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Carbohydrates as versatile platforms in the construction of small compound libraries*

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Abstract: This paper presents our recent results concerning the use of carbohydrates as cheap, chiral, and enantiopure starting materials in the construction of a variety of densely functionalized molecules. The compatibility of ring-closing metathesis with standard carbohydrate chemistry is demonstrated in the synthesis of new stereoisomers of deoxystreptamine and neamine—important building blocks for the generation of synthetic aminoglycosides with potential antibacterial activity. Ring-closing metathesis is also a key step in the rapid synthesis of new indolizidines and quinolizidines, and in a new solid-phase assisted carbohydrate-based combinatorial scaffold strategy. Further, some of our latest results in the conformational analysis of sugar amino acid-based peptide mimetics and in the development of a novel Ugi-type three-component reaction of sugar-derived azido-aldehydes are discussed.

Keywords: carbohydrates; deoxystreptamine; neamine; aminoglycosides; antibacterial; indolizidines; quinolizidines; ring-closing metathesis; combinatorial platforms; Ugi 3-CR.

INTRODUCTION

Monosaccharides have long been recognized as versatile building blocks in synthetic organic chemistry. They are readily available from natural sources and are characterized by a wealth of functional, conformational, and stereochemical variations. They are widely used in natural product synthesis and in the development of compounds with desirable biological or therapeutical properties. Research efforts over the past decades have accumulated a wealth of information, enabling the manipulation of each individual functional group in a given monosaccharide building block almost at will.

The chemical transformation of carbohydrates into compounds with added value is a well-established strategy in organic synthesis, with numerous literature examples spanning more than a century. The transformation of D-mannose **2** into D-*manno*-heptose **2** (Scheme 1), reported by Fischer in 1890 [1], can be viewed as one of the first examples of natural product synthesis. In fact, this example is preceded by an earlier report by Fischer in that year [2], comprising the partial oxidation of D-mannitol **1** to provide D-mannose **2**, which at that time had not been isolated from nature. Obviously, the number of techniques and potential transformations available to the synthetic organic chemist has risen dramatically over the years. However, the general strategy for the transformation of a carbohydrate in a desired compound, namely, addressing the desired functionality selectively where possible and relying on

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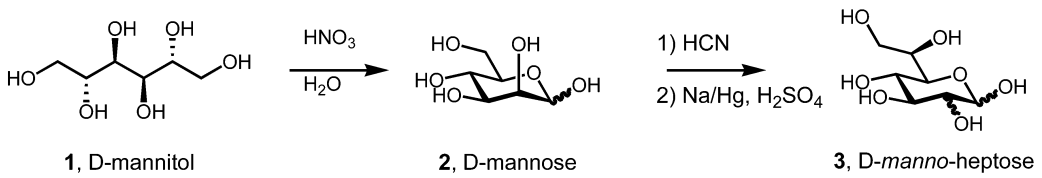
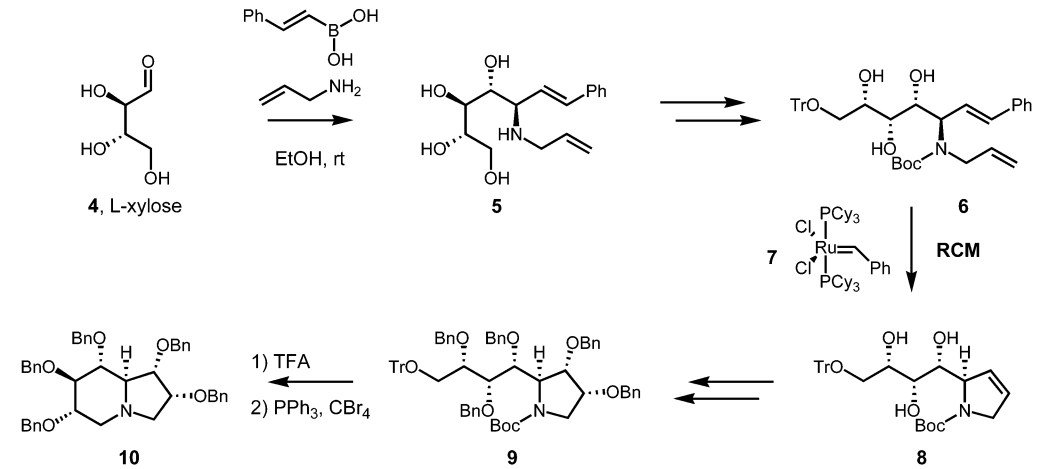


