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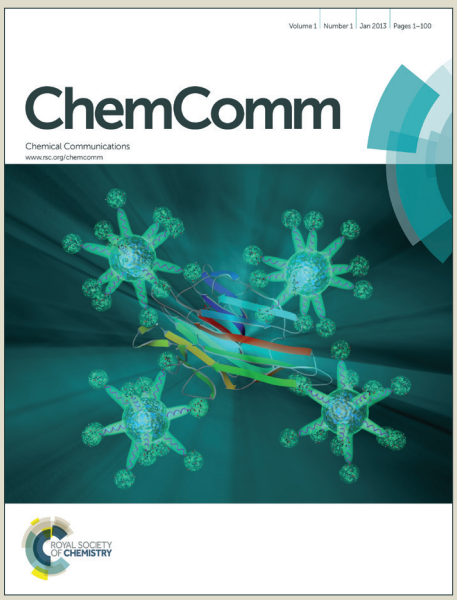

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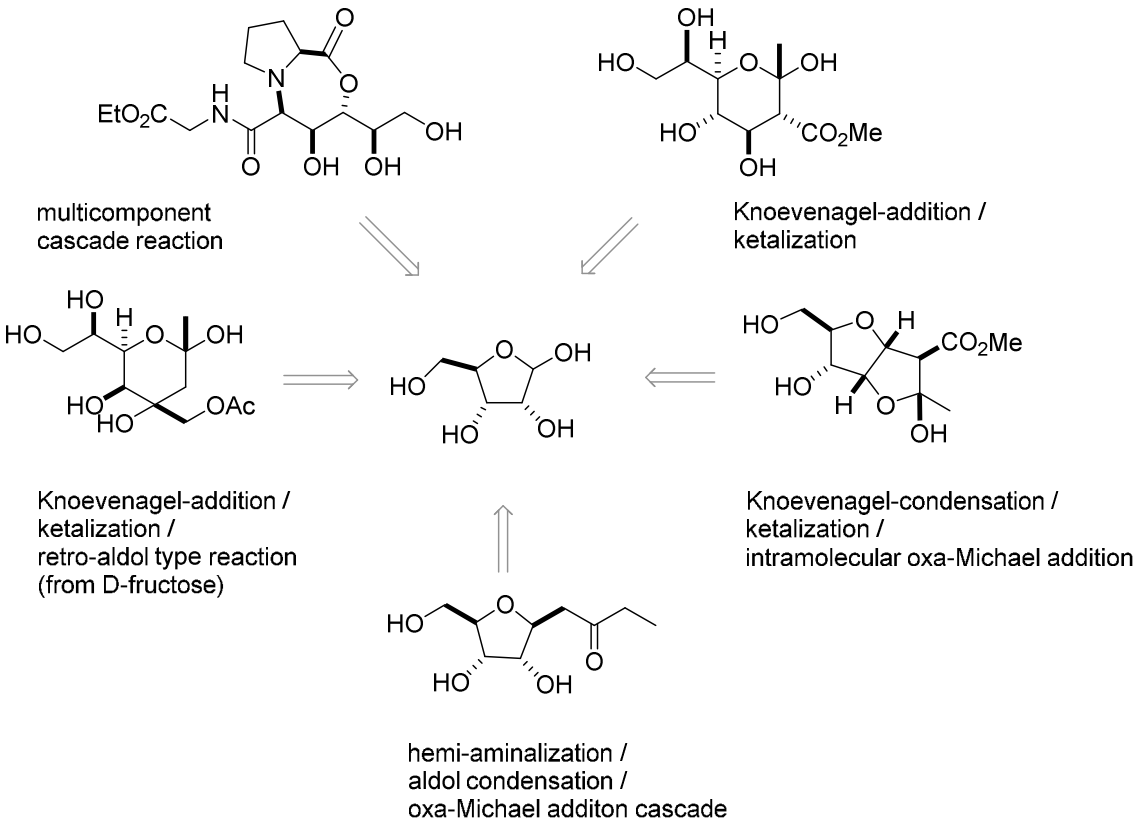

Several novel and highly stereoselective C–C bond formation processes of unprotected carbohydrates are described.

Journal Name

ARTICLE

The long underestimated carbonyl function of carbohydrates – an organocatalyzed shot into carbohydrate chemistry

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The aggressive and strong development of organocatalysis provides several protocols for the convenient utilization of the carbonyl function of unprotected carbohydrates in C-C-bond formation processes. These amine-catalyzed mechanisms enable multiple cascade-protocols for the synthesis of a wide range of carbohydrate-derived compound classes. Several only slightly different protocols have been developed for the application of 1.3-dicarbonyl compounds in stereoselective chain-elongation of unprotected carbohydrates and the synthesis of highly functionalized C-glycosides of defined configuration. In addition, C-glycosides can also be accessed by amine-catalyzed reactions with methyl ketones. By an one pot cascade reaction of isocyanides with unprotected aldoses and amino acids an access to defined configured glycopeptide mimetics is given. Depending on the reaction conditions different origin to control the installation of configuration during the bond-formation process were observed.

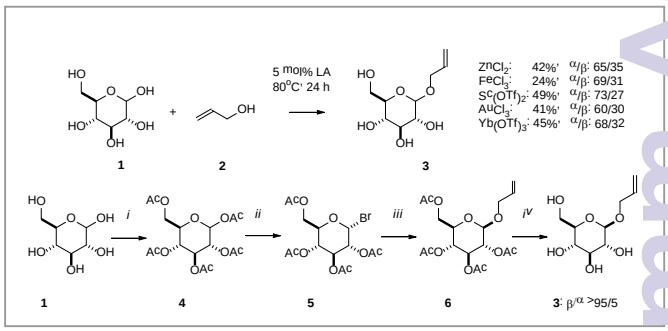
1. Introduction

The importance of carbohydrates in nature has always stimulated chemists to imitate and/or to exploit natural metabolically transformations. To realize this aim the situation for organic chemists can be summarized as follows. The complex structures of carbohydrates make their synthetic handling more diverse and not easy. Chemo- as well as stereoselective direct reactions of unprotected carbohydrates are hard to be realized due to the extremely high degree of density of different configured and chemical different hydroxyl groups. Moreover, working with unprotected carbohydrates is fraught with many additional problems: practical separation, isolation, solubility, identification, structural assignment etc. All these problems have caused a reluctance to venture into this field as explorers or scientist. 20 years ago Stephen Hanessian was talking of a “sugarphobia” in this context.[1]

To this end a manual of methods have been developed to avoid all these problems and thus allow selective transformations in carbohydrate chemistry. But these methodologies are burdened with extensive manipulations of protecting groups and activation processes.

Impressive examples in glycosylation chemistry support these considerations.

Unprotected and unactivated glucose can be directly transformed into the allyl glucoside **3** in the presence of catalytic amounts of Lewis-acids. Moderate yields and selectivities were observed.[2] In contrast to this direct glycosylation process the classical reaction path is as follows: glucose is transformed into the peracetylated glucosyl bromide **5**.[3] The subsequent glycosylation was accomplished in the presence of $HgBr_2$ and HgO. Final deprotection yields the ß-configured allyl-D-glucopyranoside **3** with high degrees of diastereoselectivity.[4] These two strategies are depicted in Scheme 1.



