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Asymmetric Organocatalysis

Direct and Catalytic *C*-Glycosylation of Arenes: Expeditious Synthesis of the Remdesivir Nucleoside**

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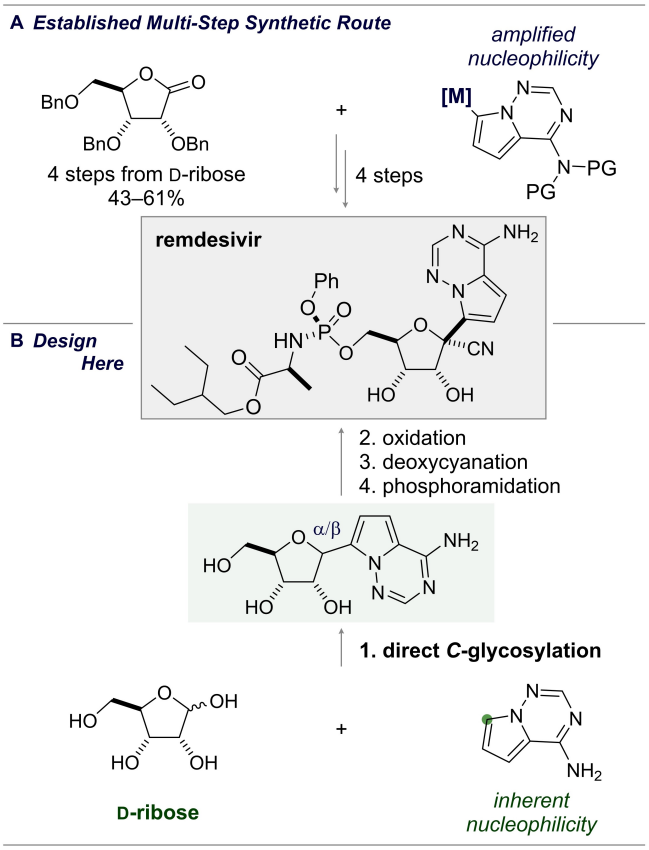
In memory of Helmut Vorbrüggen

Abstract: *Since early 2020, scientists have strived to find an effective solution to fight SARS-CoV-2, in particular by developing reliable vaccines that inhibit the spread of the disease and repurposing drugs for combatting its effects on the human body. The antiviral prodrug Remdesivir is still the most widely used therapeutic during the early stages of the infection. However, the current synthetic routes rely on the use of protecting groups, air-sensitive reagents, and cryogenic conditions, thus impeding a cost-efficient supply to patients. We have, therefore, focused on the development of a straightforward, direct addition of (hetero)arenes to unprotected sugars. Here we report a silylium-catalyzed and completely stereoselective C-glycosylation that initially yields the open-chain polyols, which can be selectively cyclized to provide either the kinetic α-furanose or the thermodynamically favored β-anomer. The method significantly expedites the synthesis of Remdesivir precursor GS-441524 after a subsequent Mn-catalyzed C–H oxidation and deoxycyanation.*

More than a year after COVID-19 spread worldwide, humankind is still striving for a sustainable solution. Nevertheless, we have witnessed the striking effect of applied and basic science on restraining the impact of SARS-CoV-2. This outbreak has been tackled especially intensively from the pharmaceutical sector through the use of small-molecule therapeutics, vaccinations, and biomedical devices. The pandemic has also driven a global effort to repurpose existing drugs to enable a rapid and targeted response.[1] Remdesivir (Veklury) is an antiviral prodrug that was originally evaluated in clinical trials to fight the Ebola virus[2,3] and, although showing somewhat mixed results against COVID-19, it is still the most widely used treatment during the early stages of infection.[4] Nucleotide analogues such as Remdesivir are a class of compounds that are generally known for their (RNA) antiviral properties.[5,6]

Although tremendous progress has been made in the synthesis of the ubiquitous monosaccharide motif and also of nucleoside analogues,[7–9] such syntheses still rely on multistep sequences and the use of protecting groups because of the selectivity challenges inherent in the functionalization of unprotected sugars. In the case of Remdesivir, Gilead's industrial route starts with the perbenzylated D-ribonolactone (Scheme 1A)—which is obtained in



Scheme 1. A) Established sequence towards the synthesis of remdesivir. B) Design here: direct *C*-glycosylation of the artificial nucleobase.

