Synthesis of Rare Sugar Isomers through Site-Selective Epimerization

Nature **2020**, *578*, 403-408

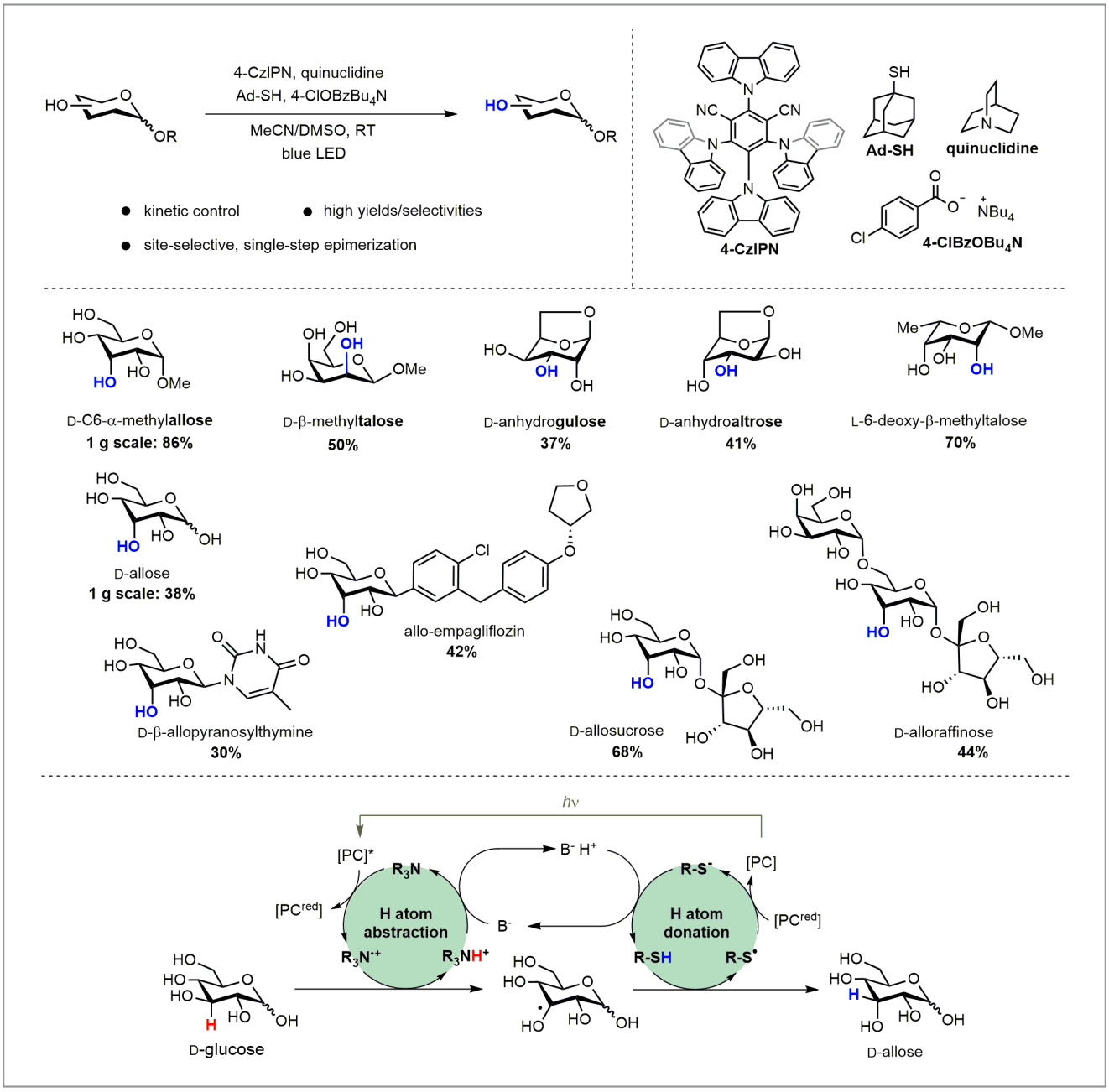
Rare sugars (e.g. D-allose, D-gulose, D-talose, L-glucose) feature prominently in glycosylated natural products and find important applications in the pharmaceutical, cosmetic, and food industries. Current strategies for the synthesis of rare sugars from biomass carbohydrates (e.g. D-glucose, D-galactose, D-xylose, L-arabinose, sucrose) remain very limited, and often involve chemical or enzymatic isomerizations resulting in intractable thermodynamic product mixtures. Recent groundbreaking work from the group of Professor Alison Wendlandt from the Massachusetts Institute of Technology (Cambridge, USA) developed and validated a dual catalyst system capable of promoting a highly site-selective epimerization of secondary alcohols in a kinetically controlled manner, and ultimately transforms naturally abundant sugars into their rare counterparts. "Synthetically, the product yields through this single-step epimerization reaction exceed almost all the other isomerization yields reported thus far," explained Professor Wendlandt, who continued: "Mechanistically, this transformation is realized through the sequential action of a hydrogen atom abstractor (quinuclidine radical cation) followed by a hydrogen atom donor (alkyl thiols), employing photochemical energy as the thermochemical driving force to reach this 'out-of-equilibrium' process. As a result, the consecutive C–H bond breaking and forming protocol represents a significant conceptual advancement."

