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Modern Organocatalyzed Methods in Carbohydrate Chemistry

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Contents

Chapter 1
Introduction

This review intends to call the reader's attention to the power of the carbonyl function of carbohydrates in several important transformations. The exhaustive utilization of this functionality has been made possible by the strong and aggressive development of organocatalysis. Several important reactions and methods have been established under the aura of organocatalysis, such as glycosylation, cascade reactions and total syntheses of carbohydrates. Besides that several other organocatalyzed methods have been elaborated in carbohydrate chemistry, e.g. organocatalyzed introduction of protective groups (for highly selective O-arylidenation of carbohydrates see [1], for selective acylation of carbohydrates see [2–6]). These methods though are not the subject of this discussion here. Also, corresponding enzymatic or chemoenzymatic processes will not be discussed in this review.

Working with unprotected carbohydrates is fraught with many problems: practical separation, isolation, solubility, identification, structural assignment etc. 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 [7].

Considering (comparing with) the huge advances made in organic synthesis over the last 20 years, especially in the field of organocatalysis, we are still at a similar point of this discussion. Mostly carbohydrates were protected, activated, glycosylated and finally deprotected to give desired glycosides with required configurations.

But due to the aggressive development of organocatalysis new concepts and methodologies are available, which could act as strong tools to solve many problems of carbohydrate chemistry. This statement is not only a wishful thinking; it is reality. Organocatalysis has already reached the field of synthetic techniques in carbohydrate chemistry. So, the time is ripe to give an early and first overview over the first achievements of these investigations which were obtained in the field of carbohydrate chemistry.

Carbohydrates are characterized by an extremely high degree of density of defined configured hydroxyl groups. Based on that, carbohydrates can create an inter- as well as intramolecular network of hydrogen bonds, which can be

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successfully utilized in several stereoselective organocatalyzed transformations. This is the working mode of nature, as we know that from reactions catalyzed by enzymes.

On the other hand this gift of nature is completely destroyed when used with protected carbohydrates. By application of protected carbohydrates this network of hydrogen bridges cannot be developed to the full and thus cannot be extensively exployed for stereoselective transformations.

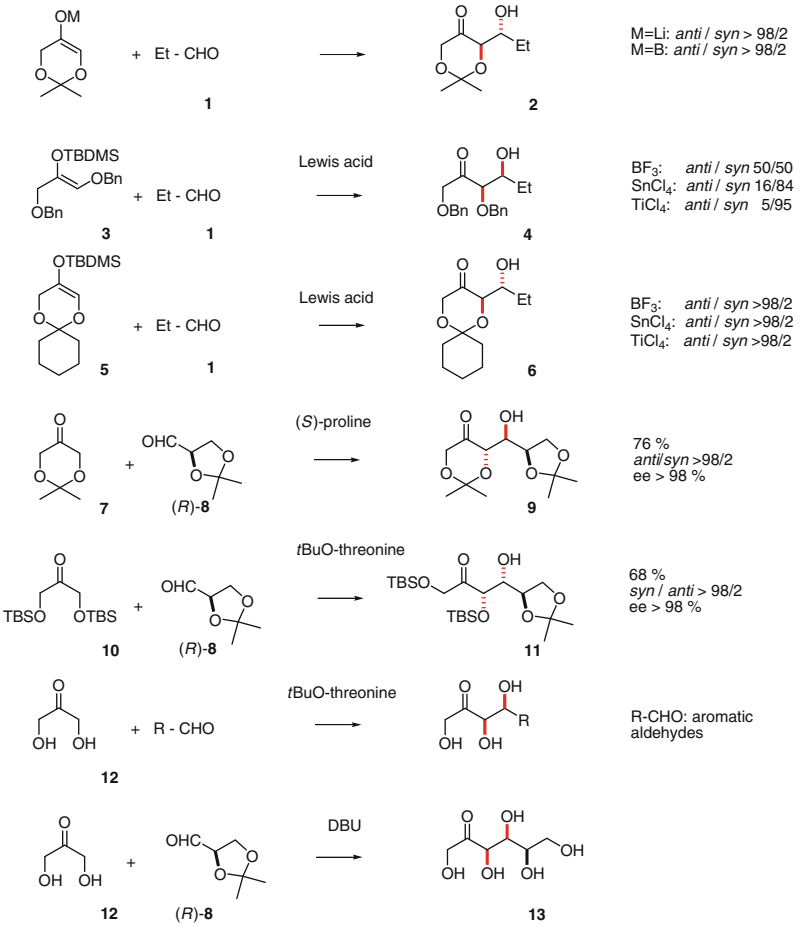
With the great progress in hands obtained by organocatalysis, for the first time a tool is given to overcome these problems. A real hydrogen bridge network enables new reactions and modes of stereochemical influences that provides optically active products with high enantioselectivities. Moreover, reactions are possible now that never have been realized in the metal catalyzed series. Sometimes extreme shortcuts of existing multistep routes were provided.

These considerations are supported by the following analysis of total syntheses of ketohexoses. Furthermore this overview illustrates the synthetic progress in the field of organcatalysis.

A formal direct access to ketohexoses is given by an aldol addition of dihydroxyacetone (DHA) and glyceraldehyde. Nature generates ketohexoses by means of enzymes without the need of protecting groups (see also Scheme 2.1) [8, 9]. This highly stereoselective synthesis is a fundamental challenge for a synthetically working chemists. Also, this synthesis has always been the proof for a concept of a new elaborated method. A brief overview of this development is given in Scheme 1.1.

Following the idea of the natural image, a few attempts have emerged to utilize preformed enolates in aldol reactions of cyclic protected dihydroxyacetone. For reasons of comparability and uniformity these reactions were described with propionaldehyde. Due to the nature of this reaction and enolate geometry these processes are notoriously *anti*-selective (boron enolate [10–12], lithium enolates [13, 14]). In contrast, the application of silylenolether of benzylprotected dihydroxyacetone **3** in Mukaiyama-reactions gives an access to *syn*-configured aldol products **4** for the first time, although only when used with titanium(IV)-chloride only. By application of several other Lewis acids a more or less unselective C–C bond formation process is observed [15]. In contrast, by application of cyclic protected silylenolether of dihydroxyacetone **5** the *anti*-configured aldol product **6** was obtained in reactions catalyzed by $TiCl_4$, BF_3 or $SnCl_4$. These results demonstrate once more the importance of the geometry of enolates in view of the configurative result of aldol additions.

Later on, the stormy development of organocatalysis has strongly influenced the area of total syntheses of carbohydrates. Several methods have been developed to access ketohexoses directly and stereoselectively. For example proline-catalyzed aldol additions of protected dihydroxyacetone **7** gave an access to *anti*-configured aldol product **9** with high degree of enantioselectivity [16–28]. Further investigations revealed that protected dihydroxyacetone **10** reacts even with enolizable aldehydes in the presence of catalytic amounts of threonine-derivatives to yield aldol adducts with high enantioselectivities [29]. Later on, Barbas and coworkers demonstrated reactions of aromatic aldehydes with unprotected dihydroxyacetone **12** in



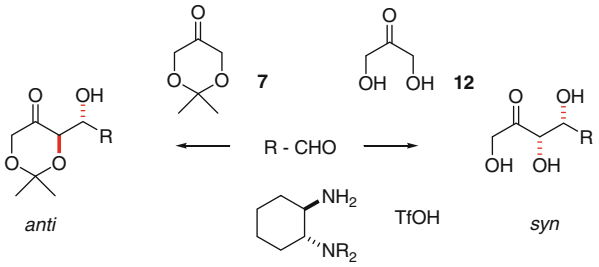
Scheme 1.1 Historical development of aldol reactions with dihydroxyacetone or derivatives

the presence of catalytic amounts of threonine-derivatives. *Syn*-configured aldol adducts were detected with high degress of enantioselectivity [30]. By a simple tertiary amine-catalyzed aldol process high *syn*-stereoselectivities were observed during the C–C bond formation (and references cited in [31]). Thus an access to sorbose **13** is given by the deployment of unprotected dihydroxyacetone **12**.

To emphasize once more the importance of the geometry of the reactive enol component for the configurative outcome of amine-catalyzed aldol reactions of dihydroxyacetone or derivatives a very instructive example was reported by Luo et al. [32] (Scheme 1.2).

Depending on the deployment of either unprotected (**12**) or protected dihydroxyacetone (**7**), a controlled access to *syn*- or *anti*-configured aldol adducts is given (Scheme 1.2). Both highly enantioselective reactions were catalyzed by the

Scheme 1.2 Stereoselective aldol additions catalyzed by chiral 1.2-diamines



same chiral diamine. These results give an excellent support for the stereochemical rules of organocatalyzed aldol additions of protected and unprotected dihydroxyacetone (diastereoselectivity is dictated by the geometry of reactive enols).

The results depicted in Schemes 1.1 and 1.2 should give a brief overview of and an introduction to the historical development, utility and advantage of organocatalysis in the total synthesis of ketohexoses. In contrast to that, an enantioselective metallorganic direct access to aldol products of dihydroxyacetone has not been reported so far.

The review in hand covers results of organocatalyzed total syntheses of carbohydrates, chain elongation processes, cascade reactions and glycosylation of carbohydrates. The examples will be discussed and compared cohesively with their metalorganic or metalcatalytic counterparts (wherever it is possible !). This combination should give support to understand the advantages of organocatalysis in biomimetic transformations. This is the base to create new reactions and synthetic pathways for carbohydrates in biological chemistry, pharmaceutical chemistry and material sciences.

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Chapter 2
Total Synthesis of Carbohydrates

Abstract For a long time carbohydrates have stood out as a class of compounds very difficult to synthesize due to complexity of configuration and functionality. Delicate chemical operations and separation problems resulted in the so-called "sugarophobia". But based on the dramatic development of organocatalysis over the last 15 years a large number of complicated carbohydrates is now accessible. Today a big manual of synthetic methods for total synthesis of carbohydrates exists. This pool of synthetic methods provides the tools to create defined and required configurations of hydroxyl groups during the total synthesis of the desired carbohydrates. Due to the nature of carbohydrates different aldol additions are the favoured transformations for the synthetic access to carbohydrates. Especially the extremely fast-growing manual of organo-catalyzed aldol reactions represents a promising tool for direct and biomimetic synthesis to unusual enantiomers of monosaccharides and to deoxy-, branched-, amino-, thio- and carbon-substituted carbohydrates.

Keywords Organocatalysis · Total synthesis · Carbohydrates · Biomimetics · Aldol reaction · Decarboxylative aldol · Mannich-reaction

Carbohydrates, an important group of natural products, not only play an extremely important role as an energy reservoir or as a resource of biomaterials such as cellulose or chitin. Amongst others they are integral elements as markers for cell-cell communication in immune responses, inflammatory and microbial virulence. In contrast to their ubiquitous importance in biological systems there are only a few examples of chemical total syntheses of this important class of natural products. In addition, a systematic chemical approach to differently configured carbohydrates does not exist. This contradiction is most likely due to the challenge of achieving the highest level of stereochemical control.

There is a big **why** we need total syntheses of a class of natural occurring substances that are readily available in large quantities and in enantiopure form. Seldom has there been a need for a de novo synthesis of carbohydrates. Moreover, even in the so-called rare-sugar series sometimes it has proven easier and much more convenient to synthesize a desired carbohydrate by chemical transformations

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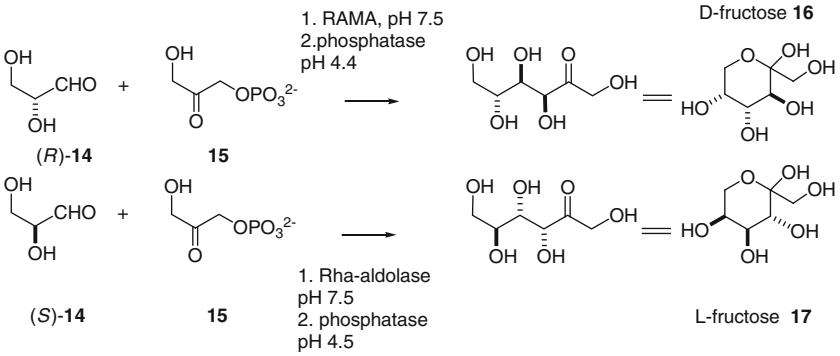
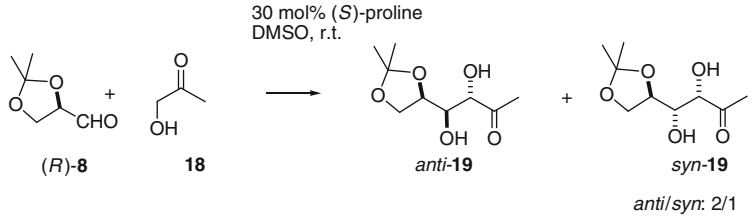


Scheme 2.1 C_3+C_3 enzyme-catalyzed approach to D-fructose **16** and L-fructose **17** (RAMA: rabbit muscle aldolase; Rha: rhamnulose aldolase)

from an inexpensive starting carbohydrate. But this argument fails when unusual enantiomers of carbohydrates are required; these considerations are also true for deoxy-, branched-, amino-, thio- and carbon-substituted carbohydrates etc. [1–9].

The role models for the total synthesis of carbohydrates are the enzymatic processes that are working in nature. 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—typ I aldolase and typ II aldolase [10]. These enzymes stereospecifely catalyze the aldol additions [11]. Two instructive examples for the selectivity of enzymes in total syntheses of carbohydrates are depicted in Scheme 2.1 [12].