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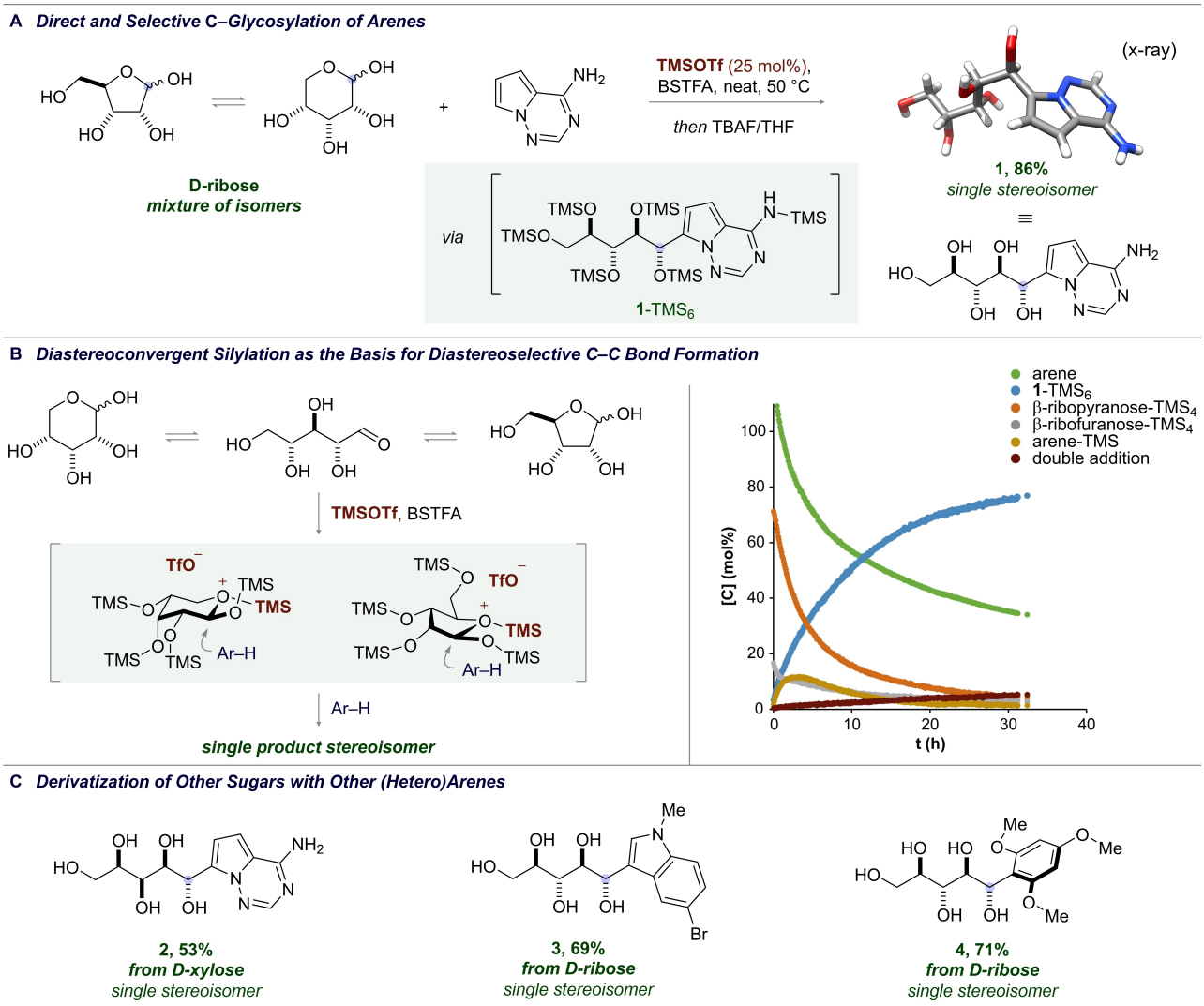
four steps from D-ribose—and requires sensitive reagents and cryogenic conditions for several of the steps involved.[10] These limitations have also inspired the organic chemistry community and fueled the development of novel synthetic methods, such as new approaches to build the heterocyclic arene[11,12] and improvements to the organocatalytic asymmetric phosphoramidation to introduce the monophosphate-like side chain.[13]

