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# Multicomponent Cascade Reactions of Unprotected Carbohydrates and Amino Acids

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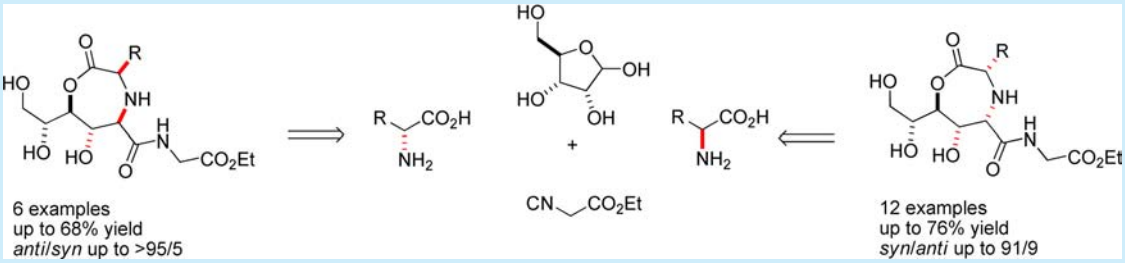
Supporting Information

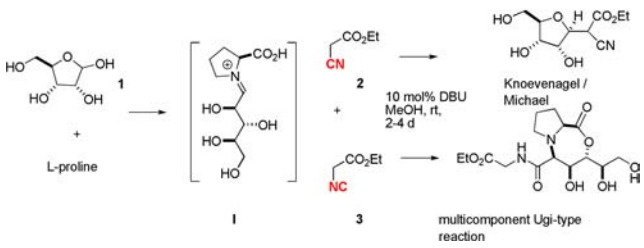



**ABSTRACT:** Herein an operationally simple multicomponent reaction of unprotected carbohydrates with amino acids and isonitriles is presented. By the extension of this Ugi-type reaction to an unprotected disaccharide a novel glycopeptide structure was accessible.

In recent years our laboratory has been concerned with the utilization of unprotected carbohydrates as carbonyl compounds in several organocatalyzed transformations. As a result of that investigation, organocatalyzed glycosylations of unprotected and unactivated carbohydrates can be realized.[1] When used with 1,3-dicarbonyl compounds in amine-catalyzed cascade reactions, chain-elongated carbohydrates[2] or C-glycosides of unprotected carbohydrates are accessible.[3] A small tweaking of these operationally simple protocols breaks a further new cascade channel. When used with isocyanides instead of cyanoacetates in reactions with unprotected carbohydrates, the incorporation of proline is observed. As a result, the selective formation of seven-membered lactones was noticed. This sharp difference is demonstrated in Scheme 1.

It is assumed that both reactions start with the formation of the imine of the acyclic structure of ribose and proline (structure **I**, Scheme 1). After this activation step the cyanoacetate **2** dictates a Knoevenagel/Michael cascade. In contrast, by the application of isocyanoacetate **3** a nucleophilic addition of the carbon atom of the isocyano group and a rearrangement reaction are observed. A subsequent optimization of these initial findings revealed a broad application of this multicomponent cascade.

**Scheme 1. Comparison between Organocatalyzed Reactions of Ribose with Ethyl Cyanoacetate 2 and Isocyanoacetate 3 in the Presence of L-Proline**




This Ugi-type reaction works without any catalyst or reagent at room temperature (rt, 2−4 days). To shorten reaction times and increase yields, working in boiling methanol and catalytic amounts of tertiary amines gave successful results. Moreover, use of an excess of carbohydrate was found to increase the yields. These reaction conditions do not influence the diastereoselectivity of the reaction but increase the yields in a much shorter reaction time.

To test the general application of this transformation, we expanded these preliminary findings to reactions of D-ribose with ethyl isocyanoacetate **3** and a wide range of proteinogenic amino acids (Scheme 2). During these investigations the isoelectric point of the amino acid proved to be essential. This reaction works best with neutral amino acids. When used with acidic amino acids (aspartic acid or glutamic acid) or basic amino acids (histidine, arginine, or lysine) a reaction was not observed under these conditions. By application of L-configured amino acids, 1,2-*syn*-configured seven-membered lactones **4**−**15** were isolated as major products with moderate to high degrees of diastereoselectivity. The diastereoselectivity observed depends on the steric demand of the amino acids deployed. The highest degrees of diastereoselectivity result from the use of valine or isoleucine (**7** and **8**, *syn*/*anti*: 91/9). It is presumed that this high selectivity is caused by the *β*-branching of valine or isoleucine. Hence, incorporating unbranched amino acids should lower the selectivity ($R^1$ = H, Scheme 2). These considerations were supported by the results