Scheme 1 Fischer's synthesis of D-mannose and D-*manno*-heptose.

protective group manipulations otherwise has remained remarkably unchanged. This is well illustrated by the recent synthesis, by Pyne and coworkers [3], of the polyhydroxylated indolizidine **10**, the structure of which (in unprotected form) was incorrectly assigned [4] to the recently isolated alkaloid uniflorine A (Scheme 2). Key steps in the synthesis comprise a stereoselective Petasis reaction of unprotected L-lyxose **4** and a ring-closing metathesis (RCM)-mediated construction of partially protected pyrrolidine **8**.



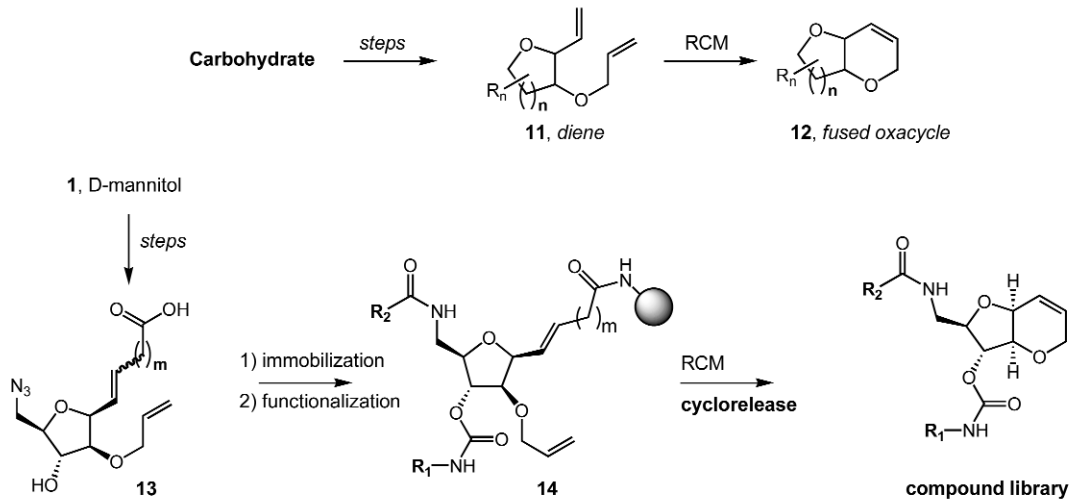
Scheme 2 Pyne's synthesis of (putative) uniflorine A.

RCM-based transformations of carbohydrate derivatives form a long-standing research objective in our group and will cover the main part of the results presented in this paper. Recent applications that will be discussed here include the generation of epimeric streptamine derivatives, a rapid preparation of diverse indolizidines and quinolizidines, and the development of a conformationally constrained pyranofuran scaffold. The remainder of this paper will present some recent advances in the use of carbohydrates as peptidomimetic scaffolds, and in the implementation of carbohydrate-derived azido-aldehydes in a new Ugi-type three-component reaction, which we term the Staudinger/aza-Wittig/Ugi, or SAWU reaction.

FURANOPYRAN COMBINATORIAL SCAFFOLD

The ease with which alkene- and alkyne-substituents are introduced at various positions onto a carbohydrate core, combined with the broad functional group compatibility of the Grubbs-type RCM catalysts, has spawned a wealth of strategies for the transformation of carbohydrates into functionalized carba- and heterocycles [5]. In the last decade, we have contributed to this area of research by the transformation of monosaccharides into enantiopure indolizidine and quinolizidine alkaloids [6], cyclopentitols [7], cyclitols [8], spiroketal derivatives [9], oxepanes [10], and fused oxacycles [11]. With respect

to the latter, the general strategy comprises the introduction of a set of ethylene functionalities at vicinal carbon atoms, as in **11**, followed by RCM to give **12** (Scheme 3). Depending on the geometry of the starting carbohydrate, both *cis*- and *trans*-fused oxacycles can be readily obtained. Control over ring size is provided by both the starting material (that is, a furanose or a pyranose) and the distance between the alkene moieties that participate in the RCM.



Scheme 3 A carbohydrate-based pyranofuran combinatorial scaffold.