However, efforts to streamline the construction of the core nucleoside itself have remained elusive.[14] Recent advancements in the direct assembly of nucleosides have focused on the formation of a C–heteroatom bond in the anomeric position,[15] whereas examples of the C–C disconnection are scarce.[16,17] We aimed at the development of a new and greatly facilitated route to Remdesivir that featured the direct arylation of D-ribose by using silylium catalysis as the key step (Scheme. 1B).

Here we report the completely regio- and stereoselective addition of (hetero)arenes to unprotected sugars, which in turn furnishes the nucleoside intermediate in a one-pot fashion. The divergent formation of the α- or the β-anomer is achieved through either kinetic control or a thermodynamically driven epimerization, respectively.[18] Finally, the new method unlocks an expedient synthesis of the Remdesivir precursor GS-441524 by virtue of a selective Mn-catalyzed benzylic C–H oxidation and diastereoselective deoxycyanation.

Our approach harnesses the native nucleophilicity of the heterocycle, which eliminates the requirement for prefunctionalization and the preparation of the air-sensitive organometallic reagent. Furthermore, we exploit a Lewis acid catalyzed transient silylation of the carbohydrate to concurrently fulfill two main purposes: *in situ* protection of all protic functionalities as well as selective anomeric activation (Scheme 2).

We found that D-ribose is rapidly silylated by catalytic TMSOTf at 25 °C, which is regenerated upon protodesilylation of the innocent silicon source *N*,*O*-bis(trimeth-



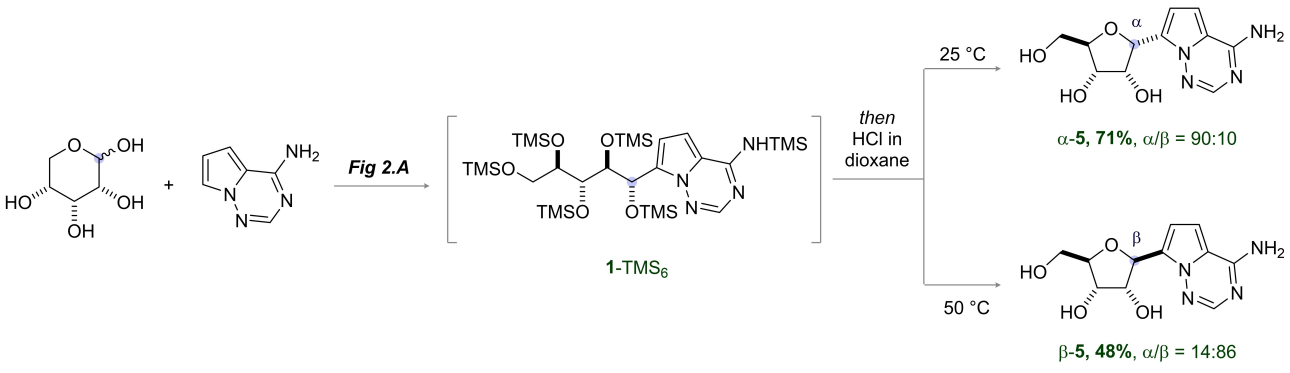
Scheme 2. A) Diastereoselective functionalization of D-ribose by transient silylation (CCDC 2123829). B) Mechanistic insights into the C–C bond formation. C) Additional examples of other sugars with other (hetero)arenes.