Scheme 1 Synthesis of allyl-D-glucoside. *i* Ac_2O, AcOH, cat. $HClO_4$; *ii* AcBr, MeOH; *iii* AllOH, $CaSO_4$, $HgBr_2$, HgO; *iv* NaOMe, MeOH

Further instructive examples are found in total synthesis of carbohydrates. The role models for the total synthesis of carbohydrates are nature’s enzymatic processes. By a set of stereochemically different working aldolases a highly enantioselective access to the naturally occurring carbohydrates is given. More than 20 different aldolases are known and have been isolated. They are divided into two main types of aldolases - type I aldolase and type II aldolase.[5] These

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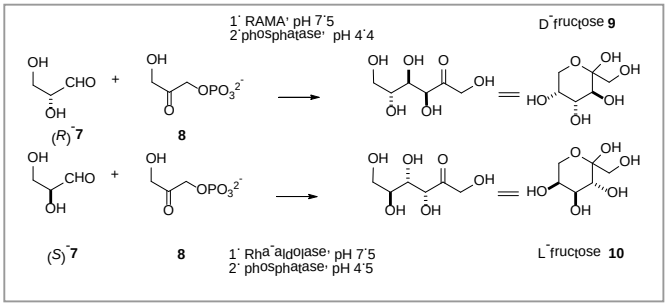
† Footnotes relating to the title and/or authors should appear here. Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

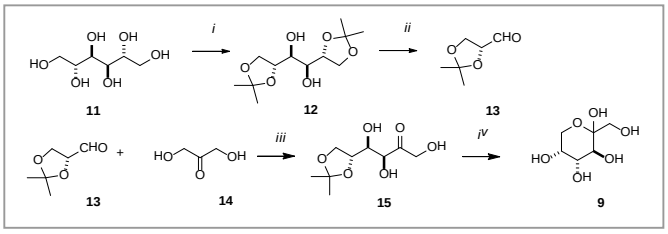
enzymes stereospecifically catalyze the aldol additions.[6] Two instructive examples for the selectivity of enzymes in total syntheses of carbohydrates are depicted in Scheme 2.[7]



Scheme 2. $C_3 + C_3$ enzyme-catalyzed approach to D-fructose **9** and L-fructose **10** (RAMA: rabbit muscle aldolase; Rha: rhamnulose aldolase)

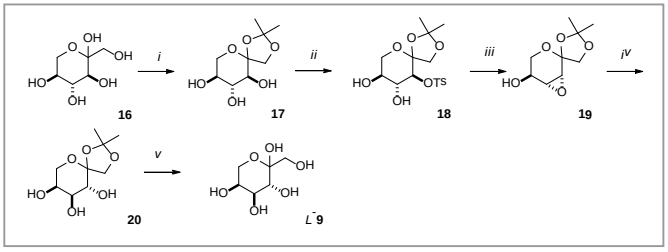
The simplicity and the selectivity with which nature handles this extremely high stereodifferentiation during the formation of the 1.2-diol junction have inspired chemists[8] and biochemists[9] for a long time.

In initial experiments concepts and reaction conditions were used that mimic the enyzme-catalyzed transformations. This approach is exemplified by the total synthesis of fructose. Based on the aldol reaction of glyceraldehyde with dihydroxyacetone a multistep sequence is necessary for this synthesis. Starting with mannitol **11** an access to protected D-glyceraldehyde **13** is given.[10] Subsequent base-catalyzed aldol reaction with dihydroxyacetone yield D-fructose **9**.[11]



Scheme 3. Total synthesis of D-fructose. *i* dimethoxypropane, $SnCl_2$; *ii* $NaIO_4$, *iii* cinchonine; *iv* DOWEX, H^+.

A similar extensive handling of protective groups was reported when L-fructose is needed. Common synthesis started with L-sorbose **16**. Following the reaction sequence in Scheme 4, L-fructose **9** was isolated with an overall yield of 7.5 %.[12]



Scheme 4 Total synthesis of L-fructose. *i* acetone, $CuSO_4$; *ii* TsCl, NaOH, Bu_4NHSO_4; *iii* NaOH; *iv* NaOH, 70°C, 52 h; *v* H_2SO_4.

These simple examples demonstrate the advantage of nature in syntheses of natural products. Nature does not work with protective groups. Thus nature meets the requirements of an atom economic synthesis to the full.[13] Moreover these examples illustrate how far away we are yet from an ideal and atom economic synthesis.

C-Glycosides or elongated carbohydrates have also gained considerable importance. These compounds are configuratively stable under enzymatic conditions and less prone to cleavage at the anomeric carbon. As such they are attractive substrates for chemical biology, medicinal and analytical chemistry. Though many of methods exist to synthesize these compounds from carbohydrate precursors or analogues[14], their applications are hampered by low yields and selectivities. This is caused by required complex and extensive manipulations of protective groups to carve out the full power of the carbonyl function of the anomeric carbon atom. As a result of that, carbohydrates are losing one of their valuable natural properties – the stereodirecting power in direct bond formation processes. This characteristic is based on directing hydrogen bonds of the different configured hydroxyl groups of carbohydrates. This statement holds true especially for the common metal-organic reactions as they are Reformatsky reactions[15], Knoevenagel reaction[16], Mukaiyama reactions[17] or aldol reaction[18]. The synthesis of C-glycosides of electron-rich aromatic aglycons were reported.[19] But these Lewis-acid catalyzed transformations are not object of discussion, since they are based on a Friedel-Crafts mechanism. For an comprehensive overview of existing methods to synthesize aryl C-glycosides see reference 20.

A big simplification of producing C-glycosides has been achieved by reactions of unprotected and unactivated carbohydrates with phosphorylides. Examples for Wittig reactions with unprotected carbohydrates are summarized in reference 21, whereas examples for Horner olefination (even in aqueous reaction medium) will be found in reference 22. The reactions were mostly carried out at higher temperature and in the presence of excess of bases.

Allylation processes with unprotected carbohydrates were also reported.[23] But these transformations were mostly carried out at high temperature for several hours. A catalytic performance under these reactions conditions have not been reported so far, with the exception of reference 23k. In this report the authors used unprotected carbohydrates, however in a nonselective Sc(OTf)$_3$-catalyzed allylation process with tetraallyltin.

15 years ago, Lubineau and coworkers reported a cascade reaction with unprotected carbohydrates. The unactivated carbohydrates were reacted with 1.3-dicarbonyl compounds to produce C-glycosides. In aqueous alkali media a Knoevenagel / Michael / retro-Claisen-aldol cascade is observed. This process was carried out at high temperature (60 - 90°C) and is associated with the loss of an acetate-fragment of the starting 1.3-dicarbonyl component (w

used with acetylacetone).[24] By application of this method an access to different mixtures of furanoid- and pyranoid-structures of α- and β-configured C-glycosides were obtained.[25] This methodology has been used in several transformations to synthesize configurative required C-glycosides.[26] For an overview of this development see reference 27.

These two different strategies

- the direct reactions of unprotected carbohydrates and the
- multistep synthesis with protected carbohydrates

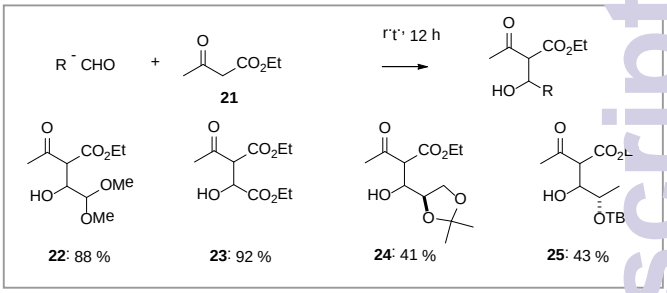
are available in general to realize organic transformations in carbohydrate chemistry (with the exception of enzymatic glycosylation).