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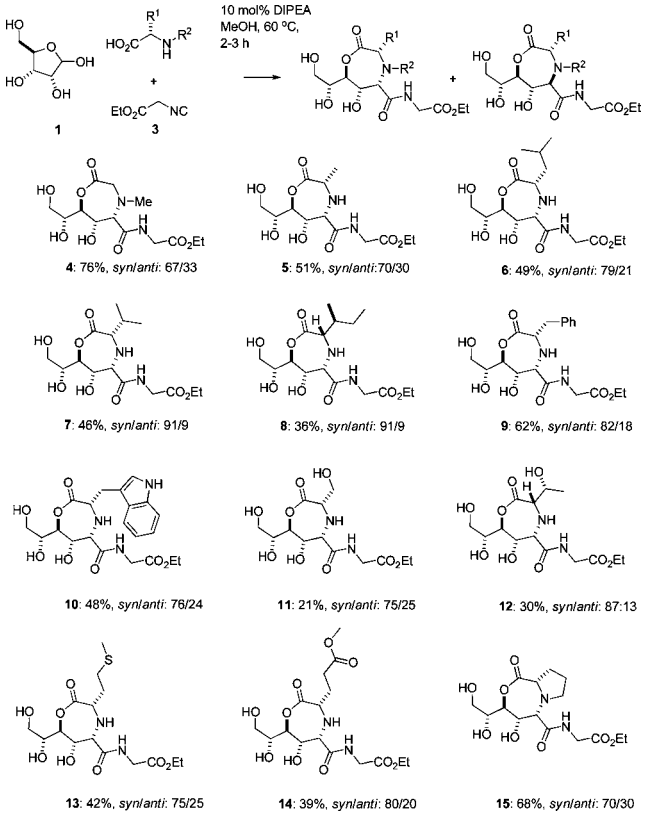
**Scheme 2. Three-Component Ugi Reactions of D-Ribose with L-Amino Acids and Ethyl Isocyanoacetate**



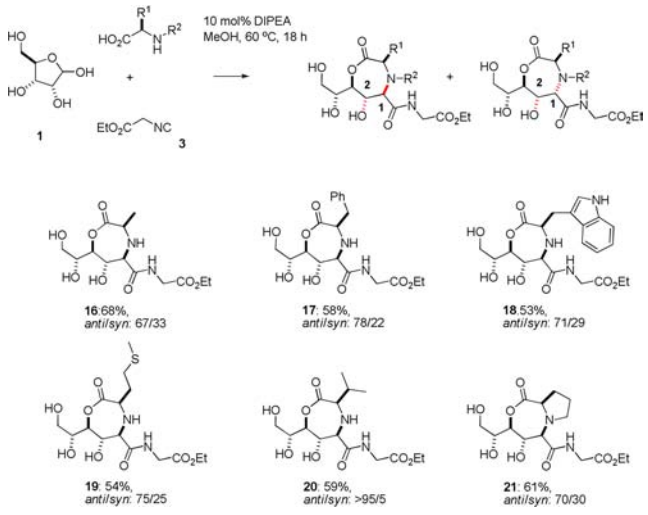

of the reactions with sarcosine. Product **4** was found with a ratio of 67/33 (*syn*/*anti*), though in good yield (76%). The results of these studies are depicted in Scheme 2.

The observation of different diastereoselectivities with L-amino acids with varying steric demand in the side chain suggests that the configuration of the amino acid influences the installation of configuration at the anomeric carbon atom. Thus, when used with naturally configured L-amino acids, 1,2-*syn* configured products were isolated. In contrast, by applying D-configured amino acids, 1,2-*anti* configured products were observed as major products (Scheme 3).

