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Four into One: Organocatalyzed Stereoselective Conjugate Addition of Unprotected and Unactivated Carbohydrates

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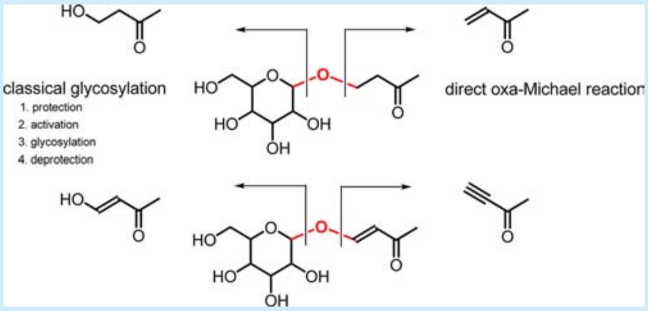
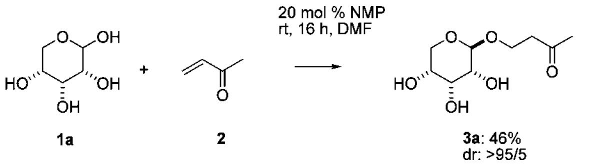
Supporting Information

ABSTRACT: This paper proposes a new and stereoselective access to glycosides. This operationally simple approach achieved via base-catalyzed conjugate additions of unprotected and unactivated carbohydrates to activated alkenes or alkynes is described.



In conjunction with our recently achieved glycosylation processes of unprotected and unactivated carbohydrates[1] we envisioned a glycosylation by a conjugate addition with unprotected carbohydrates. This idea has a serious background as we had already observed this transformation occurring in several organocatalyzed cascade reactions of unprotected carbohydrates. Based on a Knoevenagel/intramolecular oxa-Michael cascade, we formulated a protocol for the stereoselective synthesis of C-glycosides.[2] To verify a glycosylation by a conjugate addition with unprotected carbohydrates, we reacted ribose with methyl vinyl ketone in the presence of catalytic amounts of different bases in preliminary studies. First experiments that were carried out under the conditions we have elaborated for the Knoevenagel/oxa-Michael cascade of carbohydrates proved to be unsuccessful. After extensive optimization of the process,[3] however, we were able to realize a conjugate addition process. In reactions carried out in the presence of 20 mol % of *N*-methylpyrrolidine (NMP), we succeeded in isolating the unprotected riboside **3a** with 46% yield. Only the *β*-anomer was detected (dr >95/5), proving the reaction to be highly stereoselective. Reactions were carried out in DMF at room temperature (eq 1).



(1)

Furthermore, this transformation is also highly chemoselective. The Michael acceptor reacts only with the anomeric hydroxyl group of the carbohydrates deployed. Further conjugate additions with additional hydroxyl groups of carbohydrates were not detected. Finally, substantial amounts of acetylmethyldihydropyran were detected as a byproduct (dimer of the starting methyl vinyl ketone).[4]

Conjugate additions have been reported using common and typical alcohols as substrates in various different catalytic systems.[5] For an overview of this investigation, see ref 6. Recently, amine-catalyzed conjugate additions have been increasingly deployed in several useful and highly selective cascade reactions,[2,7] desymmetrization processes,[8] and epoxidation reactions.[9] In contrast to that, conjugate additions of carbohydrates, in particular, unprotected carbohydrates, are unknown so far.

To obtain more information on this conjugate addition process and expand on it, we tested several different carbohydrates in a subsequent series. Pentoses as well hexoses were reacted with methyl vinyl ketone under the optimized reaction conditions described above (eq 1). The results of this investigation are depicted in Schemes 1 and 2.

The glycosides were isolated with high degrees of stereoselectivity. The installation of configuration at the anomeric carbon appears to be dictated by the configuration at C-2 of the starting carbohydrates. On the basis of steric hindrance, a highly selective *trans*-glycosylation is detected. This observation holds true for both the conjugate additions of hexoses as well as pentoses.