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 (For the probably first total synthesis of fructose and sorbose see Ref. [13] and for first enzymatic aldol reactions in total synthesis of carbohydrates see Ref. [14–17]) for a long time. In initial experiments reaction conditions were used, that mimicked enyzme-catalyzed tranformations. The carbonyl compounds and enol components were deployed in their unprotected form. Mostly, water was used as a solvent. Several strategies of iterative chain elongation were deployed. Dihydroxyacetone (DHA) represents an ideal and comfortable starting C_3-unit for these biomimetic reactions. Several reports were published describing aldol additions of unprotected dihydroxyacetone with unprotected hydroxyaldehydes (C_3+C_2-strategies give an access to pentoses, while C_3+C_3-strategies yield hexoses) [18–25]. Also, aldol additions of unprotected hydroxyaldehydes were studied (C_2+C_2+C_2-strategies yield hexoses, C_2+C_2 strategies yield tetroses, C_3+C_1+C_1 strategy yield pentoses). Examples for these so-called prebiotic carbohydrate syntheses by aldol additions are found in reference [26–33]. However, the application of these transformations are hampered by low yields and/or low selectivities.



Scheme 2.2 C_3+C_3 proline-catalyzed approach to deoxy-tagatose and deoxy-fructose

Besides these efforts, organo-catalyzed direct transformations to carbohydrates have been investigated. This research has been developed from the question of what are the real active species of aldolases and how small an aldolase-like organic catalyst can be doing the same job as the whole enzyme.

A first step in this direction was the publication of List and Notz in 2000. The authors described an enantioselective aldol addition of unprotected hydroxyacetone **18** with several enolizable aliphatic aldehydes [34]. This reaction was catalyzed efficiently by (*S*)-proline to yield the aldol adducts with a high degree of enantioselectivity. Also, protected (*R*)-glyceraldehyde **8** was reacted with hydroxyacetone. A moderate 1,2-asymmetric induction was observed during this transformation. Protected 1-deoxy-D-fructose (*syn*-**19**) and 1-deoxy-D-tagatose (*anti*-**19**) were isolated in a ratio of 1/2 (Scheme 2.2).

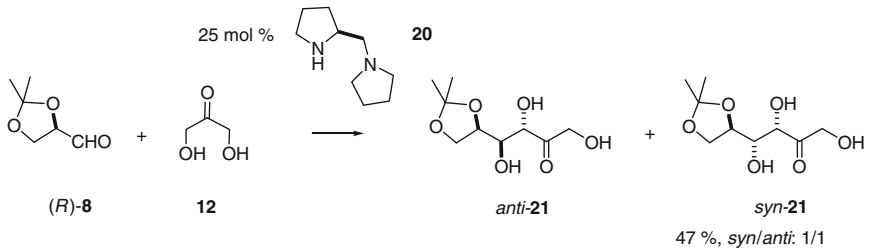
This publication was the go-ahead of a strong, still ongoing development of the so-called organocatalysis [35, 36] and represents the most promissing and direct approach to carbohydrates so far. This easy and direct aldol reaction imitates nature in an elegant way [37, 38].

In this chapter, the different organocatalyzed direct aldol additions to carbohydrates will be discussed on the base of the nature of carbohydrates in connection with the required substrates deployed.

2.1 Aldol Reactions of Aldehydes with Dihydroxyacetone, Hydroxyacetone and Derivatives: Access to Ketoses

Only 2 years later, in 2002, Barbas et al. reported the first organocatalyzed aldol addition of unprotected DHA with protected (*D*)-glyceraldehyde [39]. This reaction was catalyzed by the proline-derived chiral diamine **20** in an aqueous phosphate buffer. A 1,2-asymmetric induction was not observed. The aldol adducts of (*D*)-glyceraldehyde with unprotected DHA—protected D-fructose (*syn*-**21**) and protected D-tagatose (*anti*-**21**)—were isolated in a diastereomeric mixture of 1/1 (Scheme 2.3).

Following nature as the role model, several groups reported organocatalyzed aldol additions of aldehydes to hydroxyacetone (For threonine-catalyzed aldol



Scheme 2.3 Amine-catalyzed aldol reaction with unprotected dihydroxyacetone

addition of hydroxyacetone) [40] or derivatives of dihydroxyacetone [41]. The results of these investigations clearly demonstrate that unprotected hydroxyacetone or dihydroxyacetone are not useful substrates for proline-catalyzed aldol addition. This also holds true for threonine-derivative-catalyzed aldol additions. Several protecting groups of dihydroxyacetone have also proved to be unsuitable for this transformation (e.g. Bn, TIPS, TMS, NPhth) [42]. With regard to diastereoselection, mainly *anti*-configured up to non-selective aldol adducts were obtained. Some examples of this tremendous work in the protected DHA-series are depicted in Scheme 2.4 [43–45]. An access to protected D-tagatose **9** and protected D-psicose **22** is given when used with protected glyceraldehyde under these conditions.

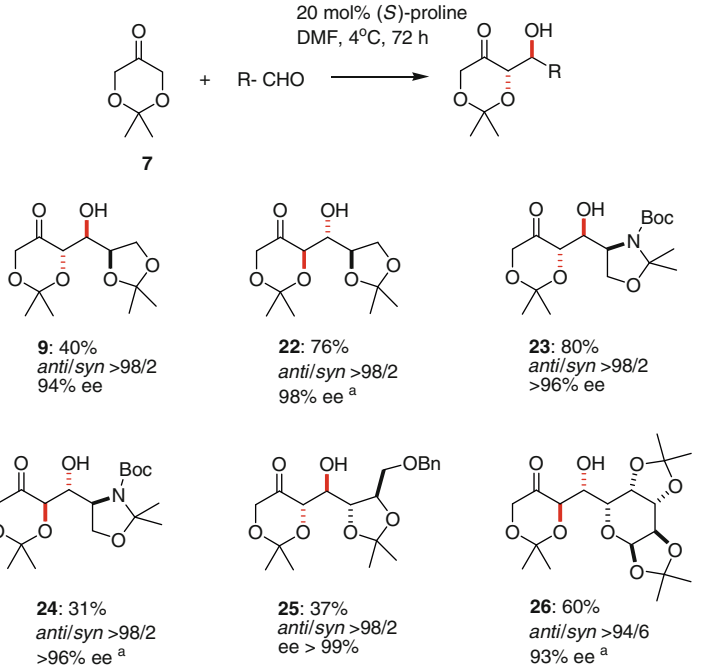
By comparing results of **9** and **23** ((*S*)-proline) with those obtained in the (*R*)-proline series (**22** and **24**), matched- and mismatched-situations becomes propable.

The *anti*-preference of (*S*)-proline-catalyzed aldol reactions provides an additional and efficient tool for enantioselective synthesis. Enantiopure a*nti*-configured 1.2-diols are difficult to access by Sharpless-dihydroxylation. This is due to the less favoured (*Z*)-olefins and with that the reduced enantioselectivities by their application in Sharpless-dihydroxylations [46].

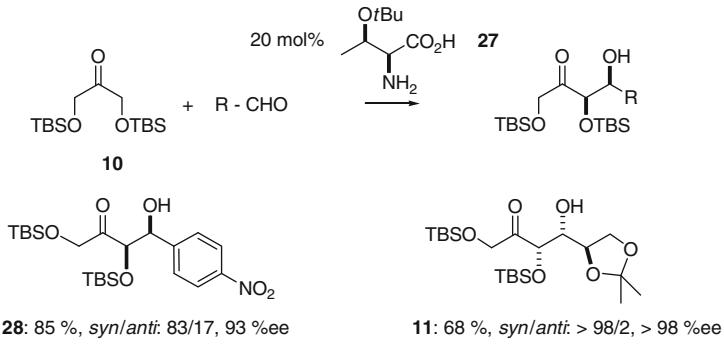
To test further amino acids as catalysts in direct aldol additions Barbas et al. have demonstrated the utility of threonine-derivatives in asymmetric organocatalyzed aldol additions with TBS-protected dihydroxyacetone **10** [47]. Under these reaction conditions the authors were able to isolate aldol adducts of *p*-nitrobenzaldehyde and (*R*)-glyceraldehyde (**28** and **11**) with high degrees of enantioselectivity and with high *syn*-diastereoselectivity (Scheme 2.5). Compound **11** represents a diversely protected D-fructose.

A slight improvement with regard to yields was noticed when used with bulky threonine amide catalysts. By deployment of 15 mol% of catalyst **29** a variety of even enolizable aldehydes can be reacted with protected dihydroxyacetone **10** to give aldol adducts in high to quantitative yields [48]. When used with (*S*)-configured glyceraldehyde an access to L-fructose is given (**32**, Scheme 2.6).

A further breakthrough with regard to a biomimetic execution of this aldol reaction was achieved by the successful deployment of unprotected dihydroxyacetone in organocatalyzed aldol additions. These conditions allow for the formation of *Z*-enolates of dihydroxyacetone. Thus for the first time a selective access to *syn*-configured aldol adducts of DHA is given. Barbas et al. have demonstrated this

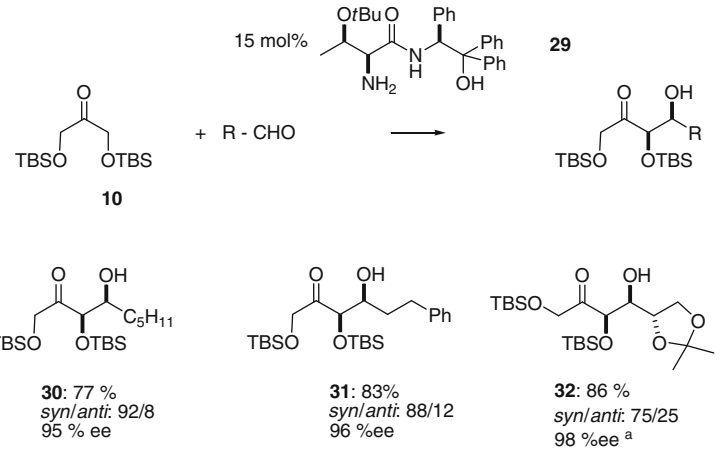


Scheme 2.4 Proline-catalyzed aldol additions of protected dihydroxyacetone (*R*)-proline was used as catalyst

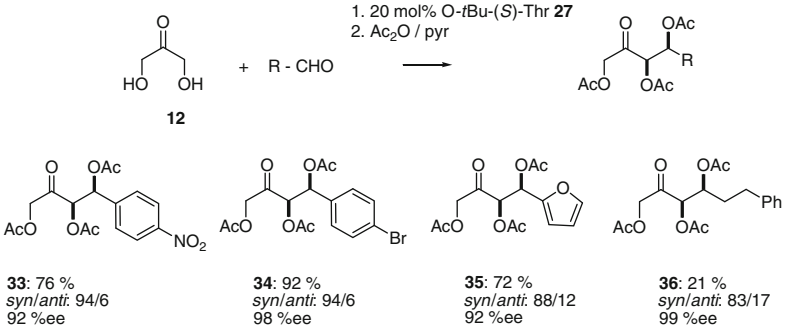


Scheme 2.5 *Syn*-selective aldol additions of protected dihydroxyacetone

method by aldol reactions with the threonine-derived catalyst (O-*t*Bu-(*S*)-threonine **27**). However, under these conditions mostly nonenolizable, aromatic aldehydes were successfully deployed (with the exception of hydrocinnamaldehyde → low yields). The aldol adducts were obtained with high degrees of diastereo- as well as enantioselectivities [49] (Scheme 2.7).



Scheme 2.6 Threonine amide catalyzed *syn*-selective aldol additions of enolizable aldehydes

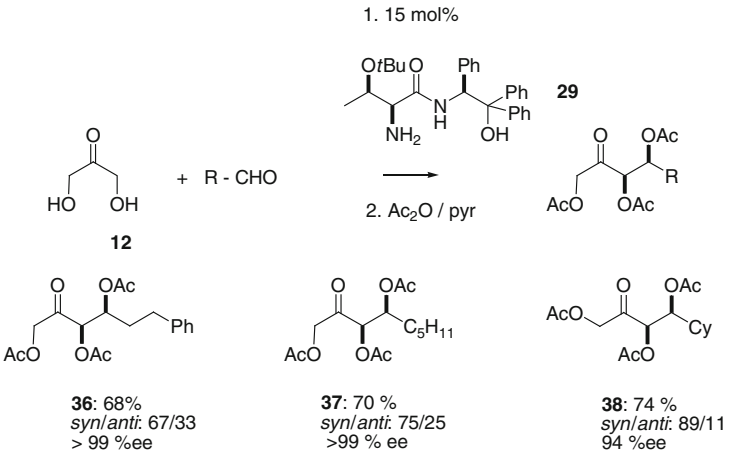


Scheme 2.7 *Syn*-selective aldol additions of unprotected dihydroxyacetone (*S*)-configured glyceraldehyde was used

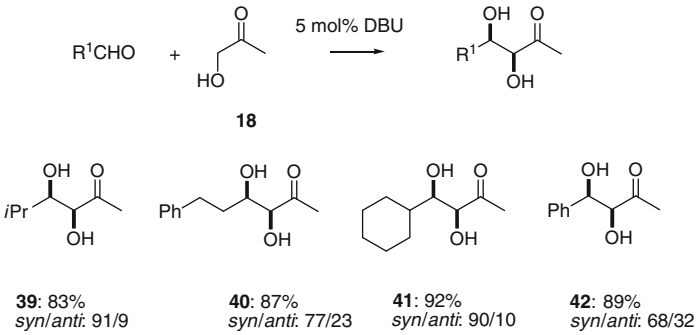
A continuous improvement of this strategy was achieved by the deployment of threonine amide catalyst **29** in reactions with unprotected dihydroxyacetone. Under these conditions even enolizable aldehydes were successfully reacted with unprotected dihydroxyacetone. Again, *syn*-configured products were isolated with high degrees of selectivity (Scheme 2.8).

During this development it was found that aldehydes react in the presence of catalytic amounts of tertiary amines with hydroxyacetone **18** to give the corresponding aldol adducts. High *syn*-diastereoselectivities were observed during this aldol-step [50].