In the meantime organocatalysis has conquered the field of organic chemistry. With the great progress in hands obtained by organocatalysis, for the first time a tool is available to overcome several serious problems of organic chemistry. Real hydrogen bridge networks enable new reactions and modes of stereochemical influences, which provide optically active products with high degrees of enantioselectivities. Moreover, catalytic reactions are possible now, that never have been realized in the metal-catalyzed series before. Sometimes extreme shortcuts of existing multistep routes were provided. In the beginning of this development the application of organocatalyzed methodologies in total syntheses of carbohydrates were in the spotlight. Several reports were published to describe direct and highly stereoselective approaches to defined configured carbohydrates. Furthermore, the optional performance and thus the diversity of these transformations were demonstrated conclusively. This holds true for both catalysts as well as substrates. For reviews in this field see reference 28.

The aim of this article is to focus the reader's attention to the long underrated carbonyl function of unprotected carbohydrates, which can be successfully used in several important organocatalyzed C-C bond formation processes to synthesize C-glycosidic structures. This is achieved by operationally simple amine-catalyzed reactions of unprotected carbohydrates.

2. Amine-catalyzed Knoevenagel-additions

The starting point of our investigation were observations that have been made in aldol additions of aldehydes with 1.3-dicarbonyl compounds.[29] These reactions proceed without any reagent or catalyst. A condensation process was not observed under these conditions. The products were isolated with quantitative yields in part. Some examples are depicted in Scheme 5.

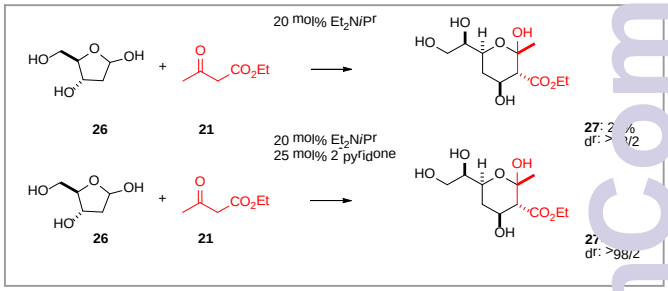


Scheme 5 Catalyst-free aldol additions of aldehydes with ethyl acetoacetate

Inspired by these results we envisioned Knoevenagel reactions with unprotected carbohydrates instead of aldehydes. Carbohydrates are known to exist in an equilibrium of acyclic structure (aldehyde) and cyclic structures (hemiacetal). The degree of formation of different cyclic structures (α- and β-configured pyranose or furanose) is dictated by the configuration of hydroxyl groups. The acyclic structures (hydroxyaldehydes and hydrates of these aldehydes) were detected at a very low level in this equilibrium (<0.1 % for aldohexoses and <0.5 % for ketohexoses).[30]

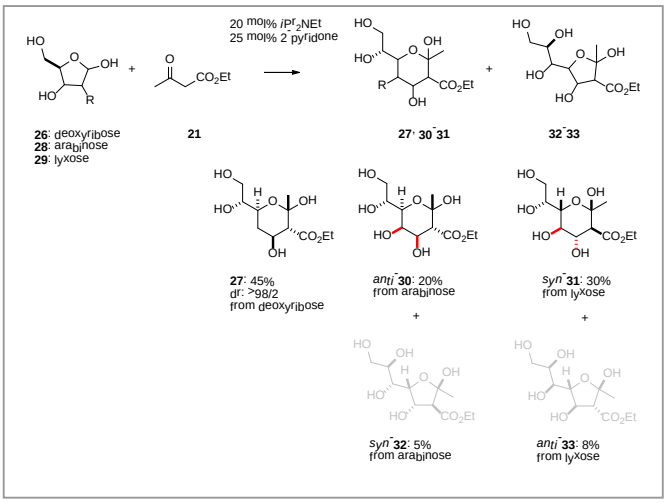
Thus, reactions of the acyclic structures of carbohydrates pose a challenge in organic synthesis.[31] But there are some tools which helpto utilize carbohydrates as aldehydes or ketones to a full extent, which will be discussed in this article.

In initial experiments we reacted D-deoxyribose **26** with ethyl acetoacetate **21** in the presence of catalytic amounts of ethyl diisopropylamine. A chain elongation was observed - the deployed 1.3-dicarbonyl compounds were incorporated into the carbon skeleton of the carbohydrates (Scheme 6).[32]



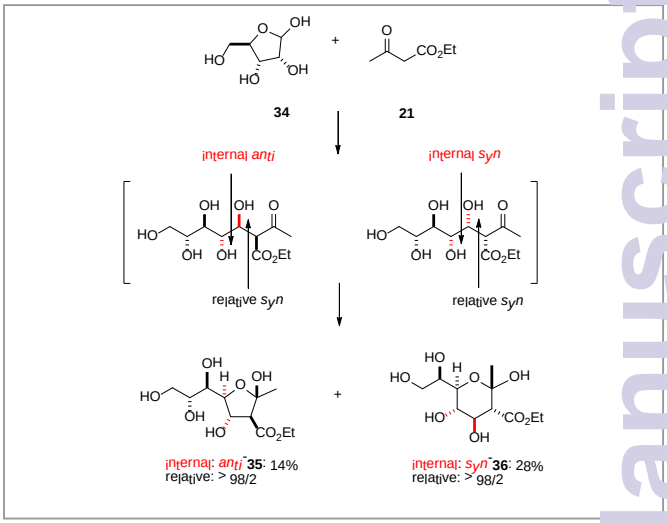
Scheme 6 Base-catalyzed Knoevenagel reaction of ribose with ethyl acetoacetate

The hemiketal **27** was detected as a single diastereoisomer, although with low yields (29 %). To overcome the problems of low yields we tested 2-hydroxypyridine as an additive in this reaction. 2-Hydroxypyridine is known as a catalyst that strongly influences the anomeric equilibrium of carbohydrates by developing hydrogen bonds.[33] Indeed, an addition of catalytic amounts of 2-hydroxypyridine increased the yields in the reaction of D-deoxyribose with ethyl acetoacetate (**27**: 29% → 45%). The same high level of diastereoselectivity was noticed (dr: >98/2). These conditions were applied to reactions of acetoacetate with several different pentoses as well hexoses. Selected examples of this investigation are depicted in Scheme 7.