Based on the success of these conjugate additions with methyl vinyl ketone, we next investigated activated terminal as well internal alkynes as substrates in these addition reactions. First experiments with ribose **1a** and ethyl propiolate **6** yielded a complex mixture of products, when the reaction conditions of the enone-series were used (20 mol % NMP, rt). After subsequent extensive optimization a general protocol was developed.[3] With a reduced reaction temperature of 0 °C, a double-conjugate

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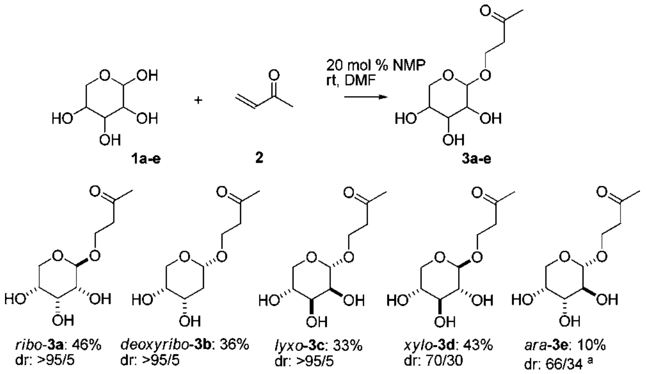
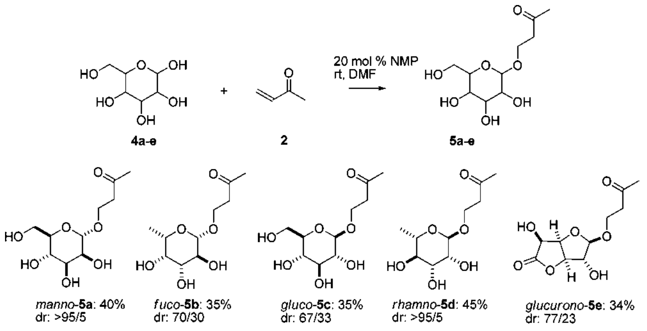
Scheme 1. Reactions of Pentoses with Methyl Vinyl Ketone



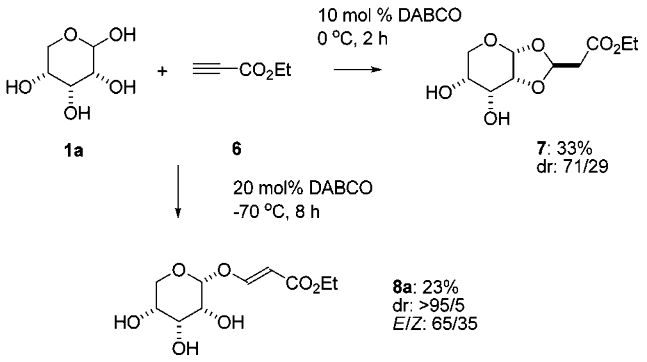
[a]The same results were obtained when used with L-arabinose; see ref 3.

Scheme 2. Reactions of Hexoses with Methyl Vinyl Ketone

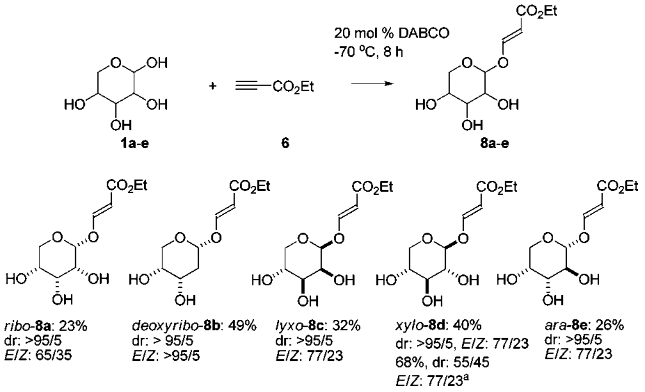


addition (dihydroalkoxylation) was observed. As a result, a mixture of diastereomeric acetals **7** was isolated (dr 70/30).[10] A clear and selective formation of the corresponding enol riboside **8a** was detected at −70 °C (Scheme 3). Under these conditions the riboside **8a** was observed as a single diastereoisomer at the anomeric carbon atom (dr: >95/5). An *E*/*Z*-ratio of 65/35 was detected for the double bond geometry, indicating the intermediate formation of allenyl enolates during the reaction.[11]