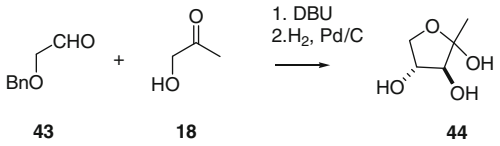
An application of this amine-catalyzed direct aldol addition in total synthesis of carbohydrates is given by the synthesis of 2-deoxy-xylulose (Schemes 2.9 and 2.10).



Scheme 2.8 Aldol additions of unprotected dihydroxyacetone with enolizable aldehydes



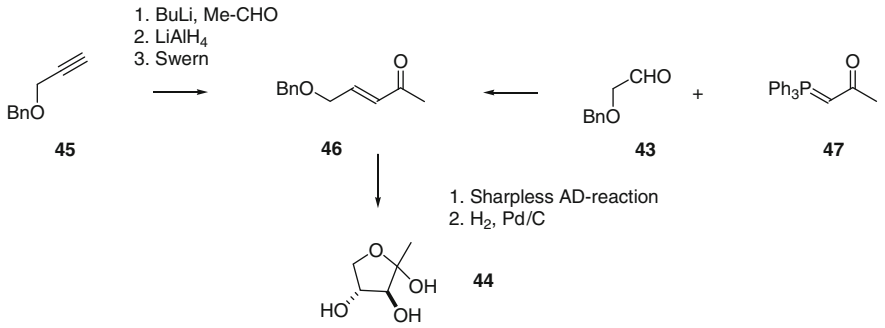
Scheme 2.9 Amine-catalyzed aldol addition with hydroxyacetone



Scheme 2.10 Amine-catalyzed access to 1-deoxy-xylulose

For a comparison between this operationally simple organocatalyzed approach to 1-deoxy-xylulose and classical syntheses see Scheme 2.11 [51].

The successful results of the hydroxyacetone series were transferred to amine-catalyzed direct aldol additions of dihydroxyacetone. With the help of chiral aldehydes this transformation provides an easy access to optically pure

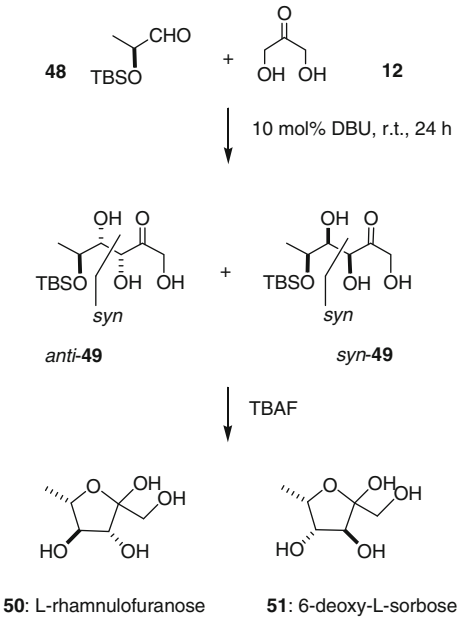


Scheme 2.11 Classical routes to 1-deoxy-D-xylulose

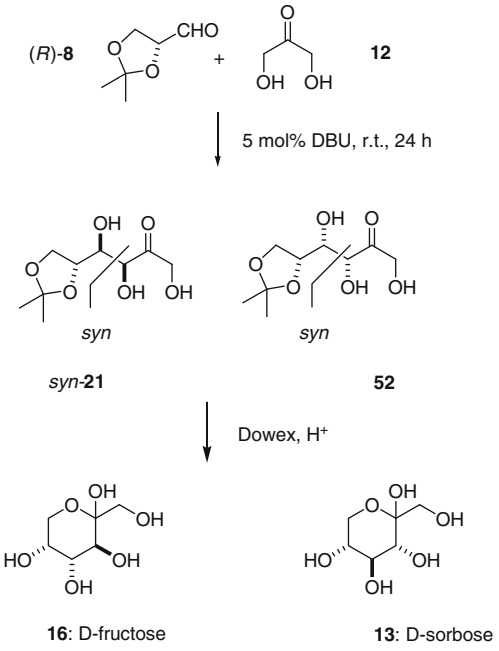
ketohexoses. To this end (*S*)-lactaldehyde and isopropylidene-protected (*R*)-glyceraldehyde were tested as substrates in these reactions. An unselective reaction was observed when DBU was employed as a tertiary amine. Under these conditions a diastereomeric mixture of the corresponding L-rhamnolufuranose **50** and L-deoxysorbose **51** was obtained. A 1,2-asymmetric induction of the protected (*S*)-lactaldehyde **48** was not observed (*anti*/*syn*: 1/1, Scheme 2.12). As discussed above, an extremely high *syn*-diastereoselectivity during the C-C-bond formation was detected again (*syn*/*anti*: >98/2).

Moreover, similar results were observed when protected (*R*)-glyceraldehyde was applied in this reaction. In the presence of 5 mol% of DBU protected D-fructose

Scheme 2.12 *Syn*-selective amine-catalyzed aldol additions of unprotected dihydroxyacetone



Scheme 2.13 *Syn*-selective aldol additions to D-fructose and D-sorbose

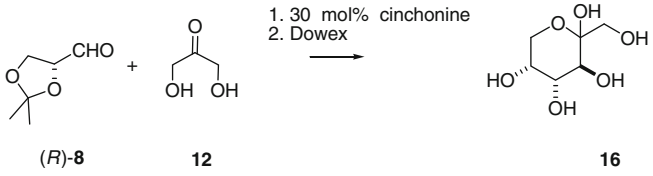


syn-**21** and protected D-sorbose **52** were identified with a ratio of 1/1 (Scheme 2.13). Similiar ratios were obtained by deployment with other tertiary amines.

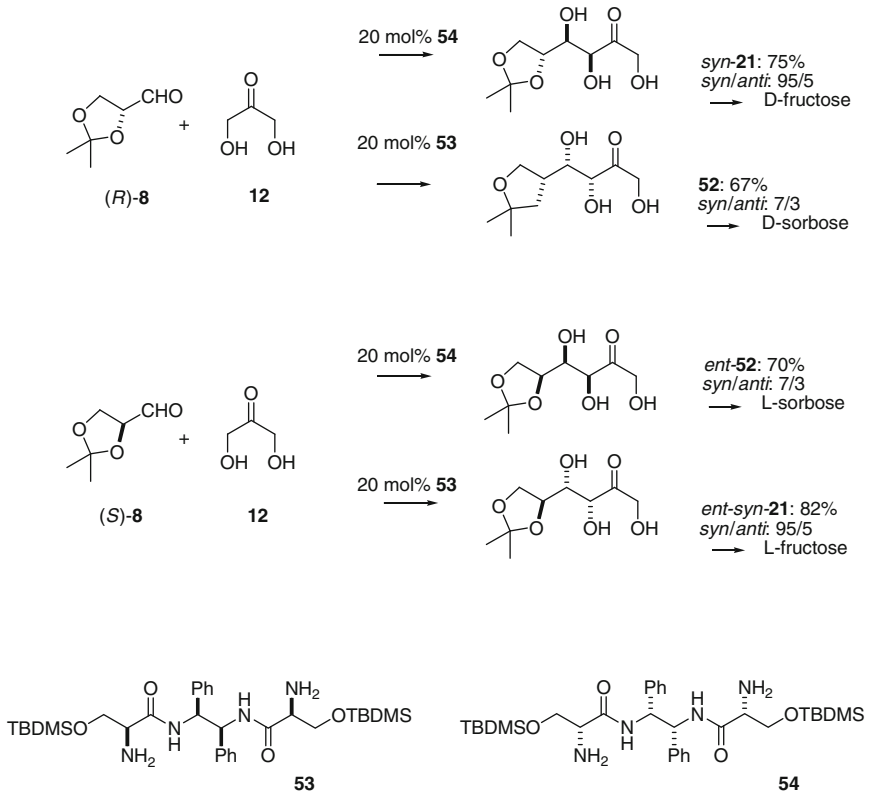
By deploying cinchonine as the tertiary amine extremely high diastereoselectivities were observed. Under these conditions the exclusive formation of D-fructose **16** was detected (Scheme 2.14).

Furthermore, a similar *syn*-selective direct aldol reaction of unprotected dihydroxyacetone with glyceraldehyde has been realized using serine-based organocatalysts **54** and **53**. By application of these catalysts (20 mol%) protected fructose or sorbose were observed with excellent degrees of diastereoselectivity (up to 95:5 dr) [52, 53]. Based on a matched/mismatched situation a selective access to both series, D- as well L-ketoses is given (Scheme 2.15).

On the basis of these results the actual situation in the de novo organocatalyzed-aldol additions to carbohydrates can be summarized as follows. The synthetic



Scheme 2.14 C_3+C_3 strategy to D-fructose

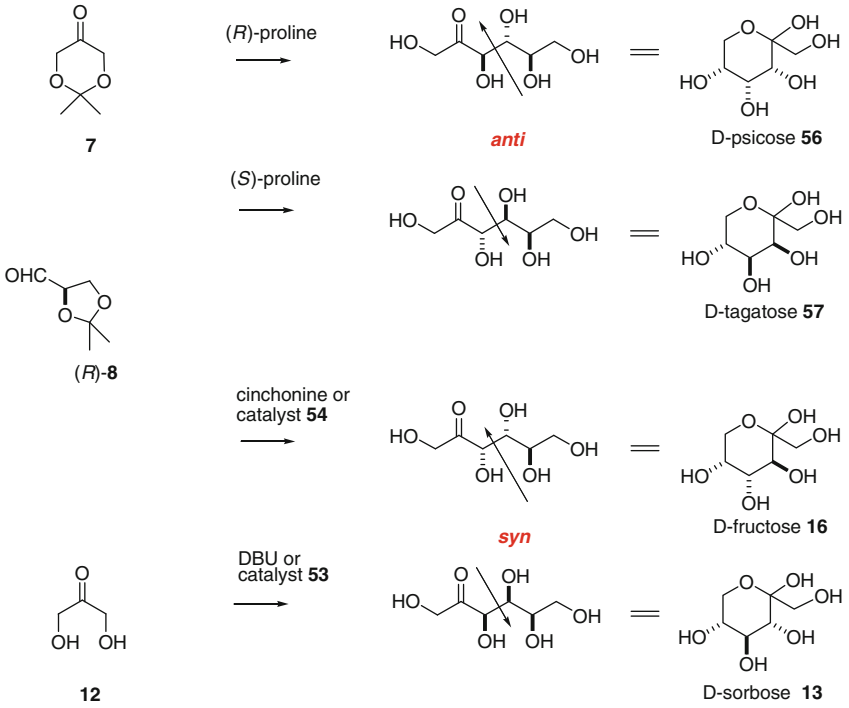


Scheme 2.15 Optional access to D- or L-ketoses

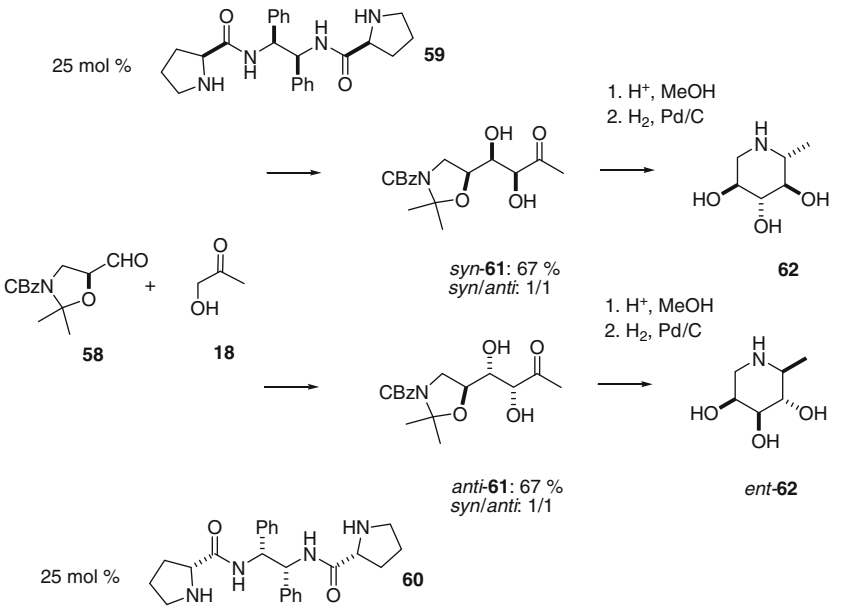
approach to the four D-ketohexoses appears to be solved by the methods described above. As discussed, there exist several different possibilities to synthesize psicose, tagatose, fructose and sorbose. This can be easily accomplished by the C_3+C_3 strategy for the de novo carbohydrate synthesis. Additionally, by deployment of (*R*)-glyceraldehyde and protected derivatives of DHA in proline-catalyzed aldol additions an optional approach to psicose **56** and tagatose **57** is given. This is due to the *anti*-preference of proline-catalyzed aldol additions with protected dihydroxyacetone (Scheme 2.16). On the other hand D-fructose and D-sorbose are accessible, with the required *syn*-configuration, by tertiary amine-catalyzed aldol addition of unprotected DHA and (*R*)-glyceraldehyde **8** (Scheme 2.16).

When used with protected isoserinal **58** and hydroxyacetone in prolinamide-catalyzed aldol additions iminocarbohydrates **62** can be accessed easily (Scheme 2.17) [54].