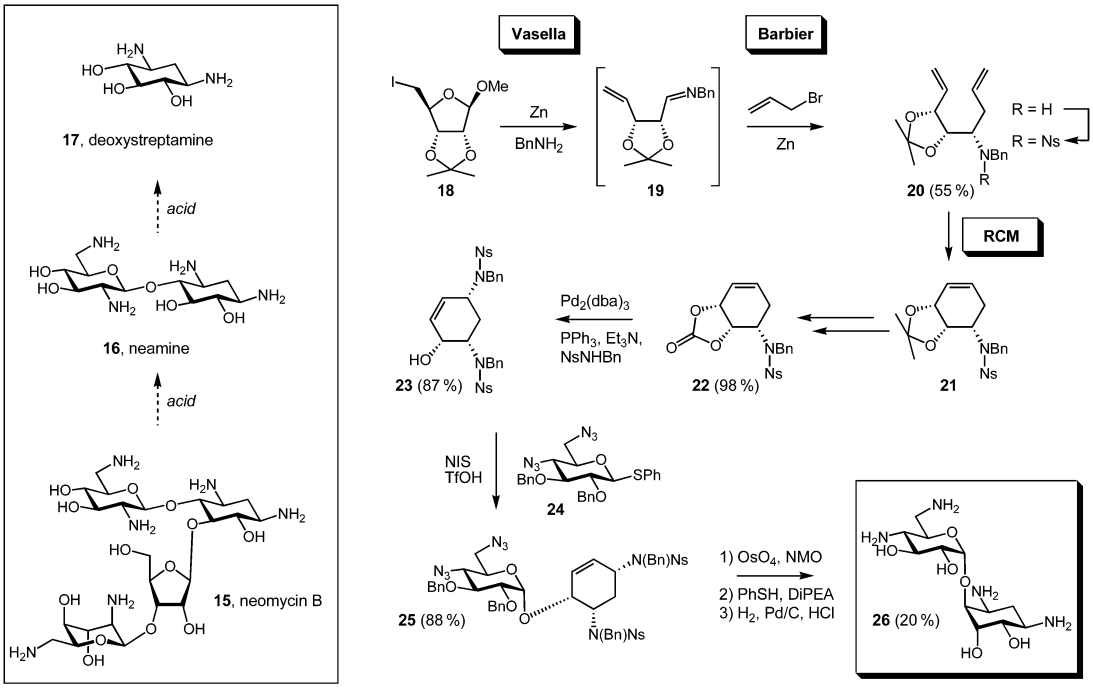
Next to being important structural elements present in a variety of natural products such as the marine toxins brevetoxin B and ciguatoxin, the presence of an annulated ring onto a carbohydrate core reduces to a large extent its conformational freedom. Further, although two functionalities are sacrificed to enable installation of the fused ring, ample functionalities remain for ensuing derivatization. These observations made us realize that carbohydrate-based fused oxacycles might well be useful templates in combinatorial chemistry. The synthetic validity of this concept is demonstrated as follows [12]. D-mannitol (**1**) is transformed into functionalized tetrahydrofuran derivative **13**. Immobilization through condensation of the acid with an amine-functionalized resin is followed by reaction of the secondary alcohol with a set of isocyanates, reduction of the azide, and subsequent acylation of the azide with a set of acid chlorides. RCM-mediated cyclorelease now affords a small compound library of 9 compounds **15** with overall yields after purification, and based on **13**, ranging from 74 to 99 %.

RAPID ENTRY TO ENANTIOMERIC STREPTAMINE ANALOGS

Aminoglycoside antibiotics are a broad class of oligosaccharide derivatives endowed with multiple amine groups. The antibacterial activity of aminoglycosides is based on electrostatic interaction between the amine groups that are protonated under physiological conditions, and the phosphodiester linkages present in bacterial ribosomal RNA. The exact positioning of the cationic residues that stems from the three-dimensional structure of the aminoglycoside is thought to contribute heavily to the antibacterial activity of aminoglycoside antibiotics.

Many research groups are actively involved in the development of synthetic aminoglycosides. Most of these strategies are based on the degradation of natural aminoglycosides. For instance, careful treatment of neomycin B (**15**) with acid results in the formation of neamine **16**, whereas, upon prolonged acid treatment, the remaining interglycosidic linkage is hydrolyzed and deoxystreptamine (**17**) is obtained. Synthetic aminoglycosides are normally obtained by modification of either **16** or **17**. An obvious drawback of this procedure is the lack of control over stereodiversity in the synthetic analogs.