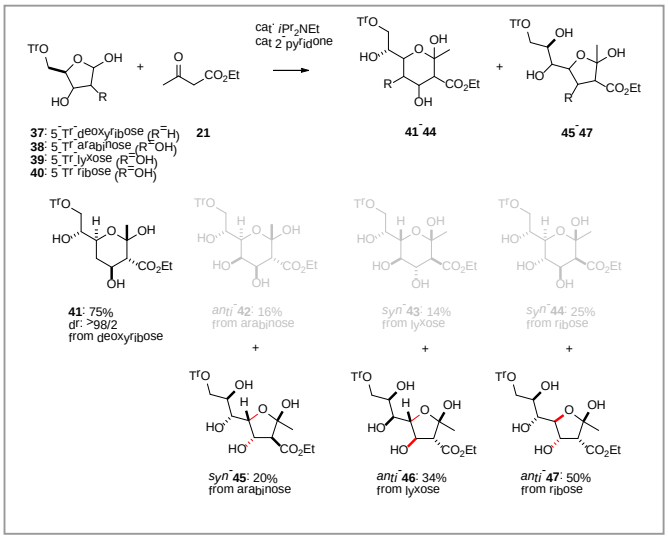
Scheme 7 Amine-catalyzed reactions of carbohydrates with ethyl acetoacetate

Compared to reactions with D-deoxyribose, two stereoisomers were detected in reactions with all other pentoses or hexoses. To discuss these results the configurative outcome of reactions of D-ribose with ethyl acetoacetate is exemplarily depicted in Scheme 8. The C-C bond formation process (Knoevenagel reaction) proceeds with an extremely high degree of *syn*-diastereoselectivity (relative diastereoselectivity >98/2). This is demonstrated by the two acyclic structures depicted in bracket (not isolated, Scheme 8). In contrast, the internal diastereoselectivity is dictated by the configuration of the 2- and 3-hydroxyl group of carbohydrates employed (dr: 7/3 – 8/2). A preferred formation of pyranoid structures is observed, when used with D-ribose.



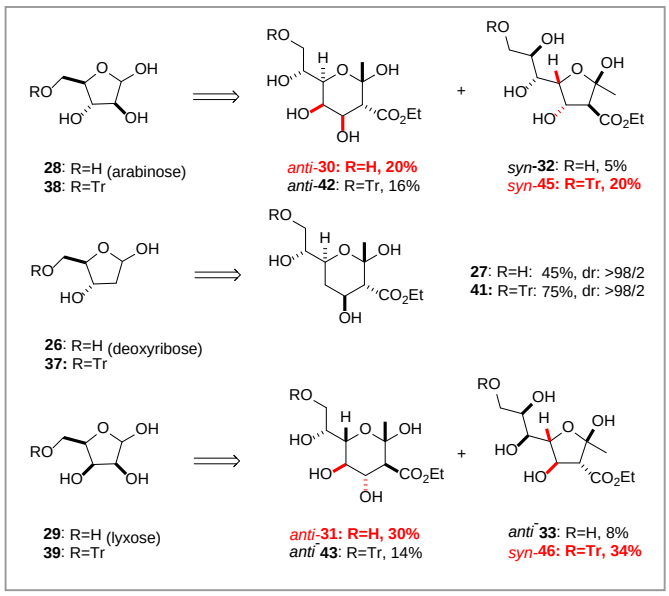
Scheme 8 Configurative outcome of reaction of ribose with ethyl acetoacetate

This high relative *syn*-stereoselectivity was found in all reactions we performed. This configurative outcome based upon the following requirements. A *Z*-enolate of acetoacetic ester is the only reactive species in the following *like*-approach (*Re*-side attack of *Z*-enolate of acetoacetic ester to the *Re*-side of carbohydrate aldehyde or *Si*-side attack of *Z*-enolate of acetoacetic ester to the *Si*-side of acyclic carbohydrate aldehyde). The preferred generation of pyranoid or furanoid products can be explained by a competition between the formation of the thermodynamically favoured pyranoid structures and destabilizing 1.3-diaxial interactions in the transition state. The avoidance of these unfavoured interactions during the transition state causes the formation of furanoid carbohydrates. Support for these considerations is given by reactions of D-deoxyribose with acetoacetic ester **21**. The absence of the interfering 2-hydroxyl group causes the formation of only one single stereoisomer **27.** Further investigation revealed that the results of these transformations are also influenced by the 5-hydroxyl group. This applies to both yields and stereoselectivity. To this end readily available 5-tritylated pentoses **37**-**40** were reacted with ethyl acetoacetate **21** under the described conditions. A significantly increasing of yields was observed. Moreover, the same exceptionally high relative *syn*-diastereoselectivity was observed again in this series. However, by comparing these results (Scheme 9) with those obtained with unprotected pentoses **26**, **28** and **29** (Scheme 7) a complete reversal of the internal stereoselectivity is detected, indicating a general steric shielding (trityl group). These steric interactions work independently of hydrogen bonds. As a result of the avoidance of these unfavoured steric interactions the formation of the furanoid structures is obtained. For a detailed discussion of the diastereoselectivity observed and for more examples of this reaction see reference 34.



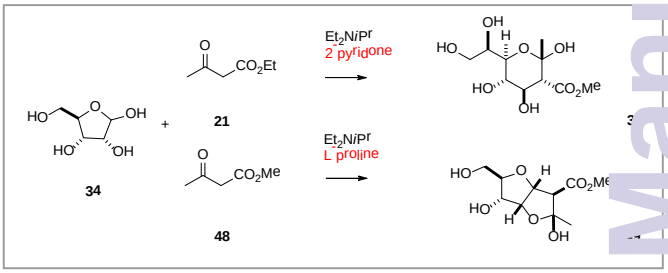
Scheme 9 Amine-catalyzed cascade reactions of 5-tritylated carbohydrates

The results of both series (Scheme 7 and 9) are summarized in Scheme 10. In general yields increase when 5-tritylated carbohydrates are employed. A divergent trend in stereoselectivity is observed when used with 5-tritylated pentoses instead of unprotected pentoses. This statement does not hold true when deploying deoxyribose. In both series only one single stereoisomer was detected. The tendencies of stereoselectivity are highlighted by red color in Scheme 10.



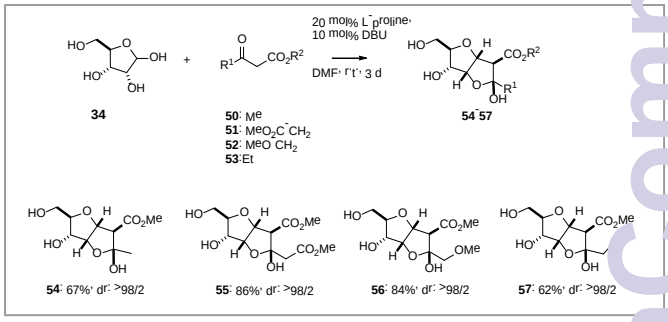
Scheme 10 Schematic overview of amine-catalyzed cascade reactions with unprotected or with 5-tritylated carbohydrates ethyl acetoacetate. Red color indicates major product.

Changing the reaction conditions only slightly by using 20 mol% proline instead of 20 mol% hydroxypyridine resulted in major changes of products. This different chemical behavior is depicted in Scheme 11. When used with the same substrates – ribose **34** and ethyl acetoacetate **21** – the formation of C-glycoside **49** was observed with an exceptionally high degree of stereoselectivity. The compound was generated by a Knoevenagel condensation / ketalization / oxa-Michael cascade reaction.[35]



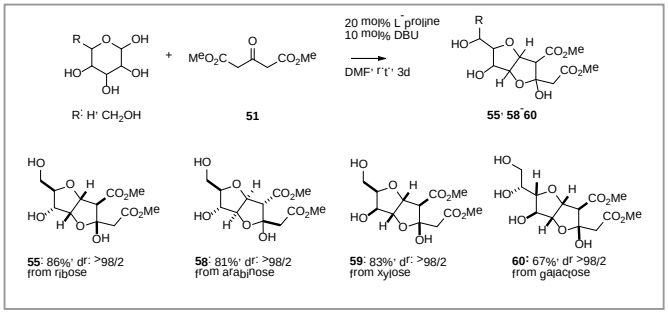
Scheme 11 Organocatalyzed reactions of ribose and ethyl acetoacetate

Further optimization resulted in the following protocol. When used with 10 mol% DBU and 20 mol% proline in DMF at room temperature C-glycoside **49** was isolated in good yields as a single stereoisomer. Inspired by these results we tested scope and limitation of this cascade reaction. In a first series we reacted unprotected ribose with several different substituted β-keto esters **50**-**53**. The corresponding C-glycosides **54**-**57** were isolated as single stereoisomers. They were found in their furanoid structure to be α-configured at the former anomeric carbon atom. Some examples of this investigation are depicted in Scheme 12.