This reaction is catalyzed by both enantiomers of the prolinamide-derived catalyst (**59** or **60**) with the same excellent relative *syn*-diastereoselectivity. Once more though, an asymmetric induction was not observed. *Syn*- and *anti*-configured aldol

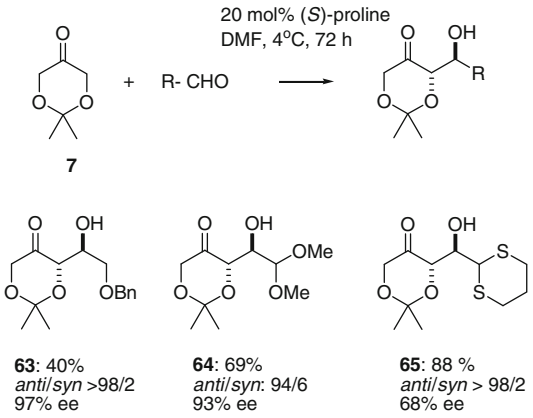


Scheme 2.16 General overview of de novo synthesis of ketohexoses



Scheme 2.17 Iminocarbohydrates by the C_3+C_3 strategy

Scheme 2.18 Proline-catalyzed aldol additions of C_2-aldehyde-derivatives to protected dihydroxyacetone



products **61** were detected in a ratio of 1/1. Thus, by deployment of enantiomeric prolinamide catalysts **59** or **60** the same results with regard to configurative outcome was obtained in both series.

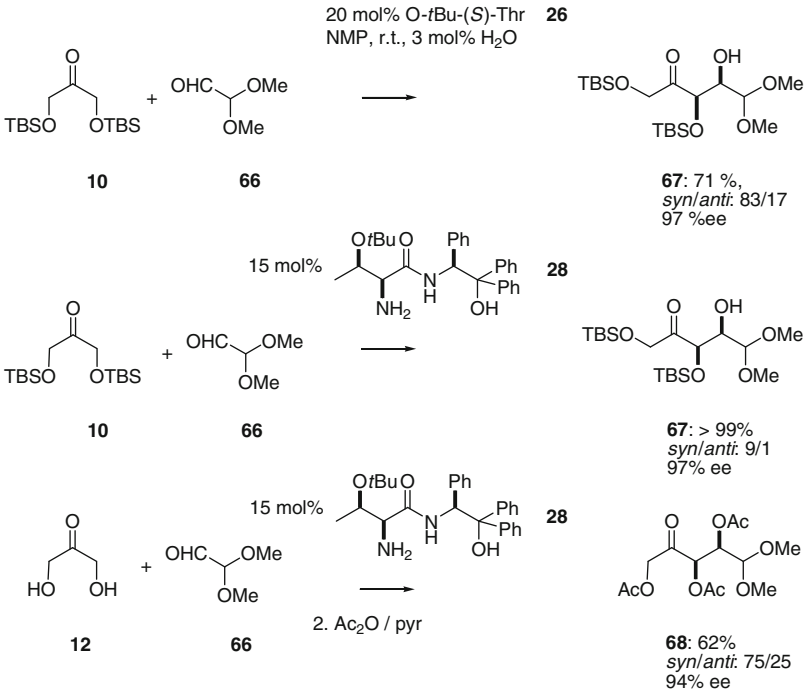
The C_3+C_2 strategy promises to be a valuable synthetic tool for the total synthesis of pentoses. Enders and Grondal have highlighted the utility of this concept [55]. Aldol adduct **63**, **64** or **65** were isolated with high degrees of enantio- as well as *anti*-diastereoselectivity in reactions of protected DHA **7** (C_3-unit) with dimethoxyacetaldehyde or benzyloxy acetaldehyde (C_2-unit) in the presence of substoichiometric amounts of (*S*)-proline under these reaction conditions (Scheme 2.18). By further stereoselective reduction an easy access to ribose or lyxose is given.

For similar results obtained by BINAM-prolinamide-catalyzed aldol addition using the same substrates see reference [56].

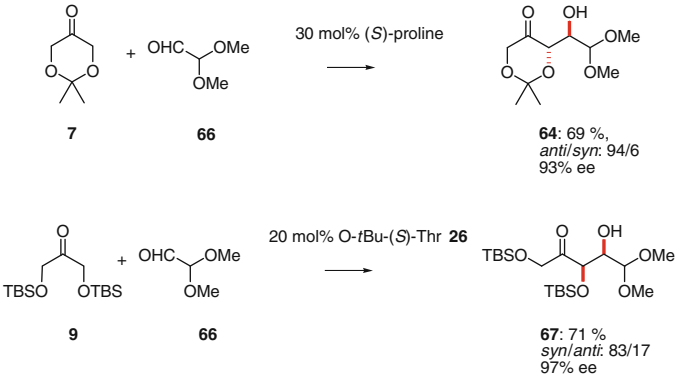
An access to *syn*-configured aldol adducts of protected DHA with protected glycolaldehyde has recently been reported by the group of Barbas (**67** and **68,** Scheme 2.19) [47, 48]. Substoichiometric amounts of derivatives of threonine were used as catalysts in these aldol transformations. Even unprotected dihydroxyacetone can be deployed under these conditions.

As a summary, the two optional approaches to *anti*- or *syn*-configured pentoses are depicted in Scheme 2.20. By proline-catalysis and optional subsequently stereoselective reduction an access to D-ribose or L-lyxose precursor is given, whereas by threonine-catalysis and subsequent reduction precursors of D-xylose are accessible.

The totalsynthesis of thioketoses can be realized via C_3+C_2 strategy through aldol additions of protected dihydroxyactone with acetylmercatoacetaldehyde **69** by means of proline [57]. Alternatively, same authors have synthesized thioketose **71** by aldol additions of protected DHA with halogen acetaldehyde and subsequent substitution with sodium sulphide. The same results with regard to diastereoselectivity were obtained in both sequences (Scheme 2.21).

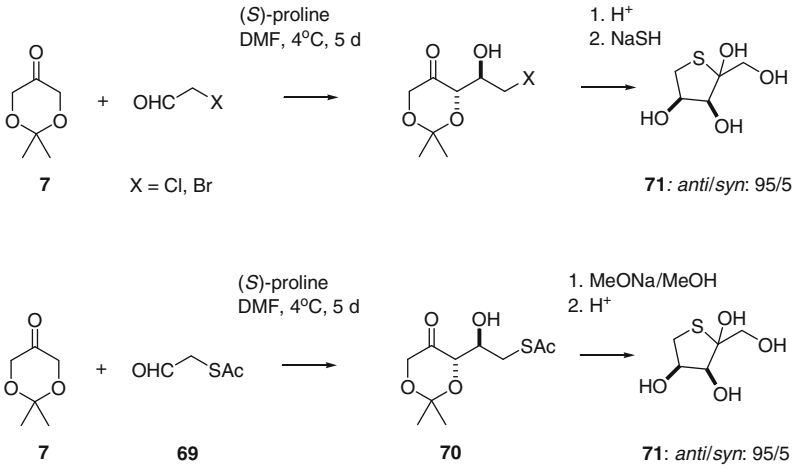


Scheme 2.19 *Syn*-selective C_3+C_2 approach to L-threo-pentuloses

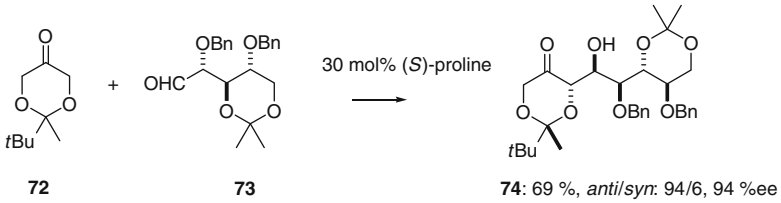


Scheme 2.20 Comparison between *anti*- and *syn*-selective C_3+C_2 approach to pentoses

By proline-catalyzed aldol reactions of protected dihydroxyacetone **72** with chiral hydroxylated aldehyde (**73**: C_5-unit) an access to "higher" carbohydrates is given (C_3+C_5 → octulose) [58]. The corresponding *manno*-configured octulose **74** was isolated with a high degree of distereoselectivity (Scheme 2.22).



Scheme 2.21 C_3+C_2 strategy to thioketoses

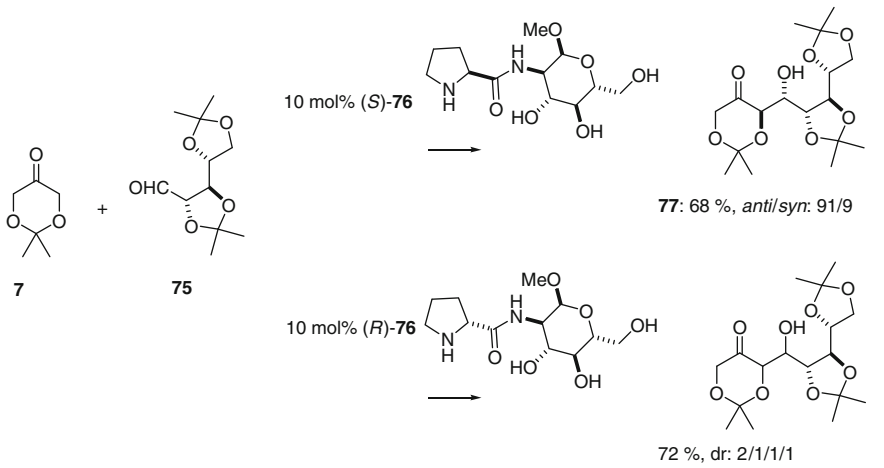


Scheme 2.22 C_3+C_5 strategy to precursor of m*anno*-octulose

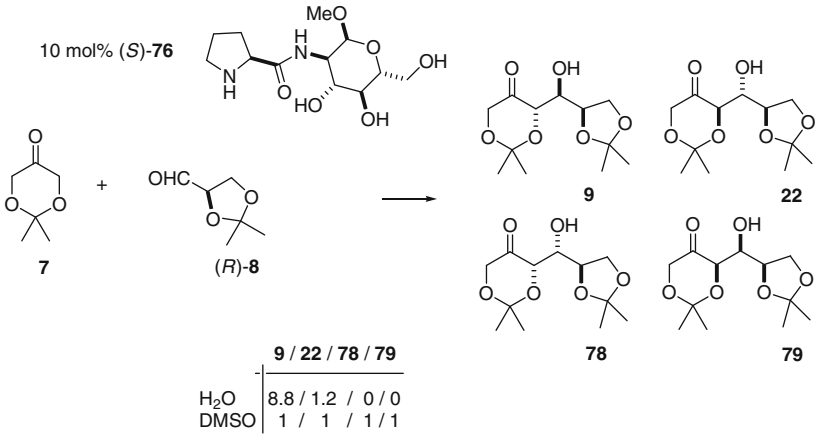
When prolinamide-derived catalyst (*S*)-**76** was used in this strategy (C_3+C_5 → octulose) *gluco*-configured octulose **77** were isolated with high degrees of diastereoselectivity (Scheme 2.23) [59]. A total mismatched case was observed when used with the corresponding *R*-configured catalyst **76**. In this reaction all possible 4 diastereoisomers were detected in a ratio of 2/1/1/1.

During these investigations the authors detected a strong influence of the solvent on the configurative outcome of this aldol reaction. High stereoselectivities were obtained with water as the solvent. In strong contrast to that, a completely unselective reaction was observed with DMSO as the solvent (Scheme 2.24).

Recently, two reports have been published that describe organocatalyzed access to C-nucleosides. Interestingly, though the authors followed different strategies to synthesize C-nucleosides, they obtained comparable results. Britton and co-workers elaborated a one-pot variation of a proline-catalyzed α-chlorination of aldehydes followed by a proline-catalyzed aldol reaction with protected dihydroxyacetone [60]. The resulting aldol adduct **81** can be reduced in a 1,3-*syn*- or 1,3-*anti*-selective fashion. Thus D- or L-configured C-glycosides optionally can be accessed as depicted in Scheme 2.25.



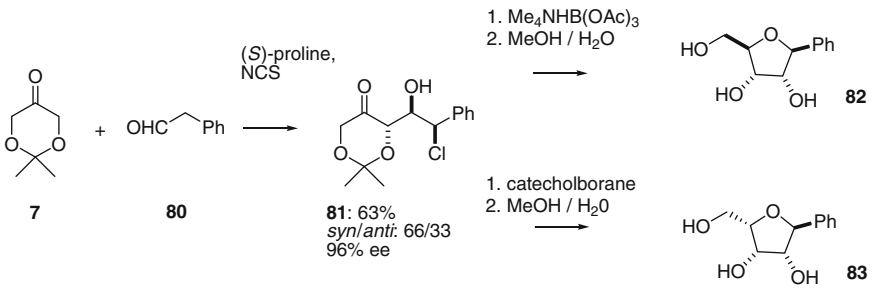
Scheme 2.23 *Gluco*-octulose by C_3+C_5 strategy



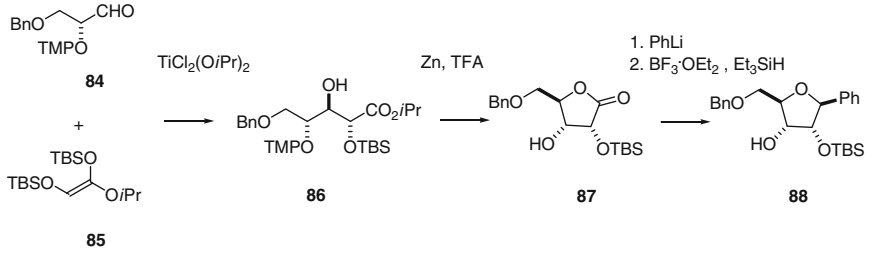
Scheme 2.24 Solvent dictates the configurative outcome

To compare this elegant proline-catalyzed access to C-glycosides see also a Lewis-acid catalyzed optional construction of the pentose-skeleton elaborated by MacMillan and co-workers [61]. This sequence is made up of a combination of metal- and organocatalyzed transformations. The sequence starts with an organocatalyzed α-oxidation of 3-benzyloxy-propionaldehyde to yield the TMP-protected aldehyde **84**. This process was elaborated by the MacMillan group itself very recently [62].