Scheme 3. DABCO-Catalyzed Conjugate Addition of Ribose to Ethyl Propiolate

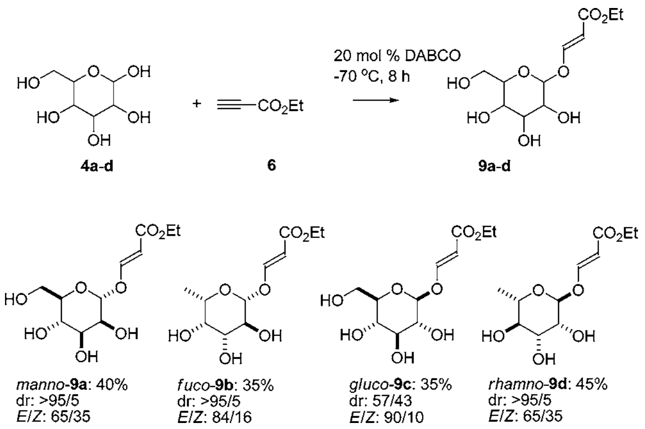


Scheme 4. Conjugate Additions of Ethyl Propiolate with Pentoses



[a]2.0 equiv of xylose was used.

Scheme 5. Conjugate Additions of Ethyl Propiolate with Hexoses

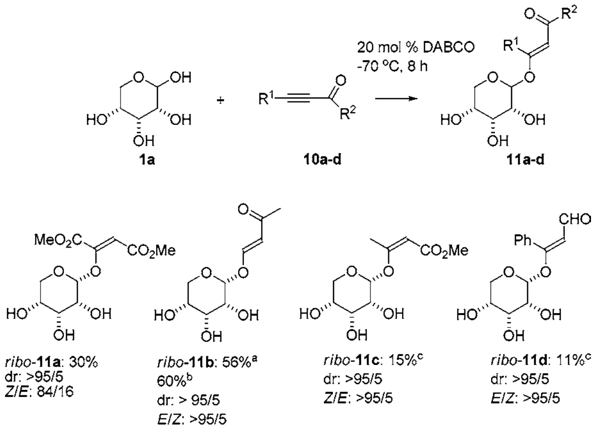


Using this optimized protocol we were able to elaborate a general conjugate addition of unprotected carbohydrates with activated alkynes. To this end, we reacted pentoses as well hexoses with ethyl propiolate **6** in the presence of 20 mol % of DABCO at −70 °C. The results of these investigations are depicted in Schemes 4 and 5. Again, the reaction proceed with an extremely high degree of stereoselectivity (dr >95/5), with the exception of reactions with glucose. Enol glucoside **9c** was isolated with a diastereomeric ratio of 57/43 (Scheme 5). The exclusive formation of pyranoid glycosides and the observed configuration at the anomeric carbon atom indicates thermodynamic reaction control. On that basis, a preliminary explanation for the extremely high stereoselectivity is given by comparison of the potential conformations. These considerations have been realized for compounds **8c**, **8d**, and **8e** (see the Supporting Information).

The enol glycosides **8a**−**e** and **9a**−**d** were formed with mostly high degrees of *E*-configured double bonds. These results agree with the stereochemical rules of the base-catalyzed conjugate additions to activated alkynes established by Winterfeldt.[11] Further support for the stereochemical course of the conjugate addition to ethyl propiolate based on intermediately formation of allenyl enolates was derived by in-house NMR experiments.[3]

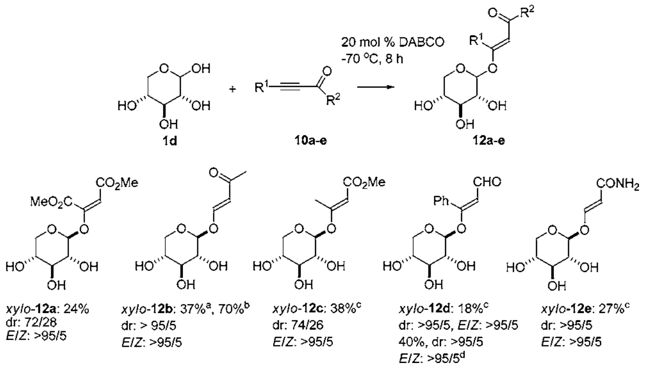
In a further series, we tested several different alkynes with ribose and xylose as substrates (Schemes 6 and 7). The results indicate that even internal alkynes can be employed in conjugate additions with unprotected carbohydrates, albeit at higher reaction temperatures (−40 °C). An instructive comparison is derived from the application of butyn-2-one, and the corresponding 4-(trimethylsilyl)butyn-2-one, as substrates. The same high diastereoselectivities and high *E*/*Z* ratios were detected in both series, using ribose as well xylose. However, the yields differed significantly, with higher yields in the xylose series (compare **11b** in Scheme 6 with **12b** in Scheme 7).