ylsilyl)trifluoro acetamide (BSTFA). The key C–C bond formation occurs at 50 °C under neat conditions, leading exclusively to the single linear isomer **1**-TMS_6 in quantitative yield. This selectivity is quite remarkable when taking into consideration the complex structure of free D-ribose, which consists of a mixture of five isomers: the α- and β-pyranose and -furanose, as well as the open form.[19,20] However, during the transformation, this dynamic mixture converges diastereoselectively to a single product. Subsequent desilylation of the crude reaction mixture with TBAF delivers the linear analogue **1** in a one-pot fashion (86 %), thereby rendering the use of silicon traceless. Preliminary studies have revealed that the method is also competent for the functionalization of alternative sugars and (hetero)arenes (Scheme 2C); for example, the reaction with D-xylose also delivers product **2** as a single diastereoisomer in slightly lower yield (53 %). Moreover, the addition of an indole derivative occurs in good yield at 25 °C to afford polyol **3** (69 %). Finally, 1,3,5-trimethoxybenzene similarly enables derivatization to afford **4** in 71 % yield.

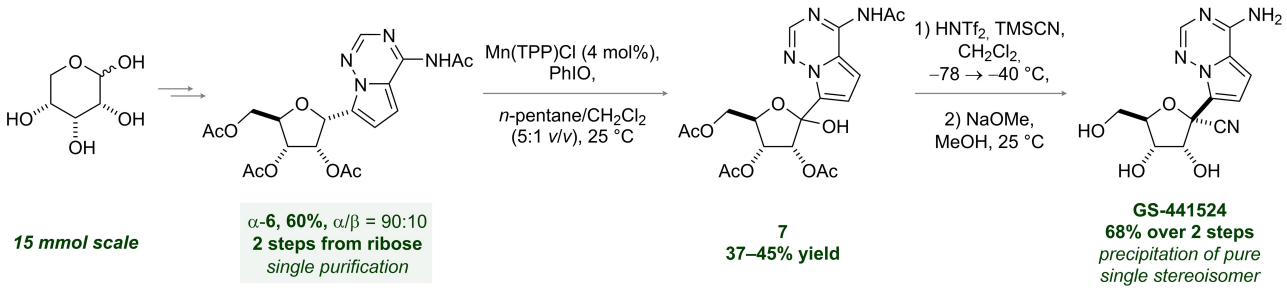
Lewis acid catalyzed nucleophilic additions to carbohydrate derivatives are generally believed to proceed via oxocarbenium intermediates that are derived from the activation of the anomeric substituent.[21–24] However, this assumption is questioned here in light of the formation of a single linear product. Instead, we propose a mechanism in which TMSOTf coordinates to the endocyclic oxygen atom of the sugar prior to reaction with the heterocycle leading to ring-opening (Scheme 2B).[25] Thorough analysis of NMR spectra confirmed that the silylation of the sugar at 25 °C delivered the TMS-protected β-ribopyranose and -furanose in 77 % and 21 % yield, respectively (see the Supporting Information, Figure S46 for DFT calculations). Consequently, successive nucleophilic substitution through an S_N2-type mechanism converges to the product as a single diastereoisomer. Kinetic analysis at 50 °C revealed that the consumption of the arene mirrors the formation of the product. Traces of double addition were also detected.