Indeed, most aminoglycosides from natural sources contain either the neamine (**16**) or deoxystreptamine (**17**) motif. Diastereomeric 1,3-diaminocyclitol derivatives can, therefore, be obtained only through organic synthesis. Our synthetic strategy toward this goal is inspired by recent work from Madsen and coworkers [13,14], who demonstrated that zinc-mediated Vasella fragmentation of a 5-iodofuranoside (as in **18**) in the presence of benzylamine leads to in situ trapment of the resulting aldehyde to provide the corresponding imine **19**. Ensuing addition of allyl bromide, still in the same reaction vessel, leads after in situ formation of the Barbier-type allyl zinc reagent, to nucleophilic addition to the imine, furnishing octadiene **20** in good yield and stereoselectivity. At this stage, the secondary amine was protected with the *ortho*-nitrobenzenesulfonyl (Ns) group [15], after which RCM gave **21**. The *cis*-1,3-diamine functionality is now installed after formation of cyclic carbonate **22** and Pd(0)-catalyzed allylic displacement with an appropriately nucleophilic amine derivative (here represented by BnNHNs; other, more functionalized nucleophilic amines work equally well). Glycosylation of the allylic alcohol in **23** with donor phenylthioglucoside **24** under the agency of NIS and triflic acid provides disaccharide **25**, which, upon dihydoxylation of the internal alkene and ensuing deprotection, is transformed into neamine analog **26** [16,17].

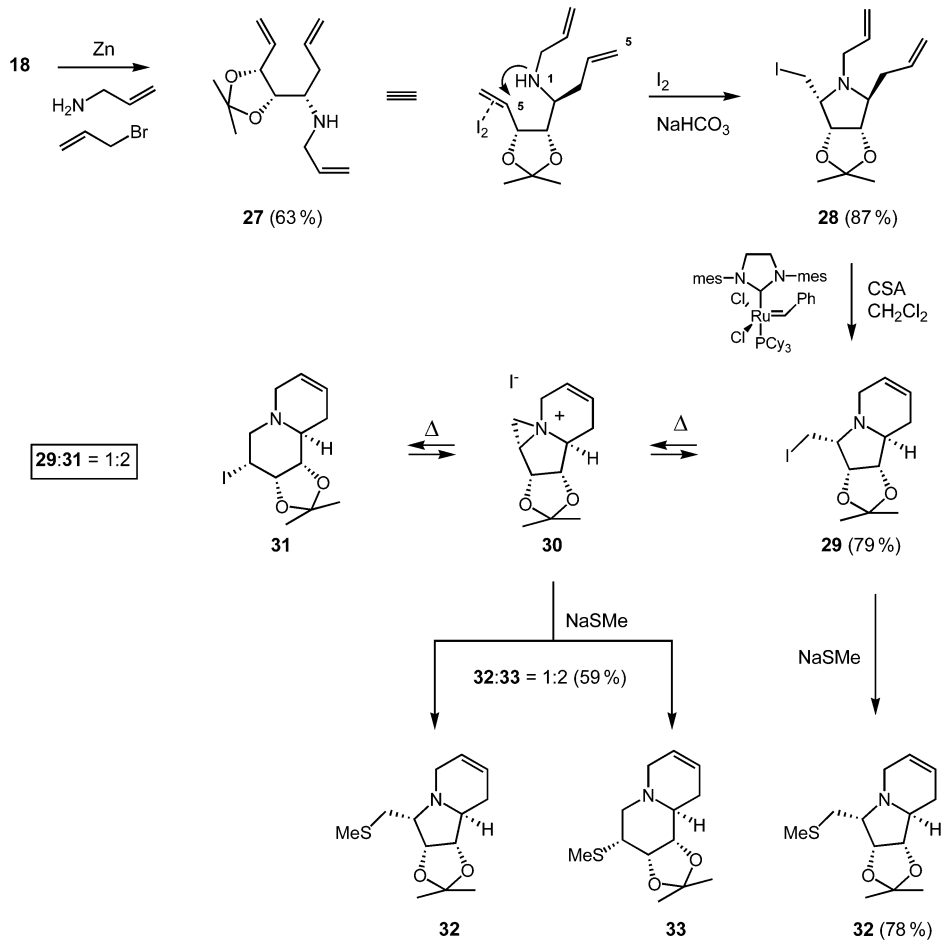


Scheme 4 Vasella–Barbier–RCM approach to the synthesis of neamine analogs.