A subsequent Lewis-acid catalyzed substrate-controlled Mukaiyama reaction of chiral aldehyde **84** with silylenol ether **85** yields the carbohydrate skeleton **86** (with



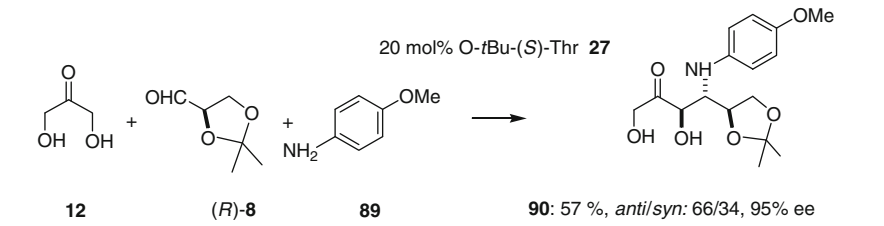
Scheme 2.25 Proline-catalyzed access to C-glycosides



Schema 2.26 MacMillan organocatalyzed approach to pentoses TMP = 2,2,6,6-tetramethylpiperidinyl

the required ribose-configuration). Reductive cleavage of TMP group and subsequent cyclization give an access to the lactone **87** (Scheme 2.26).

Furthermore, the organocatalyzed aldol reaction of protected dihydroxyacetone allows an access to amino-carbohydrate derivatives. When used with primary amines in organo-catalyzed Mannich-reactions, optically active aminosugar-derivatives can be obtained [63–71]. For an example of a threonine-catalyzed Mannich reaction see Scheme 2.27. The *anti*-selectivity, which is observed in this reaction with threonine-derived catalyst **27**, can be explained by considering the transition states. It is assumed that the bulky PMP-group directs the incoming aldehyde in the reactive Si-side position [72].



Scheme 2.27 Asymmetric organocatalyzed Mannich reaction: total synthesis of protected aminoketoses

2.2 Organocatalyzed Aldol Reactions of Aldehydes with Aldehydes: Access to Aldoses

Via the C_2+C_2+C_2 strategy a synthetic access to aldohexoses is possible. A necessary prerequisite for a successful execution of this strategy is the defined and stereoselective connection of three protected glycolaldehydes. This prerequisite was accomplished by Northrup et al. [73, 74]. The authors employed an organocatalyzed aldol addition/Mukaiyama aldol addition reaction sequence. By a proline-catalyzed aldol addition of O-protected glycol aldehydes the *anti*-configured aldol adducts **91** or **92** (chiral C_4-unit) were isolated with high degrees of enantioselectivities (Scheme 2.28).

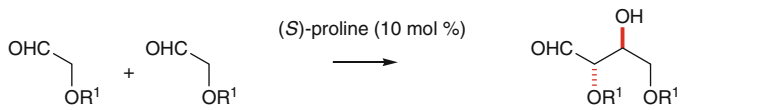
Depending on the conditions of a subsequent stereocontrolled Mukaiyama-reaction an access to protected L-allose **95**, L-mannose **96** or L-glucose **97** is possible. Following this protocol, protected carbohydrates were isolated with high degrees of stereoselectivities (Scheme 2.29).

Also, MacMillan and coworkers describe an application of this methodology in the total synthesis of brasoside and littoralisone. Starting with a (*R*)-proline-catalyzed homodimerization of benzyloxyacetaldehyde **43** the synthesis of the configurative defined aldol product **91** was accomplished. Subsequent Mukaiyama-reaction catalyzed by $MgBr_2$ yielded the required intermediate **98** by the same strategy as discussed above (Scheme 2.30) [75].

A further application of this methodology was reported by Mainkar et al. [76]. The authors used this Mukaiyama/proline approach for the synthesis of O-spiro-C-aryl glycosides.

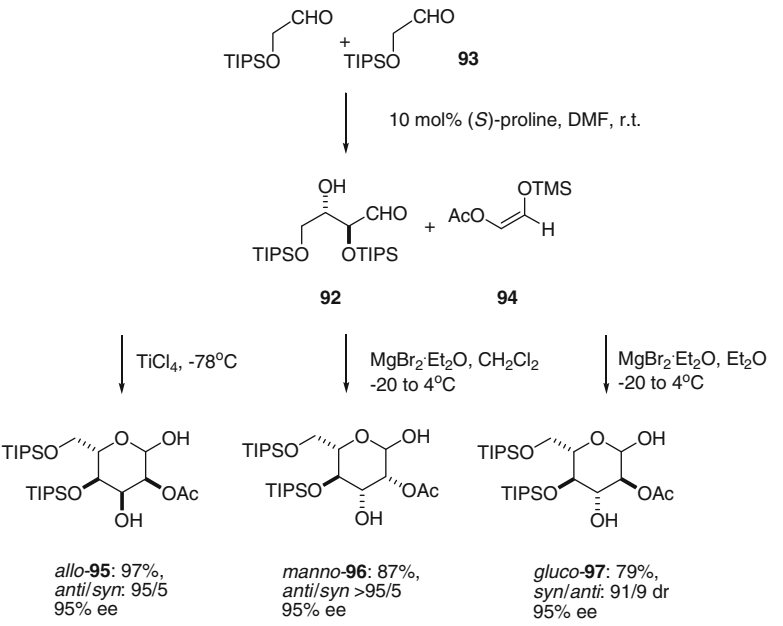
A full proline-catalyzed approach to carbohydrate derivates by the C_2+C_2+C_2 strategy was developed by Casas and co-workers [77]. The authors employed a one-pot, two-step aldol approach for the stereoselective construction of aldohexoses. By optional deployment of (*R*)- or (*S*)-proline an access to D- or L-configured carbohydrates is given.

When used with (*R*)-proline followed by (*S*)-proline-catalysis, D-configured carbohydrates can be accessed. In contrast to that, by the deployment of (*S*)-proline followed by a (*R*)-proline-catalysis, L-configured carbohydrates were obtained (compare **101** and *ent*-**101** in Scheme 2.31). As an example, by the iterative application of (*R*)- and (*S*)-proline an access to L-*manno*-configured carbohydrate-derivative **102** is given (Scheme 2.31) [78].

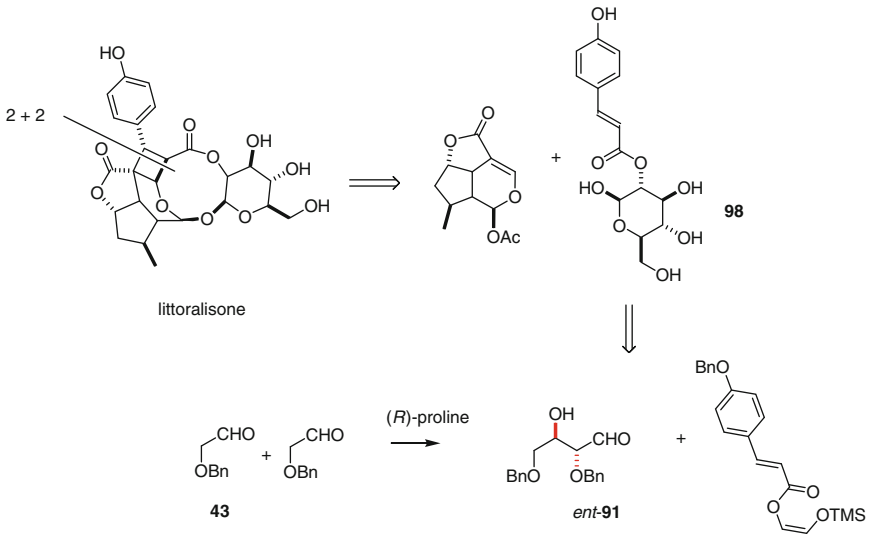


91: R^1= Bn: 78%, *anti*/*syn*: 80/20, 98% ee
92: R^1= TIPS: 92%, *anti*/*syn*: 80/20, 95% ee

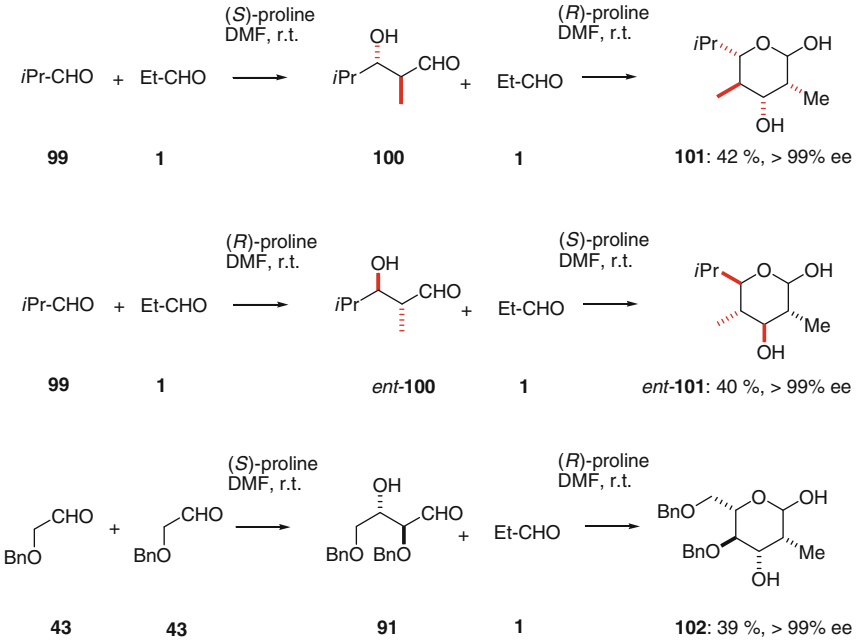
Scheme 2.28 (*S*)-Proline-catalyzed homodimerization of oxygen-substituted acetaldehydes



Scheme 2.29 Organocatalyzed aldol /Mukaiyama-aldol C_2+C_2+C_2 approach to L-configured aldohexoses



Scheme 2.30 Total synthesis of littoralisone



Scheme 2.31 Iterative deployment of (*R*)- and (*S*)-proline in total synthesis of aldohexoses

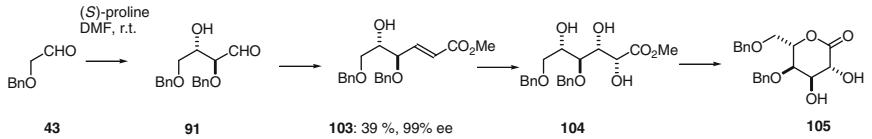
Zinc-proline-complex catalysis gives a nonselective access to all eight aldohexoses. This catalyst was tested in aldol reactions of hydroxyacetaldehyde (C_2+C_2+C_2 strategy) [79–81].

The C_2+C_2+C_2-strategy, utilizing nitroolefines as C_2-building blocks, gives an access to a precursor of carbohydrate derivates by intermolecular Michael/Henry cascade reactions [82].

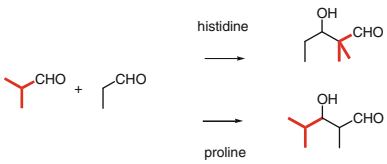
Several reports were published for the total synthesis of tetroses by the C_2+C_2 strategy. These transformations were realized by the deployment of catalytic amounts of proline amide [83] or N-Me leucine ethylester [84].

Moreover, a combination of this C_2+C_2 strategy followed by a Horner-olefination provides an access to carbohydrate precursor **103** with high degrees of stereoselectivity. Subsequent dihydroxylation allows access to protected L-*altro*-configured lactone **105** (Scheme 2.32) [85].

Recently, a histidine catalyzed cross-aldol reaction between enolizable aldehydes was reported. This method represents a breakthrough in direct cross-aldol additions of enolizable aldehydes. Histidine is able to differentiate between two enolizable aldehydes based on their electronic properties. This feature contrasts the nature of proline as a catalyst. Proline differentiates between two different enolizable aldehydes on the base of the steric situation at the α-position of the carbonyl



Scheme 2.32 C_2+C_2 aldol /Horner sequence to aldohexoses

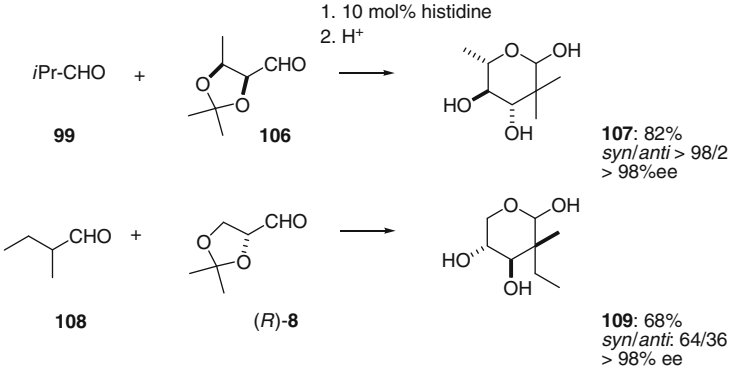


Scheme 2.33 Chemoselectivity of proline- and histidine-catalyzed aldol reactions of enolizable aldehydes

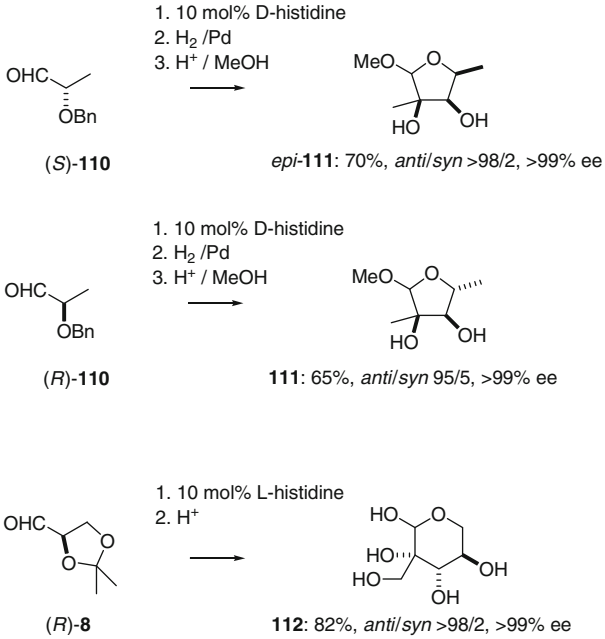
group [86]. α-Substituted aldehydes cannot act as enol-component in proline-catalyzed reactions. This different reaction behavior of proline and histidine is demonstrated in Scheme 2.33.