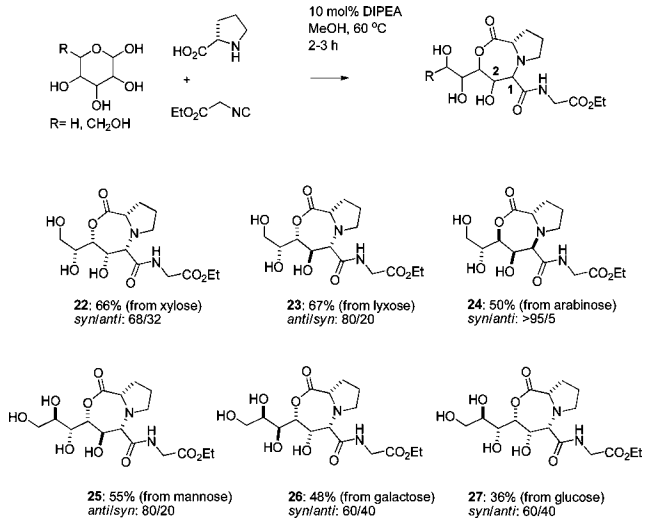
In a further series, we tested several different pentoses and hexoses in these multicomponent reactions with L-proline and ethyl isocyanoacetate **3**. Seemingly independent of the configuration of the amino acids utilized, the configuration of the deployed carbohydrates dictates the installation of the configuration at the carbon atom C-1 of the former carbohydrates (former anomeric carbon atom). Thus, setting the configuration at C-1 induces formation of the relative 1,2-configuration of the products **22**−**27** (Scheme 4). Support for these considerations is given by the results of reactions with deoxyribose. In these transformations, complex and unselective mixtures of all possible stereoisomers were detected. These results impressively demonstrate the importance of a defined configuration for the hydroxy groups at C-2 and C-3 in determining the configurative outcome of this multicomponent reaction.

To evaluate the influence of a carbohydrate and an amino acid on the stereoselective course of this multicomponent reaction, different D-configured pentoses were reacted with both D- and L-proline in the presence of *p*-toluenesulfonyl-

**Scheme 3. Three-Component Ugi Reactions of D-Ribose with D-Amino Acids and Ethyl Isocyanoacetate**




**Scheme 4. Reactions of Pentoses and Hexoses with L-Proline and Ethyl Isocyanoacetate**




methyl isocyanide **28**.[4] The results of these investigations are depicted in Scheme 5. They reveal a correlation between formation of the 1,2-*syn*- or 1,2-*anti*-configured product with the absolute and relative configuration of the carbohydrate and the configuration of the amino acids employed.

In reactions with 2,3-*anti* configured pentoses (ribose or lyxose), the configurative outcome at the C-1 atom is controlled by the configuration of L- or D-proline. The reaction of D-ribose with L-proline yields 1,2-*syn*-configured product **29** as the major diastereoisomer, whereas by reaction with D-proline the 1,2-*anti*-configured lactone **33** is identified as the major product. As the 2,3-*anti*-configuration of lyxose is inverted at C-2 and C-3 (in comparison with ribose), the reactions with L- or D-proline yield the same absolute configuration at C-1 (in comparison with ribose), but an inverted relative configuration for C-1 and C-2. Based on these results and the observed diastereoselectivities, a mismatched situation for *ribo*-**29**/*lyxo*-**35** and a matched case for *lyxo*-**31**/*ribo*-**33** can be discussed.

In contrast, the installation of the configuration at the former anomeric carbon atom is not influenced by the configuration of



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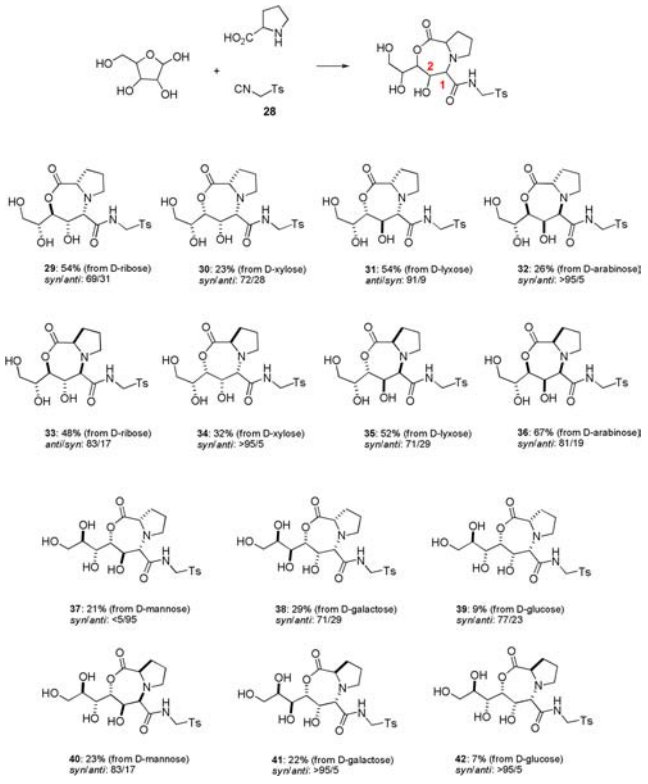
**Scheme 5. Multicomponent Reaction of D-Pentoses and Hexoses with D- or L-Proline**




the amino acid, when used with 2,3-*syn*-configured pentoses (arabinose or xylose). Thus, the configuration at C-1 cannot be controlled by the configuration of the amino acid. Extremely high degrees of relative *syn*-selectivity at C-1 and C-2 were observed. The extremely high diastereoselectivity in this series is solely influenced by the 2,3-*syn*-configuration of carbohydrate deployed.