EASY ACCESS TO INDOLIZIDINES AND QUINOLIZIDINES

An extention of the Vasella–Barbier–RCM methodology, developed in our laboratory, entails replacement of benzylamine in the one-pot domino process (**18** to **20**, see Scheme 4) with allylamine [18]. Also in this case, the sequence of reactions proceeds with high efficiency and good stereoselectivity, to provide chiral triene **27** from 5-iodoriboside **18** (Scheme 5).

Treatment of **27** with iodine and base now resulted in selective 5-*exo*-trig [19] iodoamination to give pyrrolidine **28** as the single diastereoisomer, RCM of which afforded indolizidine **29**. At this stage, we observed that, upon heating, indolizidine **29** rearranges into quinolizidine **31** in an eventual equilibrium of 1:2. Both compounds can be isolated, and exposure of either to elevated temperature results in



Scheme 5 A facile synthesis of chiral functionalized indolizidines and quinolizidines.

the same compound mixture. The presence of intermediate aziridinium ion **30** was corroborated by treatment of an NMR sample in $CDCl_3$ with silver perchlorate and comparison of both proton and ^{13}C spectra with those of **29**. A significant downfield shift of essentially all protons indicates the presence of an ammonium ion, as in **30**. Starting from **29**, functionalized indolizidines and quinolizidines can be obtained in two ways. We reacted **29** with either sodium methylthiolate, sodium azide, or cesium acetate. Soft nucleophiles, such as sodium methylthiolate, give exclusively S_N2 substitution, leading to the corresponding indolizidine **32**. With harder nucleophiles, aziridium ion formation occurs as a competing event, with indolizidine and quinolizidine product mixtures as a result (not shown here). Deliberate formation of the aziridinium ion prior to addition of the nucleophile results in different product distribution, as is demonstrated here for the formation of indolizidine **32** and quinolizidine **33** after addition of NaSMe to **30**.

UNUSUAL TURN INDUCED BY A FURANOID SUGAR AMINO ACID

Sugar amino acids (SAAs) are defined as carbohydrate-derived structures that feature both a carboxylic acid and an amine (Fig. 1). Some examples of SAAs, such as neuraminic acid **34**, are found in nature. A multitude of synthetic analogs have appeared in the literature since the pioneering work of Kessler and coworkers [20–22] on the glucose-derived SAA **35**. SAAs, with their inherent functionalities avail-

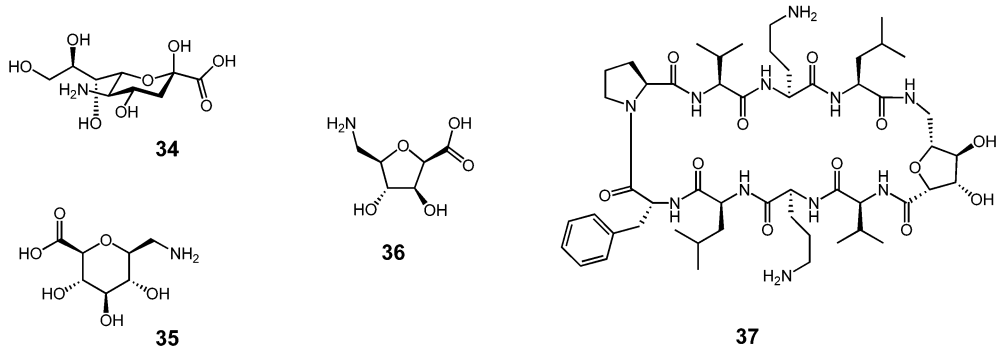


Fig. 1 Sugar amino acids: carbohydrate-peptides hybrid compounds.

able for modification and their propensity to adopt or induce specific secondary structures, are now widely regarded as useful tools in the generation of both oligosaccharide- and oligopeptide-mimetics.