This exact control allows for a rapid and direct construction of several rare carbohydrates. For example the unusual functionalized carbohydrate precursors **107** and **109** were obtained as a single enantiomer in good yields by this method (Scheme 2.34).

Histidine-catalyzed homodimerization of chiral oxygen containing aldehydes provides access to branched carbohydrates (5-deoxy-2-methyl-L-lyxose **111** and 2-hydroxymethyl-D-lyxose **112** in Scheme 2.35). During these investigations a matched and mismatched situation was observed as a function of the configuration of the α-carbon atom of the starting chiral aldehyde and the configuration of



Scheme 2.34 Histidine-catalyzed C_4+C_2 approach to 2-dimethyl D-*xylo*-boivinose and to 2-methyl-2-ethyl-2-deoxy-xylose by the C_3+C_2 approach

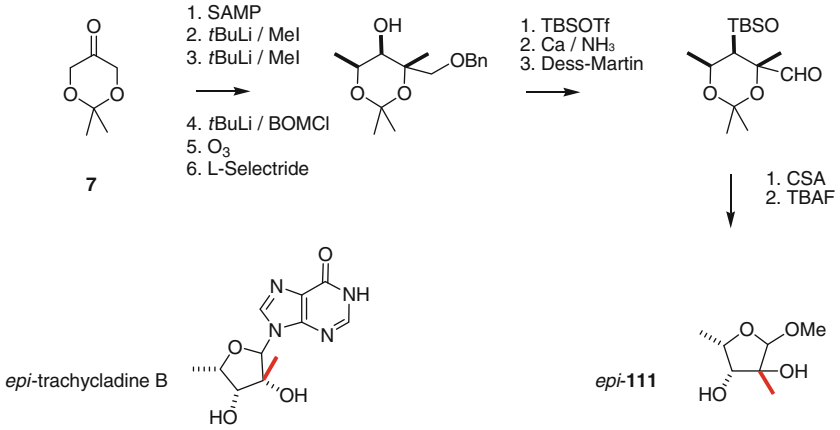


Scheme 2.35 Histidine-catalyzed aldol addition in total synthesis of branched carbohydrates

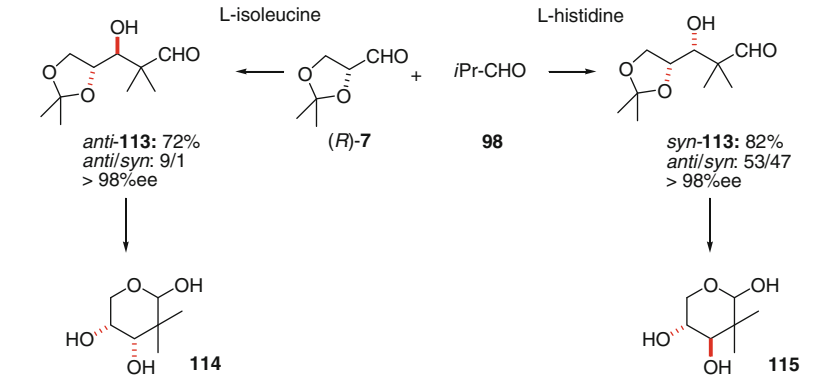
histidine deployed: *S*-configured aldehydes need D-histidine for a matched case, whereas L-histidine is needed for a matched case when using with *R*-configured aldehydes [87, 88].

Methylglycoside **111** represents the carbohydrate moiety of the natural occurring nucleoside trachycladine A and B [89]. By using protected lactaldehyde (*R*)-**110** and D-histidine this branched carbohydrate **111** can be easily accessed. This methodology again provides a shortcut as compared to existing classical total synthesis. Enders and co-workers published a total synthesis of branched carbohydrate *epi*-**111** following their own elaborated SAMP-methodology (Scheme 2.36) [90].

In contrast to the inherent notoriously high *syn*-diasteroselectivity that is detected in histidine-catalysis the application of isoleucine as an organocatalyst offers the synthesis of *anti*-configured aldol products [91]. Isoleucine discriminates between the electronic nature of enolizable aldehydes—the same chemoselectivity is observed as in the histidine-series. On the other hand, by utilization of isoleucine the same diastereoselection is observed as by proline-catalysis (*anti*-diastereoselectivity). Thus, the deployment of histidine or isoleucine gives an optional access to different configured carbohydrates, as depicted in Scheme 2.37.



Scheme 2.36 Total synthesis of *epi*-trachycladine B 2-methyl-2-ethyl-2-deoxy-xylose by the C_3+C_2 approach

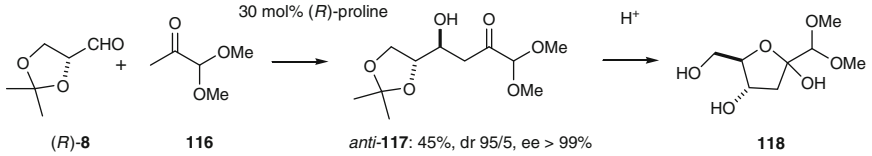


Scheme 2.37 Comparison of isoleucine- and histidine-catalyzed aldol additions with protected glyceraldehyde

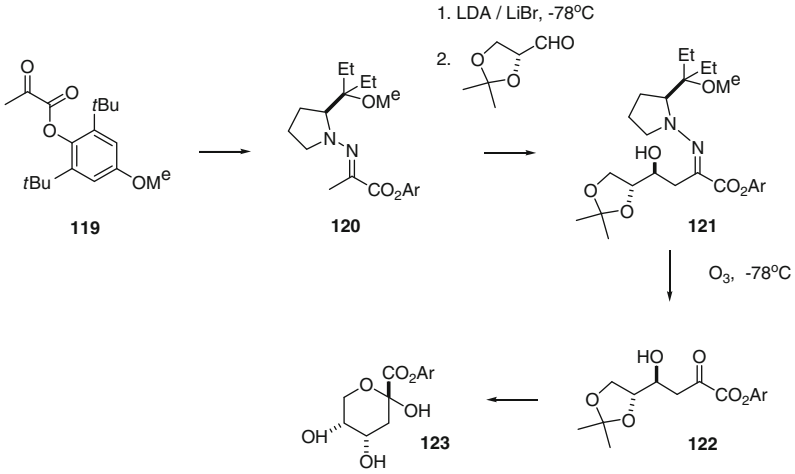
2.3 Aldol Reactions with Pyruvic Derivatives: Access to Ulosonic Acid Derivatives

Ulosonic acids are carbohydrates involving an α-keto acid structure. Precursors of ulosonic acid are easy accessible by the C_3+C_3 strategy. A proline-catalyzed access to ulosonic acid precursor **118** based on this strategy was realized by Enders and Gasperi (Scheme 2.38) [92]. The authors used dimethoxyacetone **116** as the enol-component in this transformation.

25 years ago the same group reported results of investigations to enantioselectively access these precursors by the well known RAMP- or SAMP-methodology [93–95].



Scheme 2.38 Proline-catalyzed C_3+C_3 access to precursors of ulosonic acid

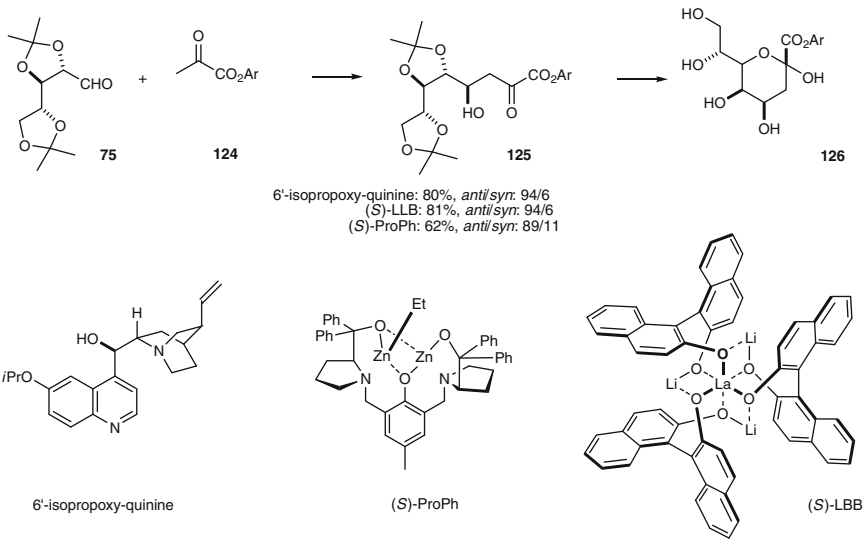


Scheme 2.39 Enantioselective access to ulosonic acid derivatives by the SAEP-method SAEP: (*S*)-1-amino-2-(1-ethyl-1-methoxypropyl)pyrrolidine

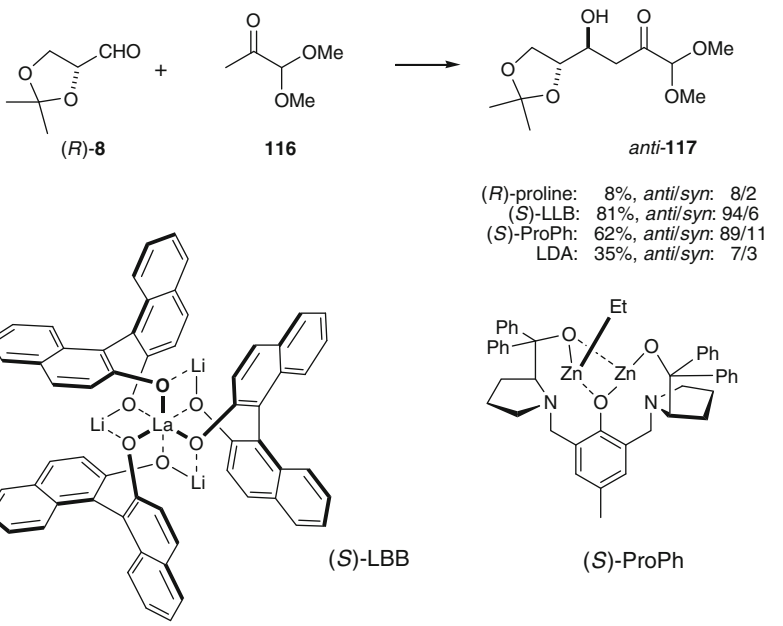
To underline the tremendous progress of organic chemistry made by the development of organocatalysis this auxiliary-based sequence is depicted in Scheme 2.39. The authors used the sterically more demanding SAEP-auxiliary instead of the SAMP-group in this sequence to increase the stereoselectivity of the aldol step.

Another example for the synthesis of ulosonic acid is the short cinchona alkaloid-catalyzed access to octulosonic acid ester **126** (KDO-ester) [96]. In the direct aldol addition of pyruvate esters **124** the authors compared substituted cinchona alkaloids, the heterobimetallic catalyst (LBB) from the Shibasaki group and the proline-derived Zn-complex (ProPh) from the Trost group as catalysts. Similar results were obtained in both series, in metalcatalyzed as well as organocatalyzed reactions (compare results of (*S*)-LBB-catalysis with results of the quinine-catalyzed reactions in Scheme 2.40). A slight decrease of both yields and diastereoselectivities was detected using with the proline-derived Zn-catalyst (*S*)-ProPh.

A further, similar comparison was arranged by the same authors in the total-synthesis of ulosonic acid precursors. These results were extended to the application of the C_5+C_2 strategy. Using this strategy a one-step access to KDO precursor **117** was elaborated (Scheme 2.41) [97].



Scheme 2.40 Total synthesis of KDO-esters by the C_5+C_3 strategy Ar = 2.6-*tert*Bu-4-MeO-(C_6H_2)



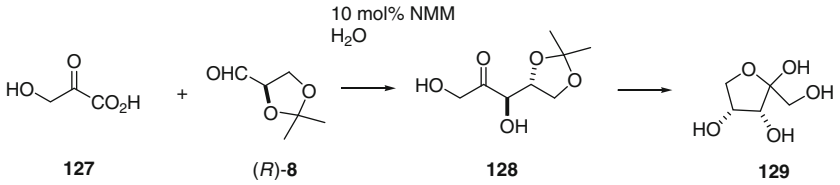
Scheme 2.41 C_3+C_3 strategy to ulosonic acid precursor

2.4 Miscellaneous

A further useful tool for the total synthesis of carbohydrates is the decarboxylative aldol reaction. For an overview of this development see reference [98–101]. During our investigations in this field we have developed several protocols for amine-catalyzed decarboxylative aldol additions using α-keto acids. By utilization of β-hydroxypyruvic acid **127** an access to optically pure ketopentoses is given (Scheme 2.42) [102]. The actual acylanion is generated by N-methylmorpholine (NMM)-catalyzed decarboxylation of β-hydroxypyruvic acid **127**.

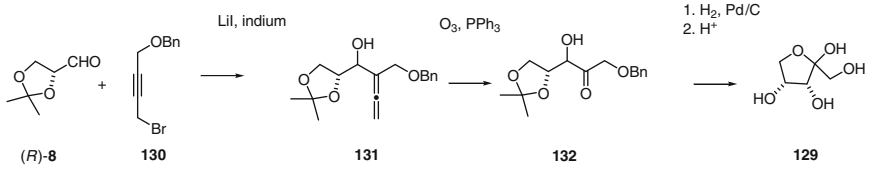
For comparative reasons and to demonstrate the efficiency of this decarboxylative process a multistep transformation for the total synthesis of *erythro*-pentulose is depicted in Scheme 2.43. In this process the "α-hydroxyacetyl anion" equivalent is generated by an indium-mediated allenylation followed by an oxidative cleavage of the allene intermediate **131** [103].