Remarkably, we found that when the reaction mixture was treated with acid rather than fluoride, the corresponding *C*-ribofuranosylated products are obtained (Scheme 3). The α-product **5** is obtained in good yield and high diastereoselectivity (71 %, α/β = 90:10) by performing the acid treatment at 25 °C . In contrast, acid treatment at 50 °C leads directly to the thermodynamically favored β-nucleoside **5** (48 %, α/β = 14:86). The epimerization from α to β could be monitored by ^{1}H NMR spectroscopy after resubmission of the isolated product α-**5** to HCl in dioxane at 50 °C (see Supporting Information, Figure S27). In the context of the synthesis of the antiviral drug GS-441524, subsequent oxidative installation of the nitrile moiety was required. Thus, we envisioned an initial C–H oxidation to furnish the stereolabile hemiacetal **7** (Scheme 4), which could in turn be diastereoconvergently deoxycyanated to provide GS-441524.

After investigating different approaches, the desired reactivity was achieved by means of a Mn-catalyzed benzylic C–H oxidation.[26] Notably, exclusive reactivity of the α-anomer **5** was observed, most likely resulting from the higher accessibility of its β-hydrogen atom to the Mn-porphyrin complex, in accordance with DFT-optimized ground-state structures (see Supporting Information, Figure S31). Shorter reaction times and portion-wise addition of the oxidant are crucial factors determining the reaction outcome, with fragmentative overoxidation to the ribonolactone being the most prominent side reaction. Ultimately, the conversion as well as selectivity were enhanced by precipitation of the polar C–H oxidation product from the solvent mixture (*n*-pentane/CH_2Cl_2 5:1 *v*/*v*). Starting from peracetylated α-ribonucleoside **6**, which was synthesized on a 15 mmol scale in 60 % yield from D-ribose with a single purification by column chromatography, led to the oxidation product **7** being obtained as an inconsequential mixture of isomers (equilibrium distribution in CD_2Cl_2: 46:54 ketone/hemiacetal, α/β = 63:37) in 37–45 % yield. Previous reports on the deoxycyanation of the benzyl-protected hemiacetal provided great insight for the final step of our route.[10] As a consequence of the neighboring acetoxy groups, however, intermediate **7** showed significantly lower reactivity. As a result, we substituted the original mixture of TfOH/TMSOTf with the even stronger Brønsted acid $HNTf_2$, which generated the active Lewis acid TMS-NTf_2 in situ upon treatment with TMSCN. In addition, reducing the



Scheme 3. Selective synthesis of both α- and β-*C*-glycosides by variation of the cyclization temperature.



Scheme 4. Benzylic C–H oxidation and diastereoselective deoxycyanation of peracetylated ribonucleoside α-6.

amount of TMSCN prevents further reaction of the product (see Supporting Information, Table S3) and an overnight reaction at −40 °C delivered the peracetylated cyanation product in 84 % yield and with good diastereoselectivity (α/β = 87:13). Notably, GS-441524 precipitated as a single stereoisomer in 81 % yield, 68 % from hemiacetal **7** during the subsequent methanolysis.

Overall, this approach greatly improves access to the target compound in just three steps requiring purification and in a total yield of 15–18 % from D-ribose; in contrast the existing process delivers GS-441524 in 7 steps (longest linear sequence) and 12 % yield (see Supporting Information, p. 45).

We have designed and developed a more practical and efficient formal synthesis of Remdesivir starting from free D-ribose. Our route features a novel and completely stereoselective nucleophilic addition of (hetero)arenes to carbohydrates without pre-installation of any protecting or activating groups. The process delivers the linear products through silylium catalysis diastereoselectively as a result of convergent silylation towards the TMS-protected β-ribopyranose and -furanose prior to the C–C bond formation. The anomeric configuration of the *C*-nucleoside is tuned simply by means of thermodynamic control during the acid-mediated cyclization. Benzylic C–H oxidation followed by deoxycyanation indeed streamlines the existing chemical synthesis of GS-441524 from D-ribose and the artificial nucleobase.

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Data Availability Statement

The data that support the findings of this study are openly available in ChemRxiv at https://doi.org/10.33774/chemrxiv-2021-889ms.

Keywords: Glycosylation · *C*-glycosides · Silylium catalysis · Remdesivir

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