Our interest in the field of SAA chemistry is not only in the synthesis of various structural and functional analogs [23–25], but also in the detailed study of the structural consequences of the incorporation of SAAs in peptide sequences. We have selected the natural antibiotic gramicidin S (GS), which has the sequence cyclo(Leu-Orn-Val-Pro-^{D}Phe)$_2$ as a model peptide. The amphiphatic nature of GS is the result of its β-sheet structure, with 4 hydrogen bonds between the Leu, Val, and Orn residues and the two Pro-^{D}Phe stretches in a type II' β-turn. We have prepared a series of GS analogs in which either one or both β-turn regions are replaced by SAA derivatives and are in the process of studying in detail the resulting secondary structures. In the course of our studies, we found an unexpected turn structure in GS analog **37**, featuring a single furanoid SAA dipeptide isoster **36** [26]. This structure (elucidated by X-ray and NMR studies) is caused by the existence of a hydrogen bond between the SAA-NH and the remaining 3'-OH on the furan ring (Fig. 2). This causes the amide linkage between the SAA and the flanking leucine residue to flip, with the carbonyl now outside the β-sheet, instead of contributing to the stabilization of the structure through hydrogen bonding.

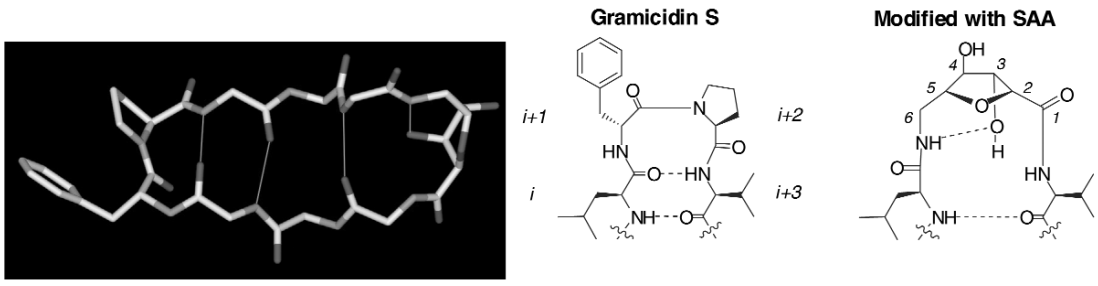
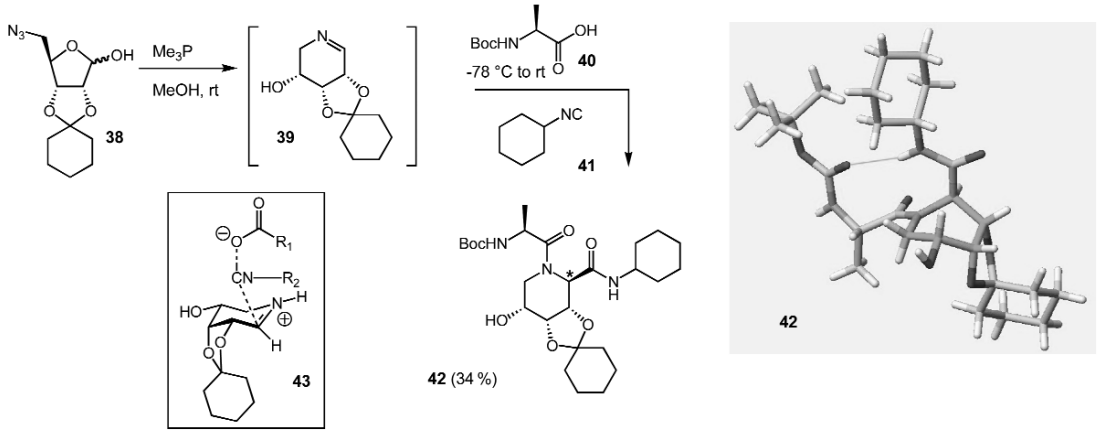


Fig. 2 Turn structures of native and modified GS (left) and X-ray derived structure of GS analog **37** (far right).