A decarboxylative approach to aminocarbohydrates has been opened, by the utilization of β-keto acids as enol component and the readily available imines of aldehydes deployed [104]. This decarboxylative Mannich-reaction proceeds catalyst-free. The basicity of the imine used proved strong enough to induce the decarboxylation of the starting β-keto carboxylic acids **133**. After optimization of this process, the products were formed with high degrees of diastereoselectivity.



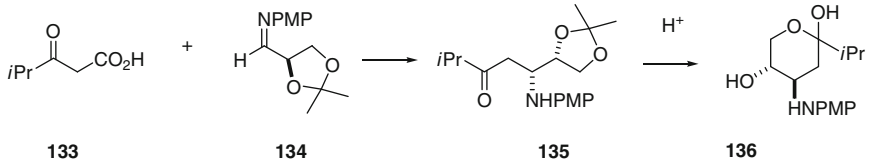
127 (*R*)-**8** **128** **129**

Scheme 2.42 Total synthesis of *erythro*-D-pentulose by decarboxylative aldol addition



(*R*)-**8** **130** **131** **132** **129**

Scheme 2.43 Total synthesis of *erythro*-pentulose



133 134 135 136

Scheme 2.44 Organocatalyzed synthesis of aminoketoses by decarboxylative Mannich- reaction

Thus, by the application of chiral aldehydes an access to optically active aminoketoses is given, as depicted for the *syn*-configured Mannich product **135** (Scheme 2.44).

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Chapter 3
Organocatalyzed Cascade Reaction in Carbohydrate Chemistry

Abstract The extensive and extremely strong development of organocatalysis over the last years provided versatile methodologies for convenient utilization of the carbonyl function of unprotected carbohydrates in C–C-bond formation processes. These biomimetic amine-activated mechanisms enable multiple cascade-protocols for the synthesis of a large scope of carbohydrate derived compound classes. Several, only slightly different protocols have been developed for the application of 1.3-dicarbonyls in stereoselective chain-elongation of unprotected carbohydrates and the synthesis of highly functionalized C-glycosides of defined configuration. Furthermore, the latter class of compounds can also be accessed by the use of methyl ketones. So a high substrate scope is available for the installation of desired functionalities in C-glycosides. By a one-pot, operationally simple cascade reaction of isocyanides with unprotected aldoses and amino acids an access to a broad range of defined glycosylated pseudopeptides is given. The elaborated organocatalyzed cascade-reactions provide defined access to highly functionalized carbohydrate derivatives. Depending on the reaction conditions different origin to control the installation of configuration during the bond-formation process were observed. The demonstrated organocatalyzed cascade sequences indicate the great potential of unprotected carbohydrates in the synthesis of highly functionalized bio-mimetic structure motifs by operationally simple, one-pot protocols.

Keywords Carbohydrate chain-elongation · C-glycosides · Selectivity · Knoevenagel/michael cascade · Multi-component –Ugi reaction · Unprotected carbohydrates · Glycopeptides

Due to the great biological importance of carbon chain elongated carbohydrates, the synthesis of this structural diverse compound class has attracted high synthetic interest from the scientific community. Among the elongated carbohydrates, C-Glycosides have gained considerable importance over the last few decades, since they are configuratively stable under enzymatic conditions and less prone to cleavage at the anomeric carbon. As such they are appealing substrates for chemical biology and medicinal chemistry.

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The result of this development is a constantly increasing demand for methods for the stereoselective synthesis of this class of glycosides. Though many of methods exist for the synthesis of these compounds from carbohydrate derivatives or analogues [1], their applications are hampered by low yields and selectivities. This is caused by necessary complex and extensive manipulations of protective groups in combination with the activation of the anomeric carbon atom.

The diversity of the developed glycosylation protocols is mainly driven by the different requirements of aglycons deployed, the availability of substrates and their complexity, as well as the achieved selectivities. A general solution for this synthetic problem does not exist as yet. This holds true especially for the common metal-organic reactions as they are Reformatsky reaction [2, 3], Knoevenagel reaction [4–7], allylation [8–11] or aldol reaction [12].

A big simplification of accessing 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 [13–23], for reviews in this field see [24–26], whereas examples for Horner olefination (even in aqueous reaction medium) will be found in reference [27, 28]. The reactions were carried out mostly at higher temperature. Also, allylations of even unprotected glycals have been reported in the presence of equimolar amounts of trimethylsilyl trifluoromethanesulfonate [29].

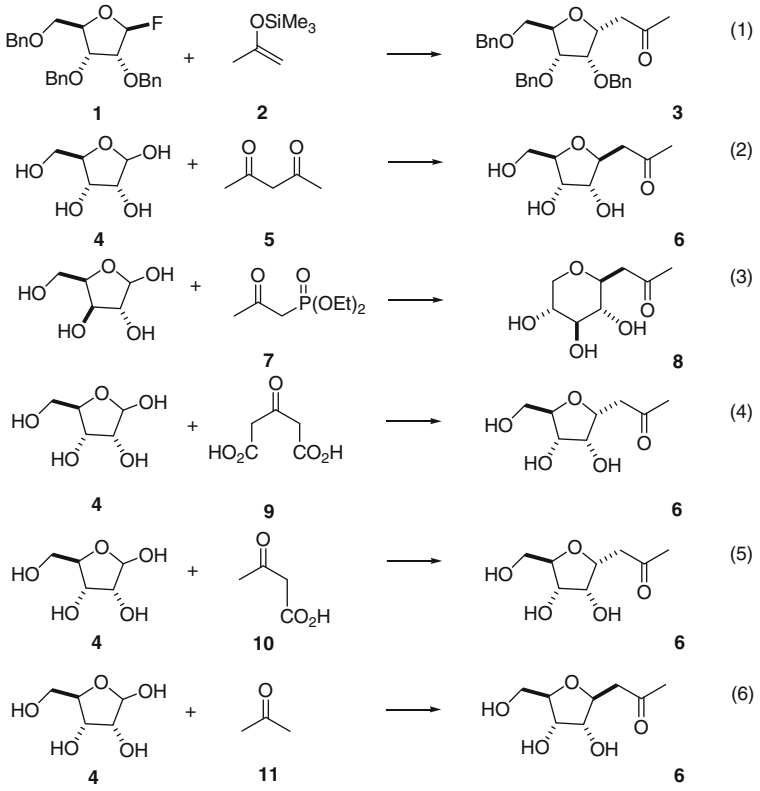
The aggressive development of organocatalysis over the last 15 years offers new strategies for C-glycosylation. In contrast to the reactions described above, these new methods give not only access to the target structural motif from unprotected and unactivated carbohydrates, but also enable catalytic procedures.

This development is briefly illustrated by the synthesis of C-glycosides of acetone and several pentoses. For reasons of comprehensibility and comparability these reactions are discussed with unprotected and unactivated ribose in Scheme 3.1. The methods depicted in Scheme 3.1 represent direct C-glycosylation processes of unprotected and unactivated carbohydrates (with the exception of Eq. 1, Scheme 3.1).

In addition there are many methods for C-glycosylation reactions using protected and activated carbohydrates in multi-step sequences [30–40]. However, these transformations are not the matter of the discussion here.

Twenty-five years ago glycosides of acetone were first synthesized by the Mukaiyama reaction. Protected and activated carbohydrates were reacted with silyl enol ether of acetone **2** in the presence of catalytic amounts of Lewis acids ($BF_3 \cdot Et_2O$). Under these conditions the expected products were isolated in partially quantitative yields (Eq. 1, Scheme 3.1) [41, 42].

Ten years later Lubineau et al. reported the direct reaction of unprotected carbohydrates with acetylacetone **5** in aqueous alkali media [43], *early cascade reactions (Knoevenagel/intramolecular oxa-Michael addition) of unprotected and unactivated carbohydrates with barbituric acid derivatives were reported by [44, 45]. By application of this method an access to different mixtures of furanoid- and pyranoid-structures of α- and β-configured C-glycosides [46, 47] were obtained. The ratio of the products depends on the conditions of execution for this reaction and the



Scheme 3.1 Syntheses of C-glycosides of acetone

carbohydrates deployed (Eq. 2, Scheme 3.1). This Knoevenagel/Michael/retro-Claisen-aldol cascade is carried out at high temperature (60–90 °C) and is associated with the loss of a C2-fragment of the starting 1.3-dicarbonyl component (when used with acetylacetone).

Applications of this direct C-glycosylation process can be found as a key step in the synthesis of glucosidase-inhibitors [48, 49], of exogene gene inductors [50], inhibitor on neoglycoprotein/cell surface binding [51], amphophilic carbohydrates [52], carbohydrates of pyrazols [53] and antiproliferative agents [54], derivatives of barbituric acid [55], activators of glycosaminoglycane synthesis [56], surface-active carbohydrates [57, 58], fluorescent labels for glycomics [59] or glycoconjugates [60]. Furthermore this transformation has been used for the synthesis of L-fucose and L-galactose [61]. For an overview of Knoevenagel reactions of unprotected and unactivated carbohydrates see reference [62].

An alternative access to C-glycosides is given by Wittig- or Horner-olefination of unprotected carbohydrates with the corresponding phosphonate. Subsequent intramolecular oxa-Michael reaction gives an access to glycoside **8** of acetone.

A big excess of base is necessary for the reaction (example of xylose in Eq. 3, Scheme 3.1) [27].

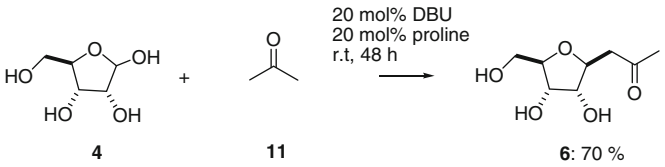
We successfully developed several amine-catalyzed decarboxylative aldol/oxa-Michael cascade reactions deploying unprotected and unactivated carbohydrates to access glycosides of acetone. Useful substrates for this transformation are acetonedicarboxylic acid **9** or acetoacetic acid **10** (Eqs. 4 and 5, Scheme 3.1). These reactions are catalyzed by tertiary amines at room temperature. The corresponding C-glycoside **6** was isolated with good yields (60 %) and selectivity (β/α: 3/1) [63].

During these investigations we observed an amine-catalyzed formation of C-glycosides of unprotected carbohydrates with acetone (Eq. 6, Scheme 3.1). This reaction is catalyzed by a combination of tertiary amines and proline. By means of this methodology an easy, catalytic access to C-glycosides can be realized under mild conditions. This operationally simple and efficient base-catalyzed transformation initiated further investigations.

In a first series an optimization of the catalytic system was conducted. A reaction was not observed when used with amine bases. The same is true for the deployment of proline. Proline alone does not induce a reaction. In contrast to these results, a clear reaction was detected when used with an equimolar mixture of proline and DBU. Thus, an access to the unprotected acetone glycoside **6** is given with good yields of approximately 70 % (Scheme 3.2).

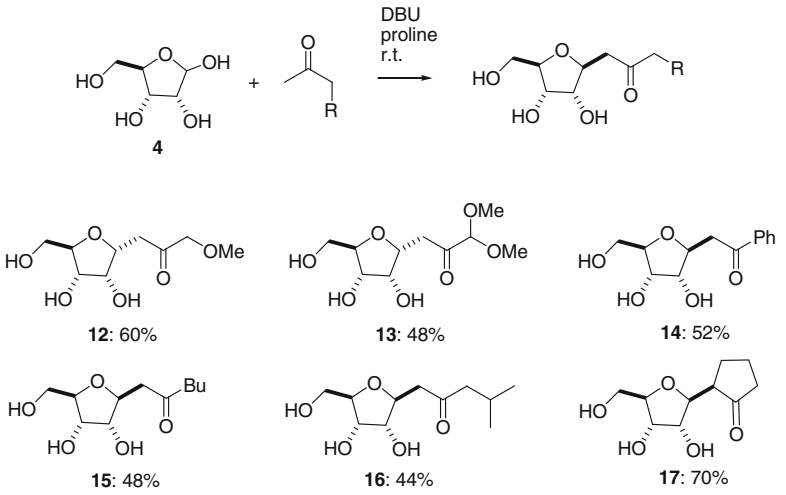
This observation was generalized by extending the substrate scope. To this end several carbohydrates and methyl ketones were tested in this transformation. For achieving quantitative yields, proline and DBU should be used in equimolar amounts at room temperature. Under these conditions not only acetone, but several unsymmetrical methyl ketones can be transformed into their corresponding C-glycosides (**12**–**17**) (Scheme 3.3) [64].

As the working model for the reaction mechanism an aldol-condensation followed by an intramolecular oxa-Michael process is assumed. Considerable degrees of β-diastereoselectivity at the former anomeric carbon atom (C-1) were detected in the isolated products (dr ∼ 7/3). Under the described reaction conditions the furanoid structure of C-glycosides was detected as the major product. When used with oxygen-containing ketones in this cascade reaction the favored formation of hemiketals was observed. The corresponding C-glycosidic ketones can be easily obtained by subsequent treatment with acidic ion-exchanger.



4 **11** **6**: 70 %

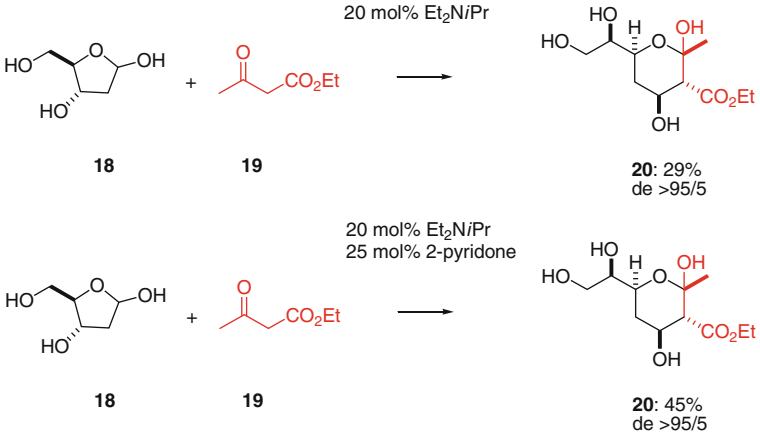
Scheme 3.2 Amine-catalyzed cascade reactions on ribose and acetone



Scheme 3.3 Synthesis of C-glycosides by cascade reactions of ribose with methyl ketones

By further expanding the variety of substrates—from methyl ketones to 1.3-dicarbonyl compounds—a chain-elongation of the employed carbohydrates instead of a C-glycosylation process was observed.