Scheme 12 Proline-catalyzed cascade reactions of ribose with 1,3-dicarbonyl compounds

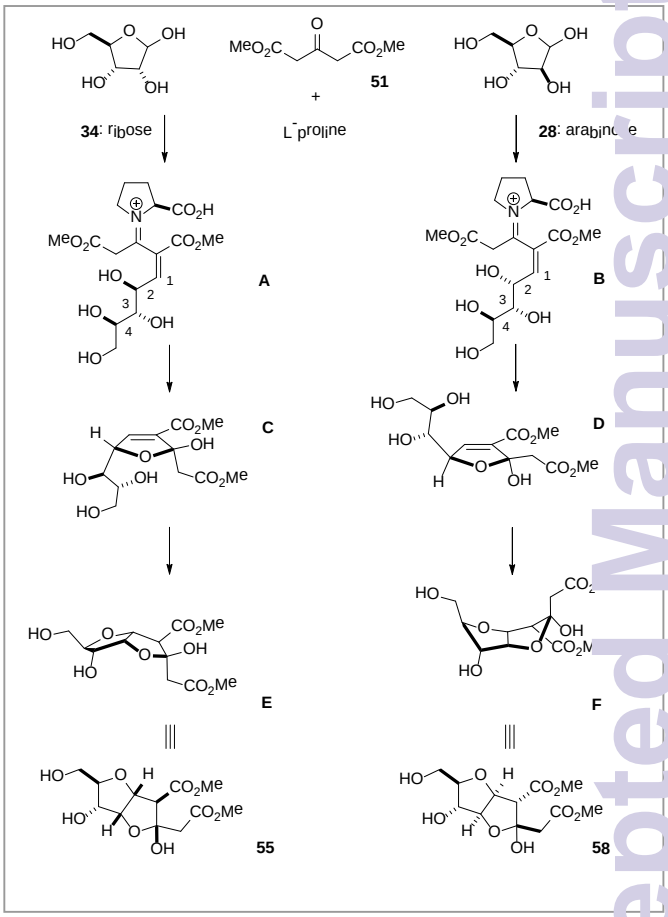
To test the scope of application several different carbohydrates were reacted in a further series with 3-oxoglutarate **51**. Selected results of these investigation are depicted in Scheme 13.



Scheme 13 Amine-catalyzed cascade reactions of methyl 3-oxo-glutarate with different carbohydrates

The corresponding C-glycosides **55**, **58**-**60** were obtained with good to high yields. Independent of the structure of carbohydrates employed, the C-glycosides were isolated exclusively in their furanoid form (compare pentoses with results of hexoses). The configuration of the hydroxyl group at C-2 dictates the configuration at the former anomeric carbon atom (compare **55** with **58**; α-configuration with ribose and β-configuration with arabinose). This process proceeds again with an extremely high degree of stereoselectivity.

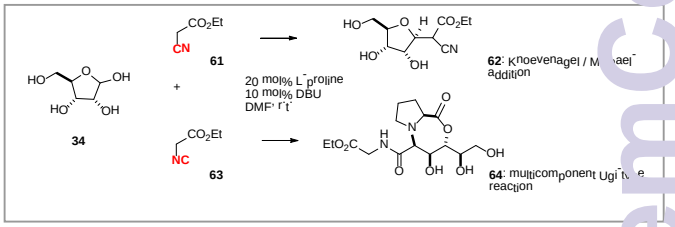
Several highly stereoselective reactions are operating within this reaction process (Scheme 14). An initial Knoevenagel condensation of proline, 4-oxoglutarate **51** and the carbohydrates establishes this cascade reaction to form the intermediates **A** (for ribose) or **B** (for arabinose). It is assumed that DBU stabilizes these intermediates by formation of hydrogen bridges. A selective ketalization follows, dictated by the configuration of hydroxy group at C-2, to form intermediates **C** (for ribose) and **D** (for arabinose). A subsequent intramolecular oxa-Michael addition of hydroxy group at C-4 furnishes fused tetrahydrofuran structures **E** (*Re*-side attack for ribose) and **F** (*Si*-side attack for arabinose). The configuration of structure **E** is identical to that of compound **55**, whereas structure **F** is the same as compound **58** (Scheme 13). The stereochemical course of the cascade reaction is dictated by the configuration of the hydroxyl groups at C-4 and C-2 of the carbohydrate employed. The configuration of proline has no influence on the reaction results as the same configured products were obtained when used with either L- or D-proline.



Scheme 14 Proposed reaction mechanism

3. Multicomponent reactions

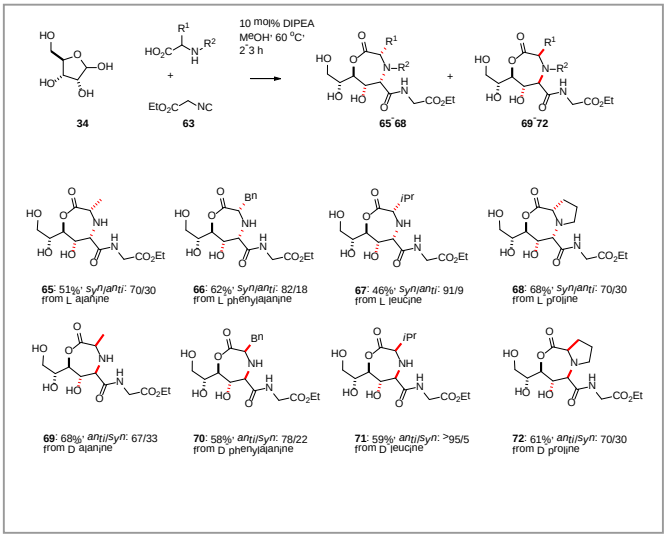
In addition, in further investigations we tested ethyl cyanoacetate in these proline-catalyzed cascade reactions. The corresponding C-glycoside **62** was isolated in approximately 50% yield. A small tweaking of these operationally simple protocols breaks a further new cascade channel (Scheme 15). When used with isocyanides **63** instead of cyanoacetates **61** in reactions with unprotected carbohydrates the incorporation of L-proline into the products is noticed. As a result of that, the selective formation of 7-membered lactones **64** was observed. This sharp difference in chemical behavior is demonstrated in Scheme 15.[36]



Scheme 15 Cyanide and isocyanide in proline-catalyzed cascade reactions

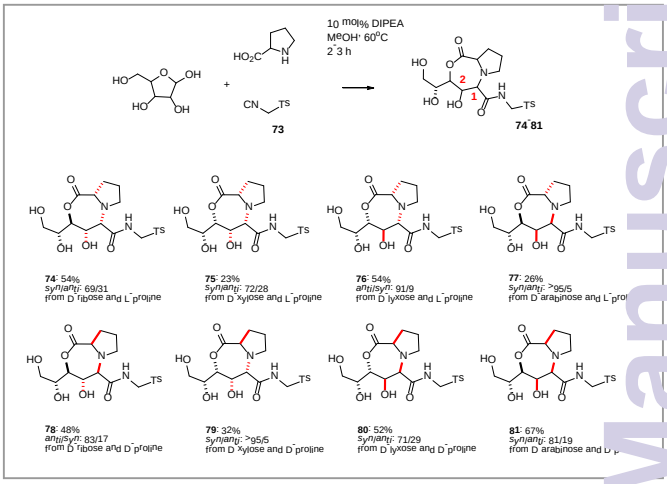
Using the following optimization process we tested scope and limitation of this new reaction sequence. In a first series ethyl isocanyoacetate **63** was reacted with a wide range of L-configured proteinogenic amino acids under similar reaction conditions. These investigations revealed that neutral amino acids seem to be the best substrates in these multicomponent transformations. No reactions were observed under application of acidic or basic amino acids.