The system is highly selective and works for a broad range of substrates, including completely unprotected monosaccharides (such as D-glucose, D-2-deoxyglucose, and L-fucose), polysaccharides, and other glycans. "In this work we also shed some light onto the underlying catalytic mechanism by carrying out a series of detailed mechanistic studies," said Professor Wendlandt. Nevertheless, the group is very keen to uncover the origin of the site-selectivity and diastereoselectivity, which remains elusive. "In parallel with the mechanistic elucidation aspect, we are equally interested in engineering different catalytic systems to epimerize other sites, so that we can streamline the synthesis of rare sugars not yet accessed by catalytic methods, including our newly developed protocol," remarked Professor Wendlandt, continuing: "For instance, the C5-epimerization of D-glucose would provide an access to D-idose, the only one of the five rare aldohexose isomers we have not achieved yet. In addition, we are trying to expand the current methodology beyond the synthesis of rare sugars and apply the selective C–H bond breaking and forming protocol to common organic molecules to selectively manipulate these stereogenic centers."

The direct, selective conversion of one completely unprotected sugar into another constitutes a 'dream reaction' according to Professor Wendlandt, who said: "Taking into account the simplicity of key factors such as reaction setup, ready accessibility of catalysts, as well as the high-yielding output of rare sugar products, this conceptually new method would circumvent the conventional lengthy synthetic route to rare sugars, simultaneously allowing to save time, energy, and resources. As both unprotected sugars and more complex glycans, such as a pyranose nucleotide, can serve as suitable reactants, this is a clear indication of the method's vast potential for biomass conversion and use in medicinal/pharmaceutical chemistry."

Professor Wendlandt pointed out that during the development of this project, several challenges in product identification and purification that are unique to carbohydrate chemistry had to be addressed. Firstly, the authors found that the paucity of full characterization data in the reported literature was a major hurdle for product identification. "Some rare sugars synthesized in our paper had not been reported before, while reports of other sugars were scattered in the literature, such as allo-sucrose which was synthesized and reported back in 1980," said Professor Wendlandt. Some data was key in helping the group confirm the identity of a sugar prior to full characterization, first and foremost ^{13}C NMR spectra. "Unsurprisingly many ^{1}H peaks of a starting material, sucrose, match closely to our observed product, allo-sucrose. Luckily, the ^{13}C NMR peaks were distinct enough for us to confirm an initial 'hit'," said Professor Wendlandt.

A second major challenge was product separation, which was quite difficult due to the high polarity and structural similarity to their parent reactants – especially in the cases of completely unprotected monosaccharides, oligosaccharides, and the pyranonucleoside. "In those cases where no separation could be achieved using classical silica gel chromatography, we had to turn to special amine-functionalized silica or ion-exchange chromatography with a self-prepared Ca^{2+} form of resin," explained Professor Wendlandt. She continued: "Un-

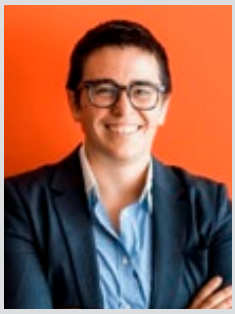


Scheme 1 Synthetic strategy, scope, and proposed mechanism

fortunately, these methods have no 'test scale', such as TLC to regular silica gel chromatography, leaving us blind in our initial purification attempts."

Glycans exhibit diverse physiological functions, ranging from energy storage and structure integrity to cell signaling and the regulation of intracellular processes. "In contrast to the biomass-derived monosaccharides, there are hundreds of distinct rare monosaccharides that are not readily accessible, thus limiting the scientific community's ability to explore the functions of the full glycan library," said Professor Wendlandt, who concluded: "We hope this effective and user-friendly synthetic protocol will change this situation."

About the authors



Prof. A. E. Wendlandt

Alison E. Wendlandt is currently the Cecil and Ida Green Career Development Assistant Professor in the Department of Chemistry at the Massachusetts Institute of Technology (USA). She was an undergraduate at the University of Chicago (USA) and carried out her PhD research at the University of Wisconsin – Madison (USA) under the supervision of Prof. Shannon S. Stahl. In 2015, Alison moved to Harvard University (USA), where she was an NIH Ruth Kirschstein Postdoctoral Fellow in the laboratory of Prof. Eric N. Jacobsen. She began her independent career at MIT in 2018.

Dr. Y. Wang

Yong Wang came from a beautiful city, Shaoxing, in Zhejiang province, China. He obtained both his B.S. (2009, advisor: Xiaonian Li) and M.S. (2012, advisors: Guofu Zhang and Chengrong Ding) degrees from Zhejiang University of Technology (P.R. of China). In 2013, he moved to the USA for his Ph.D. studies, working with Prof. X. Peter Zhang on the utilization of sulfonylhydrazones as aryl and alkyl diazo surrogates for asymmetric radical cyclopropanation and C–H alkylation via Co(II)-based metalloradical catalysis, and graduated from Boston College (USA) in 2018. He is currently working as a postdoctoral fellow in Prof. Alison Wendlandt's laboratory at Massachusetts Institute of Technology (USA), exploring novel organic transformations of carbohydrates.

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