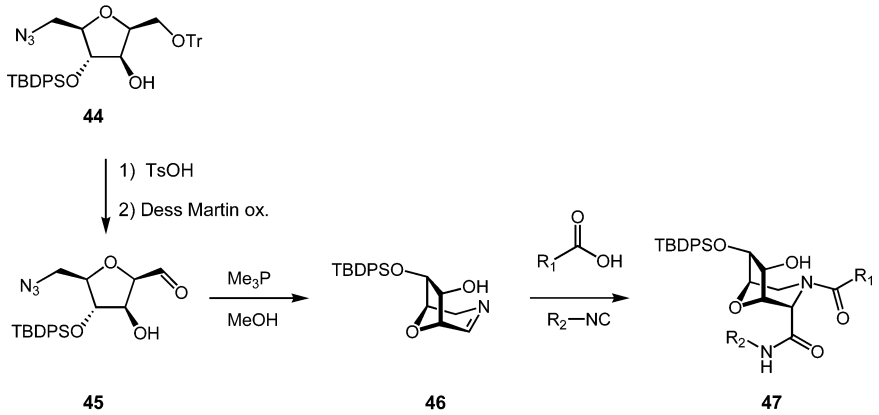
STAUDINGER-AZA-WITTIG-UGI: A NEW THREE-COMPONENT REACTION

The Ugi 4-component reaction (Ugi-4CR) comprises the condensation of an amine, an aldehyde, an isocyanide, and a carboxylic acid to form a bisamide with all the substituents of the four starting components embedded in the final product. The reaction proceeds through the initial condensation of the aldehyde and amine components to the corresponding imine. Treatment of a preformed imine with an acid and an isonitrile entails the Ugi-3CR; both multicomponent reactions are now widely applied in combinatorial chemistry [27].

Since imines are intrinsically unstable, any set of conditions that enables in situ imine formation without interfering with the ensuing Ugi condensation with the remaining two components should be a valuable addition to the multicomponent reaction repertoire. The Staudinger-aza-Wittig reaction, transforming an azide and an aldehyde to an imine under the influence of a phosphine, meets these criteria. The realization that azides are readily introduced into carbohydrate structures, and that aldehydes are an inherent feature of aldose carbohydrates, led us to study the feasibility of combining Staudinger-aza-Wittig on a carbohydrate-derived azido-aldehyde, followed by Ugi-3CR condensation of the resulting in situ formed cyclic imine with a set of carboxylic acids and isonitriles (Scheme 6) [28]. Reaction of protected 5-azido-ribose **38** with trimethylphosphine afforded cyclic imine **39** and trimethylphosphinoxide as the sole side product. As soon as nitrogen gas evolution ceased, the reaction mixture was brought to –78 °C and Boc-alanine **40** and cyclohexyl isocyanide **41** were added, yielding substituted piperidine **42** as the sole product. The formation of a single diastereoisomer, the nature of which was assigned by perusal of the crystal structure of **42** (Scheme 6, right), may be explained by envisioning transition state **43**. By varying the isocyanide- and carboxylic-acid moieties, we prepared a small library of 12 piperidines, all with absolute stereoselectivity, and with yields after purification ranging from 22 to 78 % (Table 1). Finally, the SAWU strategy can be readily transposed on other carbohydrate-derived azidoaldehydes, as is evidenced by the generation of bridged morpholines **47** from anhydroglycoside **45** (Scheme 7).

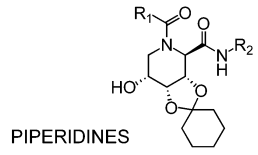


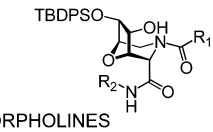
Scheme 6 SAWU-3CR toward chiral functionalized piperidines.



Scheme 7 SAWU-3CR toward bridged morpholines.

Table 1 Chiral functionalized piperidines and bridged morpholines prepared by SAWU-3CR: yields and functionalities.





R_2 \ R_1	H		BocHN	
	78 %	62 %	54 %	51 %
	51 %	36 %	34 %	51 %
	24 %	26 %	25 %	22 %

R_2 \ R_1	H		
	51 %	61 %	45 %
	40 %	53 %	36 %

CONCLUSION

The versatility of the use of monosaccharide building blocks in organic synthesis is demonstrated in this paper in a variety of applications, ranging from the synthesis of aminocyclitols and alkaloids to the design of combinatorial scaffolds, the development of a new carbohydrate-containing multicomponent reaction, and to the in-depth structural analysis of SAA-containing cyclic oligopeptides. Using only a limited number of monosaccharide building blocks (all compounds presented here are derived from either D-mannitol or D-ribose), a wide variety of structurally and functionally diverse compounds have been prepared. The large number of cheap carbohydrate building blocks available in their many disguises makes one realize that, even with the select number of synthetic manipulations as presented here, the number of imaginary structures is almost limitless.

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