The observed diastereoselectivity depends on the steric demand of the amino acids employed. The highest stereoselectivities were measured with β-branched amino acids (leucine, **67**: *syn*/*0* = 91/9). On the other hand, in reactions with unbranched amino acid (alanine) the corresponding lactone **65** was obtained in a ratio of 70/30 (*syn*/*anti*). Additionally, the configuration of the employed amino acids dictates the course of diastereoselectivity. When using D-configured amino acids, *anti*-configured products were isolated as the major compounds. Scheme 16 shows selected examples.



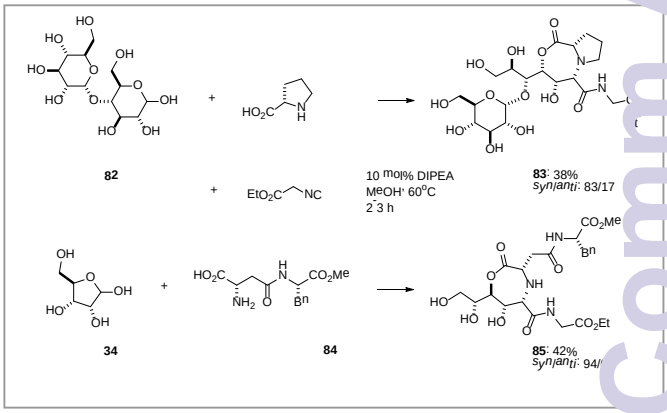
Scheme 16 Multicomponent reaction of D- and L-configured amino acids with ribose

During this investigation match / mismatched situations were observed. In general, a mismatched case can be observed, when the absolute configuration of the amino acid works in opposition to the absolute configuration of the hydroxyl group at C-2 of the carbohydrate. This trend is observed most clearly when using p-toluenesulfonylmethyl isocyanide **73** in reactions with proline. When the absolute configuration of the hydroxyl group at C-2 matched the configuration of the amino acid, the highest stereoselectivities were measured (e.g. **77**: *S*-proline and *S*-configuration at C-2 of arabinose or lactone **79**: *R*-proline and *R*-configuration at C-2 of xylose). Further support for these considerations is given by experiments with deoxyribose. By application of deoxyribose in these reactions unselective mixtures of all possible diastereoisomers were detected. Selected examples of these investigations are displayed in Scheme 17.



Scheme 17 Cascade reactions of D-pentoses with D- and L-configured proline

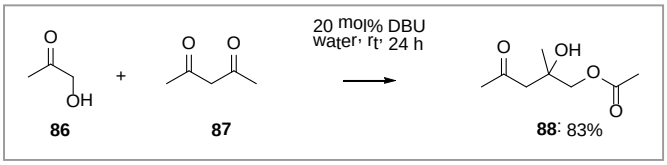
To demonstrate the power and utility of this novel multicomponent cascade reaction more challenging substrates were employed in these transformations. To this end reactions of disaccharides (maltose **82**) with L-proline and reactions of dipeptides (aspartame **84**) with ribose were carried out as examples. These transformations are depicted in Scheme 18. The expected lactones **83** and **85** were isolated with high degrees of stereoselectivity. Thus, by this operationally simple protocol an optional access to defined configured glycopeptide mimetics is given.



Scheme 18 Disaccharides and dipeptides in multicomponent cascade reactions

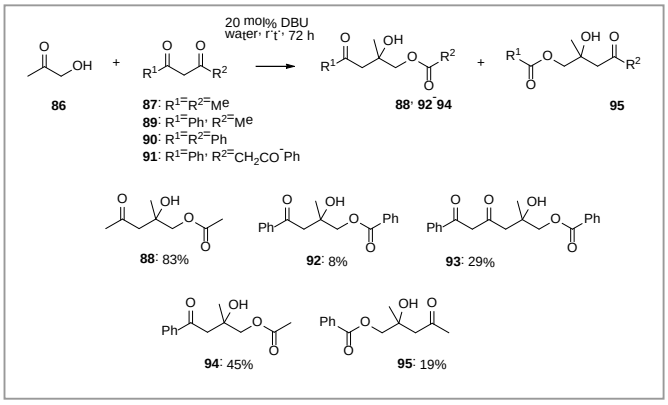
4. Amine-catalyzed cascade reactions of ketoses with 1.3 dicarbonyl compounds

At this point we wondered whether ketones instead of aldehydes could be deployed in these cascade reactions with 1.3-dicarbonyl compounds. Initial reactions of acetylacetone with acetone or several different methyl ketones in the presence of amines failed. Moreover, no reactions were observed with methoxy- or dimethoxyacetone. However, by applying hydroxyacetone **86** instead of acetone in reactions with acetylacetone **87** a clear reaction is observed. The corresponding acetate **88** was isolated with 83%. The reactions were carried out at room temperature in the presence of catalytic amounts of tertiary amines (Scheme 19). By deployment of β-hydroxybutanone no reaction was observed. These results highlight the extreme importance of the α-hydroxyl group of hydroxyacetone for the realization of this cascade reaction.[37]



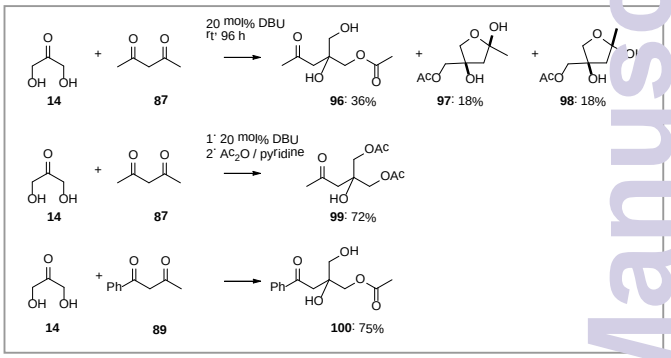
Scheme 19 Amine-catalyzed cascade reactions of hydroxyacetone and acetylacetone

Inspired by this result we tested several different 1.3-dicarbonyl compounds **87**, **89**-**92** in reactions with hydroxyacetone **86** under same conditions. The results of these reactions clearly demonstrate the dependence of yields of products as a function of bulkiness of substituents R^1 and R^2. Compare results of reactions of hydroxyacetone **86** and acetylacetone **87** (**88**: 83%) with results of reactions with dibenzoylmethane **90** (**92**: 8%). Furthermore, when using unsymmetrical methyl ketone **89** mixtures of two esters were formed (acetate **94** and benzoate **95**). The results of these investigations are depicted in Scheme 20.



