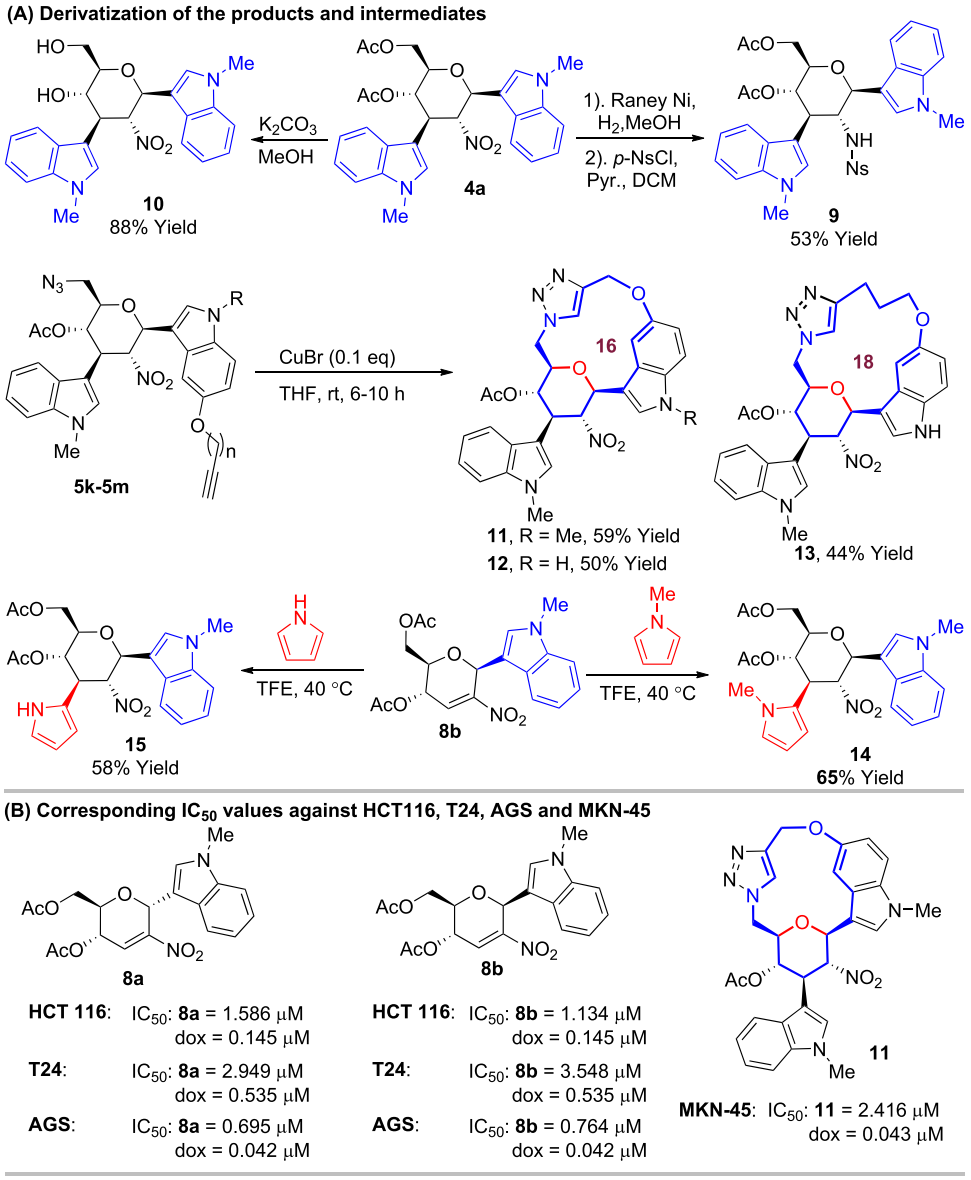
Scheme 3. Derivatization and Biological Evaluation of the Products and Intermediates



AGS, T24, and 293T) and human normal hepatocyte (L-02) were tested (for details see the Supporting Information). Interestingly, it was found that C1 monoindolyl-substituted sugars **8a** and **8b** exhibiting obvious inhibitory effect on the viability of HCT 116 and the IC_{50} values for **8a** and **8b** were 1.586 and 1.134 μM, respectively. They also exhibited a potent inhibitory effect on T24 cells with IC_{50} values of 2.949 and 3.548 μM, respectively. Additionally, compounds **8a** and **8b** had outstanding inhibitory efficacy against the AGS cell, with IC_{50} values of 0.695 and 0.764 μM, respectively. Moreover, the macrocyclic sugar **11** also shown a satisfactory inhibitory effect on MKN-45 with IC_{50} = 2.416 μM.