Scheme 6. Conjugate Additions of Ribose with Different Activated Alkynes



[a]TMS-≡-COMe was used. [b]H-≡-COMe was used. [c]Reaction temperature −40 °C.

Scheme 7. Conjugate Additions of Xylose with Different Activated Alkynes



[a]TMS-≡-COMe was used. [b]H-≡-COMe was used. [c]Reaction temperature −40 °C. [d]2 equiv xylose was used.

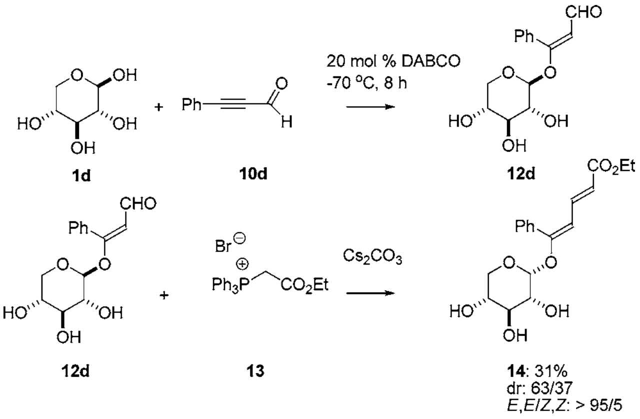
The installation of anomeric configuration occurred with an exceptionally high degree of stereoselectivity in all experiments. The same holds true for *E*/*Z* ratios of isolated enol glycosides, with the exception of **11a** in the ribose series (*E*/*Z* 16/84).

The yields of products can easily be improved by increasing the amount of starting carbohydrates. Different results concerning to stereoselectivity were obtained under these conditions. For example *xylo*-**8d** is observed with 40% yield (dr >95/5) when used with 1 equiv of xylose. By application of 2 equiv of xylose the yield increases (68%), but the stereoselectivity drops and *xylo*-**8d** is observed with a diastereomeric ratio of 45/55 (*α*/*β*, Scheme 4). When used with xylose and phenylpropargylaldehyde the yield of enol xyloside **12d** increases from 18% to 40%. The same high stereoselectivities were detected in both reactions (Scheme 7).

The intermolecular addition of alcohols to terminal and activated alkynes has previously been reported[12] and has been used extensively in radical cyclization of *β*-alkoxyacrylates,[13] in reductive cyclizations of *β*-alkoxyacrylates[14] and palladium-catalyzed cyclization in the presence of CO.[15] Conjugate additions of unprotected carbohydrates to alkynes on the other hand have not been reported in the literature so far.

To test the utility of this new synthetic method, the acrolein derived xyloside **12d** was reacted with phosphonium salt **13** to yield the *E*,*E*-configured diene **14** (Scheme 8). Similar compounds like dienoic acid ethylester **14** represent valuable starting products for Diels—Alder reactions in the total synthesis of optically active nonproteinogenic amino acids[16] or anthracyclines.[17] Existing techniques for the synthesis of carbohydrate-modified dienes like **14**,[18] carbohydrate-modified aldehydes **11d**/**12d**[19] or ketones **11b**/**12b**[20] suffer from being long and complex. The sequence described herein represents a significant short-cut compared to the classical multistep-syntheses. For an overview, see ref 21.

Scheme 8. Conjugate Addition/Wittig Sequence to Xylose-Based Dienes



In summary, we have developed a direct glycosylation process based on an amine-catalyzed conjugate addition of unprotected carbohydrates to activated alkenes or alkynes. The unprotected glycosides were isolated with exceptionally high degrees of stereoselectivity at the anomeric carbon atom. Building on that, further transformations, e.g., Wittig olefination, yield valuable building blocks for the total synthesis of natural products.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Optimization works, structure elucidations, proof of configuration, results of X-ray structure analyses, and copies of ^1H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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