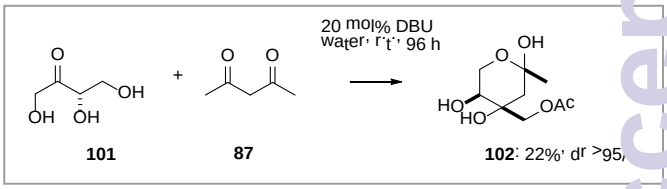
Scheme 20 Amine-catalyzed reactions of hydroxyacetone with different 1.3-dicarbonyl compounds

In a next series we tested dihydroxyacetone **14** and 1.3-dicarbonyl compounds as substrates in this amine-catalyzed reaction. The acetic acid esters were isolated with high yields. In reactions with acetylacetone **87** besides the expected ester **96** a diastereomeric mixture of the cyclized hemiketals **97** and **98** was observed. The homogenous reaction product (diacetate **99**) was isolated by subsequent acetalization in an overall yield of 72% (Scheme 21).



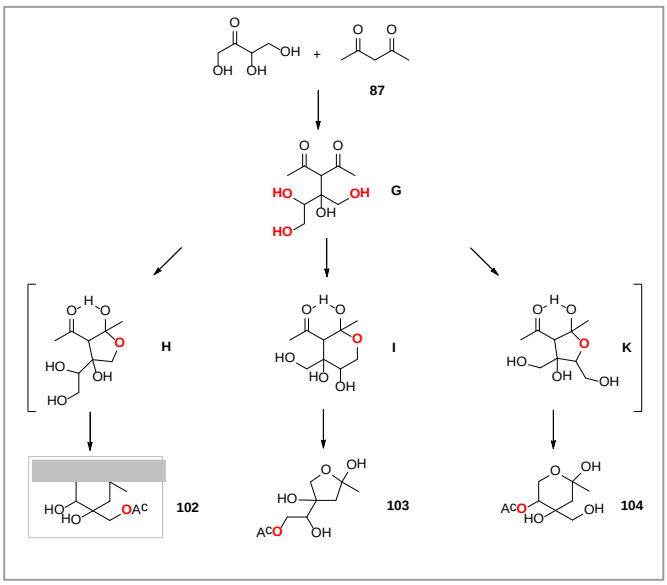
Scheme 21 Cascade reactions of dihydroxyacetone

Moreover, L-erythrulose **101** was reacted with acetylacetone under the described conditions to give the acetate **102** with 22% yield. Only one single stereoisomer was detected by ^{1}H NMR experiments (Scheme 22).



Scheme 22 Amine-catalyzed cascade reactions with L-erythrulose

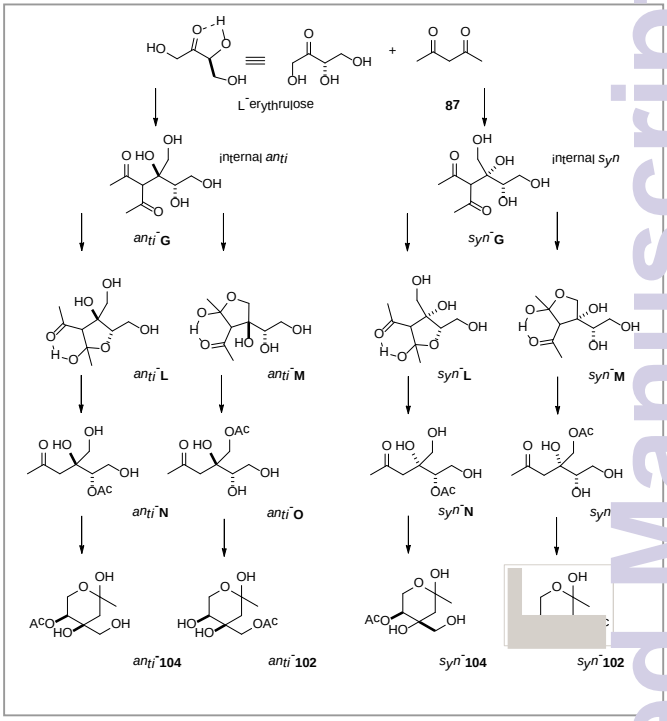
The results obtained allow a deeper insight into both the reaction mechanism and the configurative course of this cascade reaction. In this observed cascade several highly chemo- as well stereoselective reactions are operating. A Knoevenagel-addition / ketalization / retro-aldol type addition / hemikalization cascade is assumed for the overall process. The initial Knoevenagel-addition (intermediate **G**) is followed by a hemiketalization. There are three possibilities to form the hemiketals **H**, **I** and **K** (2 primary hydroxyl group and the secondary hydroxyl group). They are indicated in red in Scheme 23.



Scheme 23 Chemoselective cascade reactions of L-erythrulose and acetylacetone

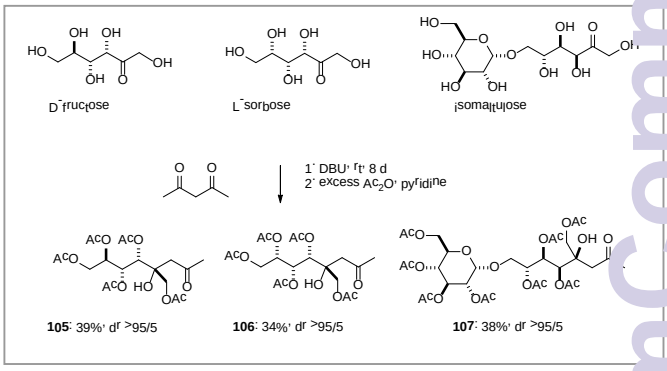
These intermediate hemiketals **H**, **I** and **K** dictate the formation of products **102**, **103** and **104** by the subsequent retro-aldol type reaction. Furanoid product **103** and pyranoid acetate **104** were not detected at room temperature. This extremely selective hemiketalization to intermediate **I** proceeds kinetically favoured. When working at 50°C nearly quantitative yields were noticed (up to 90%). However under these conditions a mixture of all possible isomers (**102**, **103** and **104**) was detected.

In addition, the configurative outcome of the reaction of L-rythrulose with acetylacetone provides an insight into the stereochemical course of this reaction. Hydrogen bonds of the S-configured secondary hydroxyl group of L-erythrulose give rise to a *Si*-side attack of acetylacetone. As a result of that, the internal *syn*-configured intermediate **G** is formed (not isolated). A preferred hemiketalization with primary hydroxyl groups gives an access to *syn*-configured intermediate **M**. A subsequent retro-aldol type reaction occurs and again a hemiketalization with primary hydroxyl group terminates this cascade reaction. The obtained configuration in connection with the observed acetylated primary hydroxyl group in compound **102** support these considerations (Scheme 24).



Scheme 24 Stereochemical course of amine-catalyzed cascade reactions of L-erythrulose

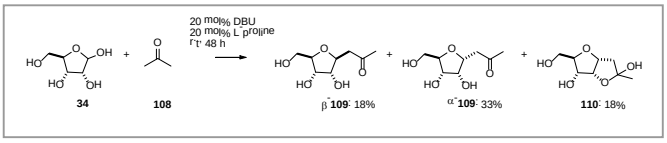
The results obtained promised to have a more general character. T demonstrate that we reacted several unprotected ketoses wit acetylacetone. Under the described conditions the expecte acetates or elongated carbohydrates were formed with an extreme high degree of stereoselectivity. For a better isolation and characterization the corresponding products were acetylated (1 **107**, Scheme 25).