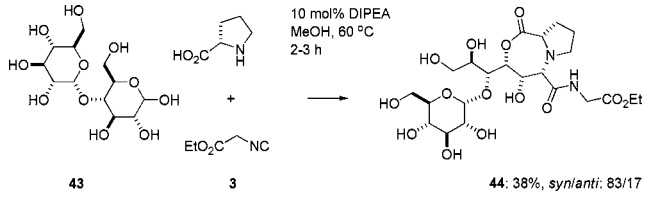
In both series, 2,3-*anti*- (ribose or lyxose) as well as 2,3-*syn*-configured carbohydrates (arabinose or xylose), a stereochemical trend for the existence of a matched or mismatched case is detected and can be discussed. However, the origin of the newly induced absolute and relative configuration is based on different modes and influences as discussed above.

In general, a mismatched case is observed if the absolute configuration of the carbon atom C-2 of the carbohydrate works in opposition to the configuration of the amino acid (**29**/**35** and **30**/**36**). In reactions where the absolute configuration of the amino acid and the configuration at C-2 of the deployed carbohydrates are the same, a matched case can be discussed (**32** /**34** and **31**/**33**).

This elaborated methodology should provide an easy access to peptide mimetics. To demonstrate the synthesis of a glycopeptide mimetic, we reacted maltose **43** as an example of the deployment of a disaccharide in these cascade reactions (Scheme 6). The expected lactone **44** was isolated in 38% yield after 3 h in methanol at reflux. This is comparable with that obtained in the reaction of glucose with L-proline and ethyl isocyanoacetate (**27**: 36%, Scheme 4). But an increase in *syn*-selectivity was detected (compare **27**: 60/40 with **44**: 83/17).

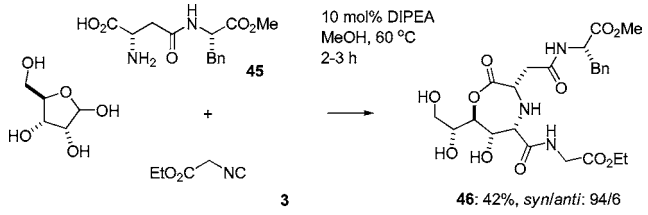
In a further experiment we demonstrated the utility of dipeptides in these Ugi-type reactions. To this end, we reacted *β*-aspartame **45** with ribose and ethyl isocyanoacetate **3**. The

**Scheme 6. Multicomponent Reaction of Maltose with L-Proline and Ethyl Isocyanoacetate**




expected lactone *syn*-**46** was isolated in 42% yield with high levels of *syn*-diastereoselectivity (Scheme 7).

**Scheme 7. Multicomponent Reaction of *β*-Aspartame and Ethyl Isocyanoacetate**




These multicomponent reactions are novel.[5] Protected carbohydrates have previously been used in Ugi-type reactions.[6] Sporadic examples of the deployment of unprotected carbohydrates in multicomponent reactions have also been reported for the synthesis of aniline and barbituric acid[7] and for the synthesis of fused pyrimidines.[8] Also, multicomponent reactions with protected[9] and unprotected amino acids[10] have been described in the literature.

Multicomponent Ugi-type reactions of unprotected carbohydrates with unprotected amino acids have not been reported previously.

In summary, we have developed an operationally simple protocol for performing a novel multicomponent cascade Ugi-type reaction. By optional deployment of unprotected carbohydrates and amino acids, high levels of stereoselectivities of defined configured carbohydrate mimetics[11] can be obtained. Thereby the configuration of the deployed carbohydrates and amino acids dictates the installation of configuration at the former anomeric carbon atom.[12]

## ■ ASSOCIATED CONTENT

### Supporting Information

Structure elucidations, characterization of compounds, proof of configuration, and copies of $^{1}$H NMR and $^{13}$C NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00887.

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### Notes

The authors declare no competing financial interest.



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(4) *p*-Toluenesulfonylmethyl isocyanide **28** was used in these reactions due to a better analysis of the stereoselectivity. The same results concerning yields as well as stereoselectivities were obtained upon comparing the results to those detected in reactions with ethyl isocyanoacetate **3**.

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