CONCLUSIONS

In summary, we have realized a fluorinated alcohol solvent (TFE) catalyzed, highly efficient, and stereoselective cascade process for the 1,3-difunctionalization of 2-nitroglycal. The substrates are easily accessed on large scale from glycal in one step, which underpins a direct and efficient procedure for C1,C3-bis-indolyl-, C1,C3-bis-pyrrolyl-substituted sugar derivatives that are inaccessible by conventional methodologies. In addition, the α- or β-stereoselectivity could be controlled by C3-OAc, while slight modification of the reaction conditions could install two different indoles at the C1- and C3-positions of sugars. Replacing TFE with a bifunctional amino thiourea catalyst leads to the formation of C3-monoindolated 2-nitroglycal, which could be further functionalized at the C1-position. By combining these three strategies, a diverse set of C1,C3-bis-indolyl-, C1,C3-bis-pyrrolyl-, C1-indolyl-C3-pyrrolyl-, and C1-pyrrolyl-C3-indolyl-substituted sugar derivatives were prepared efficiently with high regioselectivity and stereoselectivity, and many of the obtained products also exhibited potent anticancer effect on T24, HCT116, AGS and MKN-45 cells with IC_{50} ranged from 0.695 to 3.548 μM, whereas shown very low cytotoxicity against human normal hepatocyte (L-02), which would facilitate for the further development as high efficiency and low toxicity anticancer new chemical entities.

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METHODS

General Procedure for the Synthesis of 1,3-Bis-Indolylation and 1,3-Bis-Pyrrolylation of 2-Nitroglycals with Same Indoles and Pyrroles at C1- and C3 Positions (Table 1)

To an oven-dried reaction tube (10 mL) equipped with a magnetic stir bar was added indole or pyrrole (0.44 mmol, 2.20 equiv), 2-nitroglycal **1** (0.20 mmol, 1.00 equiv), and MS 4 Å (100 mg). Then, TFE (400 μL) was added via a syringe. The reaction mixture was stirred at room temperature for 2−8 h until completion (monitored by TLC). The reaction mixture was directly concentrated in vacuo and the residue was purified by FCC to give the corresponding products **3** and **4**.

General Procedure for the Synthesis of 1,3-Bis-Indolylation of 2-Nitroglycals with Different Indoles at C1- and C3 Positions (Table 2)

To an oven-dried reaction tube (10 mL) equipped with a magnetic stir bar was added **Indole-1** (0.22 mmol, 1.10 equiv), 2-nitroglycal **1** (0.20 mmol, 1.00 equiv), and MS 4 Å (100 mg). Then, TFE (400 μL) was added via a syringe. The reaction mixture was stirred at −15 °C for 12−48 h until completion (monitored by TLC). **Indole-2** (0.30 mmol, 1.50 equiv) was added, and the reaction mixture was stirred at room temperature to 50 °C for 2−24 h. Upon completion (monitored by TLC), the reaction mixture was directly concentrated in vacuo and the residue was purified by FCC to give the corresponding product **5**.

General Procedure for the Synthesis of 3-Indolylation and 3-Pyrrolylation of 2-Nitroglycals (Table 3)

To an oven-dried reaction tube (10 mL) equipped with a magnetic stir bar was added indole or pyrrole (0.22 mmol, 1.10 equiv), 2-nitroglycal **1** (0.20 mmol, 1.00 equiv), **CAT-6** (0.02 mmol, 0.10 equiv), and MS 4 Å (100 mg). Dry DCM (400 μL) was added via a syringe, and the mixture was heated at 65 °C under N_2 atm for 12−48 h. Upon completion (monitored by TLC), the reaction mixture was directly concentrated in vacuo and the residue was purified by FCC to give the corresponding product **6**.

General Procedure for the Reactions between 3-Indoly-2-nitroglycals and Indoles or Pyrroles (Table 4)

To an oven-dried reaction tube (10 mL) equipped with a magnetic stir bar was added indole or pyrrole (0.11 mmol, 1.10 equiv), 3-indoly-2-nitroglycals **6** (0.10 mmol, 1.00 equiv), and MS 4 Å (50.0 mg). Then, HFIP (200 μL) was added via a syringe, the reaction mixture was stirred at 25−40 °C for 4−12 h. Upon completion (monitored by TLC), the reaction mixture was directly concentrated in vacuo and the residue was purified by FCC to give the corresponding product **7**.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.3c00727.

Experimental details, additional experimental results, characterization data, and copies of NMR spectra for all new products (PDF)

Accession Codes

CCDC 2289839 (**3i**), 2289840 (**3k**), 2289842 (**6b**), and 2289843 (**7a**) contain 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, 12Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

The manuscript was written through contributions of all authors. CRediT: **Jiangtao Li** investigation, methodology; **Zhengyan Fu** methodology; **zeen qiao** investigation; **Demeng Xie** formal analysis; **Li Zhang** investigation; **Yazhou Liu** formal analysis; **Jian Yang** investigation; **Jia-Xin Yan** investigation; **Xiaofeng Ma** supervision, writing-review & editing.

Notes

The authors declare no competing financial interest.

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