Scheme 25 Amine-catalyzed cascade reactions of ketohexoses

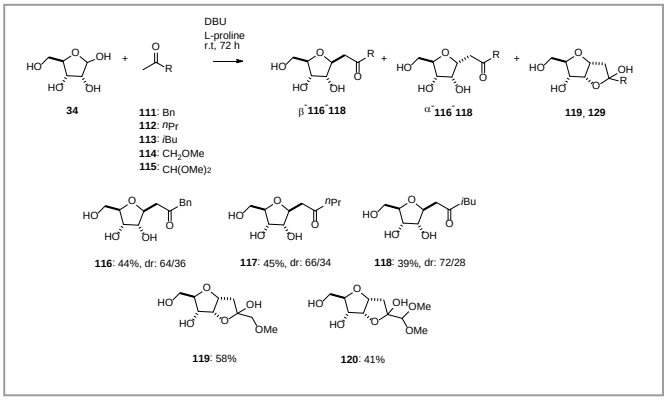
4. Amine-catalyzed synthesis of C-glycosides

At that point we envisaged reactions of methyl ketones as substrates (instead of 1.3-dicarbonyl compounds) in amine-catalyzed cascade reactions with unprotected and unactivated carbohydrates. In initial experiments we reacted acetone with ribose in the presence of catalytic amounts of L-proline and DBU. Indeed, after 48 h at room temperature we detected a mixture of α- and β-configured C-riboside **109** of acetone and the corresponding hemiketal **110** with an overall yield of 69% (Scheme 26).[38]



Scheme 26 Proline-catalyzed cascade reactions of ribose with acetone

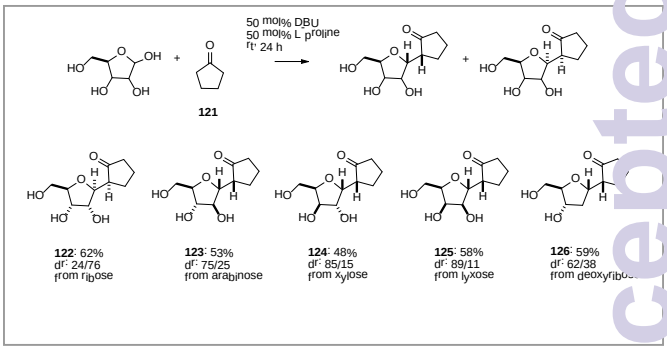
Inspired by these results we tested successfully several other unsymmetrical methyl ketones in reactions with ribose, which are depicted in Scheme 27. In general, a preferred formation of β-configured C-glycoside was observed. The diastereomeric ratios we observed under these conditions were about 2/1 (β/α). The reactions were carried out at room temperature. Working at higher temperature (40-50°C) lead to the formation of Amadori- and Maillard-products and thus to the inactivation of proline as the catalyst. By application of oxygen-containing ketones **114** or **115** we observed the preferred formation of hemiketals **119** and **120**. The corresponding ketones were detected to only a small extent under same conditions (< 5%).



Scheme 27 Proline-catalyzed synthesis of C-ribosides

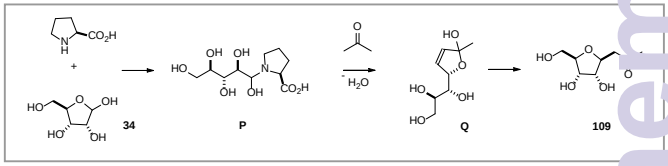
In these reactions, the ratio of the obtained diastereoisomers is dictated by the configuration of hydroxyl group at C2 and C3. This statement is supported best by stereochemical results obtained in reactions of different pentoses with cyclopentanone (Scheme 28).

The detected selectivities and the configurations differ from those obtained in cascade reaction of carbohydrates with 1.3-dicarbonyl compounds under the same reaction conditions. When used with 1.3-dicarbonyl compounds the obtained stereoselectivity is controlled by the configuration of the hydroxyl group at C2 of the carbohydrate only (Scheme 12-14). For example, in reactions of ribose with acetoacetic ester the α-configured C-glycosides were observed as the only products (**54**-**57**: dr: >98/2, Scheme 12). In contrast, when used with ribose and methyl ketones as substrates the corresponding β-configured C-ribosides **111**-**113** were observed as the major product (compare results of Scheme 12 with those of Scheme 27). In addition, a strong influence of the configuration of proline employed was detected. Extremely matched / mismatched cases were observed when used with D- or L-proline in these reactions. These results strongly contrast the findings summarized in Scheme 12-14.



Scheme 28 Proline-catalyzed cascade reactions of pentoses with cyclopentanone

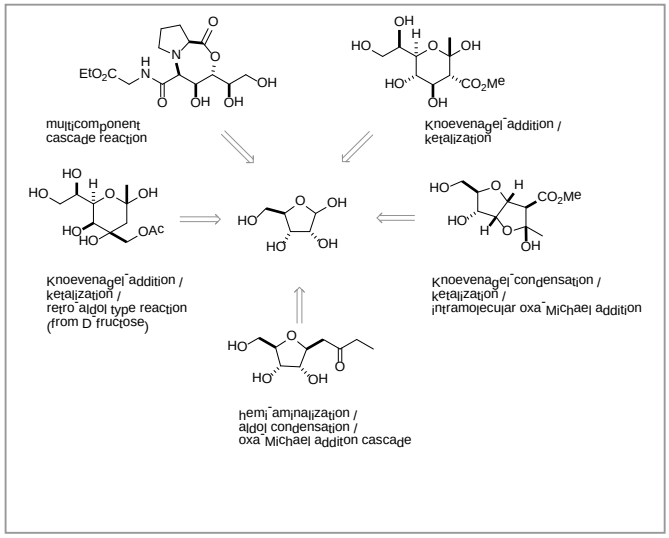
Regardless of these contradictions, which are under investigation, a first rough mechanism is exemplarily proposed for the cascade reaction of ribose and acetone. In an initial step the formation of the aminal of proline and ribose is observed (**P**, Scheme 29). This aminal is stabilized by DBU and was observed by NMR-experiments.[37] A subsequent aldol condensation occurred to form the intermediate hemiketal **Q**. Also, analog structures were isolated and characterized in cascade reactions of 1.3-dicarbonyl compounds (structure **C** and **D** in Scheme 14). A subsequent intramolecular oxa-Michael addition determines this cascade (Scheme 29).



Scheme 29 Proposed reaction mechanism

5. Conclusions

In conclusion, this overview has called the reader's attention to the power of the carbonyl function of carbohydrates in several important C-C bond formation processes. We have visualized several selective organocatalyzed cascade reactions of unprotected carbohydrates. With these operationally simple protocols access to different important carbohydrate structures is possible, including C-glycosides, chain-elongated higher carbohydrates, novel glycopeptides or exceptionally branched carbohydrates. All these novel cascade reactions are characterized by extremely high stereo- and chemoselectivities. An overview of this work is depicted in Scheme 30.



Scheme 30 Amine-catalyzed cascade reactions of unprotected carbohydrates

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