The deployed 1.3-dicarbonyl compounds were incorporated into the carbon skeleton of the carbohydrates, although with low yields. Initial experiments with deoxyribose **18** and ethyl acetoacetate **19** were conducted in the presence of catalytic amounts of diisopropylethylamine. Chain elongated 1-deoxy ketose **20** resulted from a Knoevenagel-addition/ketalization cascade reaction and was isolated in only moderate yields (29 %) but with an extremely high degree of stereoselectivity (Scheme 3.4) [65]. Only one single stereoisomer was detected by NMR-experiments. The C–C bond formation proceeds with an extremely high degree of *syn*-diastereoselectivity. The corresponding *anti*-configured product was not detected. These observations are consistent with results we obtained in amine catalyzed direct aldol additions with dihydroxyacetone [66, 67]. Further extension of this observation to other pentoses yields the corresponding Knoevenagel-addition adducts albeit with lower yields. Moreover, long reaction times are required for these conversions. When used with deoxyribose and ribose highest yields were obtained, whereas lowest yield were found by the employment of xylose. The observed yields in association with the configuration of the corresponding pentoses clearly indicate a correlation with the existence of acyclic structures of the pentoses during the course of the reaction [68, 69]. To overcome the problem of low yields of Knoevenagel addition products we tested 2-hydroxypyridine as an additional catalyst, which is known to have a large effect on the anomerization equilibration of carbohydrates by formation of hydrogen bonds [70–78]. By increasing the equilibrium constant, a higher amount of active acyclic form is available per defined time-unit.



Scheme 3.4 Base-catalyzed Knoevenagel reaction of ribose with ethyl acetoacetate

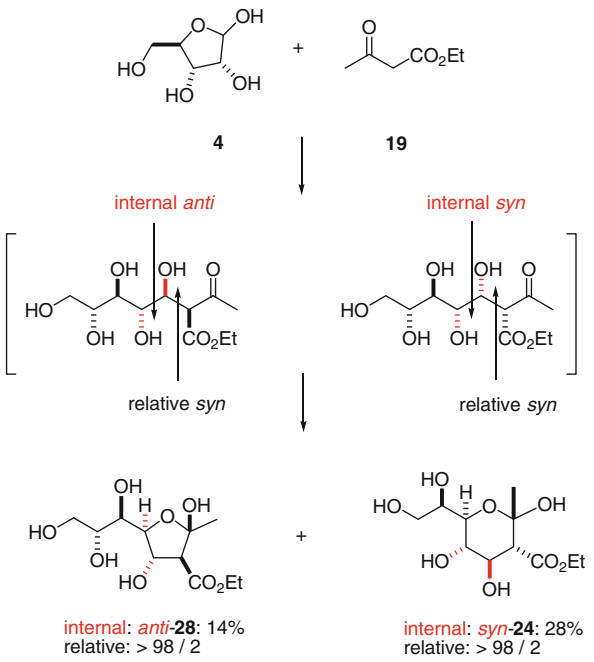
And indeed, an addition of catalytic amounts of 2-hydroxypyridine increased the yields in the reaction of deoxyribose with ethyl acetoacetate **19** (**20**: 29 % → 45 %). The results of these optimization works are depicted in Scheme 3.4.

To use consistent stereodescriptors in further discussions, the configurative results of the reaction of ribose **4** with acetoacetic ester **19** are representatively depicted in Scheme 3.5. The proposed intermediately formed acyclic structures are shown to underline the nomenclature used (in bracket, not detected or isolated).

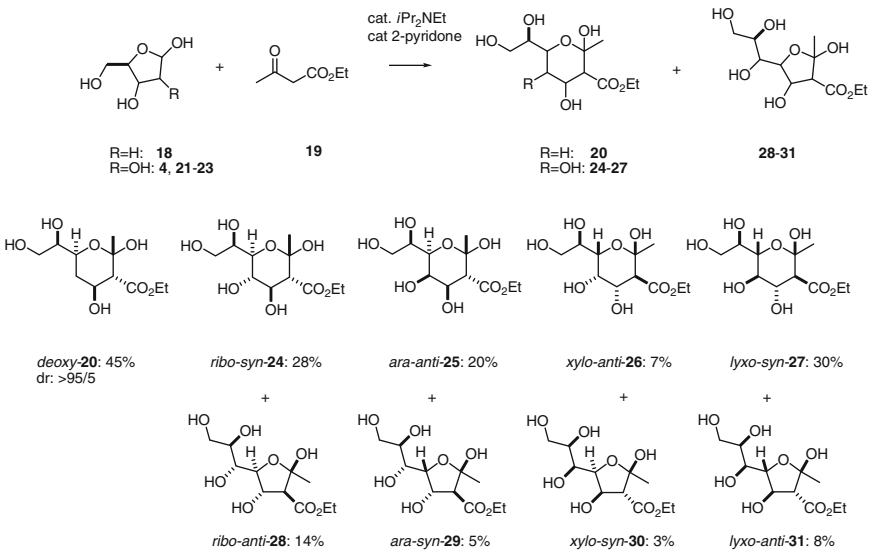
The degree of internal diastereoselectivity is dictated by the existence and by the relative configuration of the 2.3-hydroxy groups of pentoses deployed. Results of reactions of deoxyribose **18** impressively demonstrate this statement. In the deoxyribose-series only one single stereoisomer **20** is detected (missing hydroxy group in 2-position). This fact contrasts results which were obtained in reactions of ribose **4** with acetoacetate **19**. Two products, **24** and **28**, were isolated with extremely high degrees of relative *syn*-configuration. But they differ by their relative, internal configuration (dr ∼ 7/3). Moreover, the relative 2.3-configuration of the deployed pentoses does not simply determine this internal diastereoselectivity. The installation of internal configuration also dictates the formation of pyranoid or furanoid structures of the elongated carbohydrates.

Several different unprotected carbohydrates have been successfully deployed in the cascade reactions with ethyl acetoacetate **19** by subsequent systematic studies. The results of these investigations are depicted in Scheme 3.6 (pentoses) and Scheme 3.7 (hexoses).

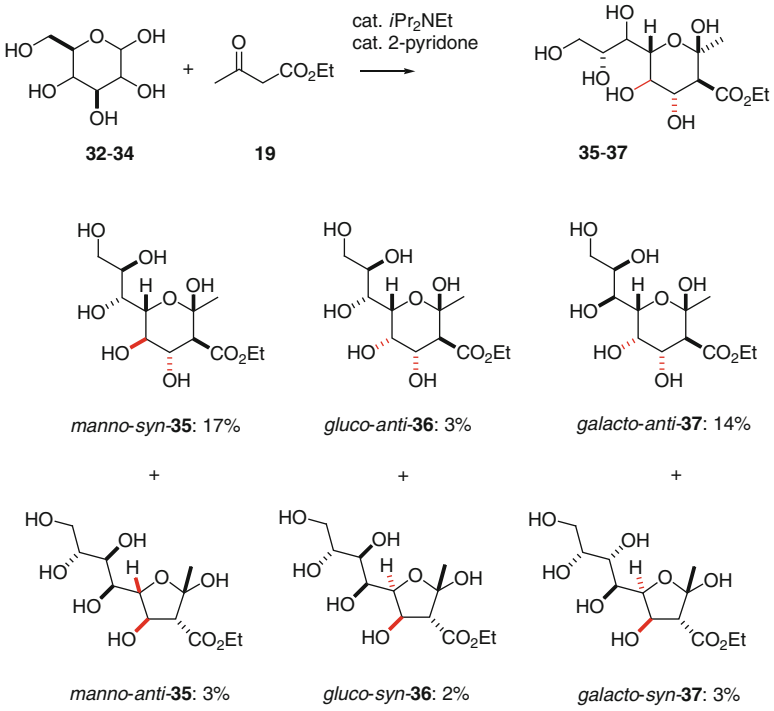
When used with ribose **4**, arabinose **21**, xylose **22** and lyxose **23** two diastereoisomers were detected in reactions with acetoacetate **19**. As discussed above, these findings contrast reactions with deoxyribose **18**. Again, extremely high degrees of *syn*-diastereoselectivity were observed during the C–C bond formation process (relative diastereoselectivity). *Anti*-configured products were not detected under these reaction conditions.



Scheme 3.5 Configurative course of aldol reaction of D-ribose with ethyl acetoacetate



Scheme 3.6 Chain elongation of D-pentoses with ethyl acetoacetate

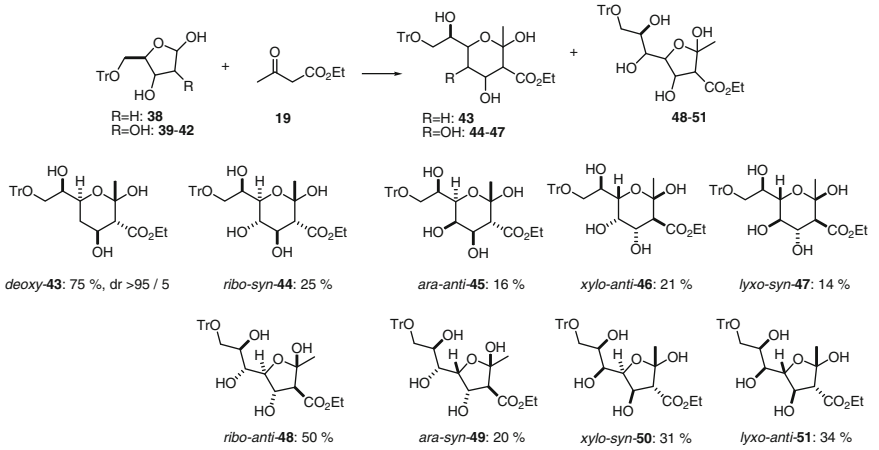


Scheme 3.7 Chain elongation of D-hexoses with ethyl acetoacetate

An additional asymmetric induction was observed concerning the relative, internal configuration. Remarkably, relative 2.3-*anti*-configured pentoses (ribose **4** or lyxose **23**) yield internal *syn*-configured **24** and **27** as the main products. In contrast, when used with 2.3-*syn*-configured arabinose **21** or xylose **22** internal *anti*-configured products **25** and **26** were obtained as main products (Ribose and lyxose are 2.3-*anti*-configured in the acyclic structure, whereas arabinose and xylose are 2.3-*syn*-configured pentoses in their acyclic structures).

Also, this transformation was expanded to reactions with unprotected hexoses albeit with lower yields (mannose **32**, glucose **33** and galactose **34**, Scheme 3.7). The observed diastereoselectivity, as well as the formation of furanoid and pyranoid products, is consistent with the results obtained in the pentose series.

At this point of the investigations we reasoned that yields could be further increased by an enhancing of the effective amount of reactive acyclic species within the mutarotation equilibrium. This can easily be accomplished by a selective protection of the 5-hydroxy group of starting pentoses. In this way the thermodynamically favored pyranoid structures of the starting pentoses are no longer available to participate in the mutarotation-equilibrium [79]. Hence, by removal of this structure from the mutarotation equilibrium the effective amount of acyclic carbonyl species should be increased.



Scheme 3.8 Amine-catalyzed reactions of ethyl acetoacetate with 5-protected D-pentoses

To proof this principle, readily available 5-tritylethers of pentoses **38–42** were deployed as substrates in the Knoevenagel-addition [80]. As expected, Knoevenagel-addition products **43–51** were obtained with higher yields under these conditions (compare results of Scheme 3.6 with those of Scheme 3.8). A strong enhancement of yields was observed in all described reactions. Especially yields of the expected Knoevenagel reaction product of notoriously difficult carbohydrate xylose **22** were quintupled (**26/30**: 10 % → **46/50**: 52 %).

Remarkably, a general inversion of internal diastereoselectivity is observed by deployment of 5-tritylated pentoses **39–42** in these transformations (compare internal diastereoselectivities of Scheme 3.6 with those of Scheme 3.8).

For an overview and a better understanding for the further discussion the results of Schemes 3.6 and 3.8 are summarized in Table 3.1.

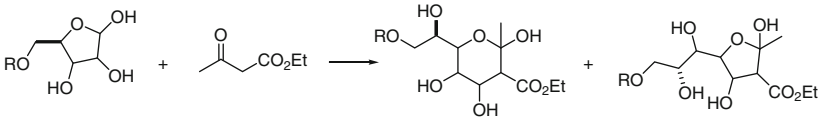


Table 3.1 Amine-catalyzed chain elongation of unprotected carbohydrates

		Yield [%][a,b]			
Entry	Carbohydrate	R=H	*Syn/anti*	R=Tr[c]	*Syn/anti*
1	Ribose	**24/28**	28/14	**44/48**	25/50
2	Arabinose	**25/29**	20/5	**45/49**	16/20
3	Xylose	**26/30**	7/3	**46/50**	21/31
4	Lyxose	**27/31**	30/8	**47/51**	14/34

[a]Isolated yields
[b]*Syn/anti* ratios were evaluated from the ^{1}H NMR spectra by integration of significant signals
[c]Tr triphenylmethyl

Explanations for these different configurative outcomes are given representatively for reactions of lyxose **23** and tritylated lyxose **42** with acetoacetic ester **19** in Scheme 3.9 and for arabinose **21** and tritylated arabinose **40** with acetoacetic ester **19** in Scheme 3.10. The extremely high relative *syn*-diastereoselectivity that is observed in all reactions during the C–C bond formation process is based upon two configurative requirements:

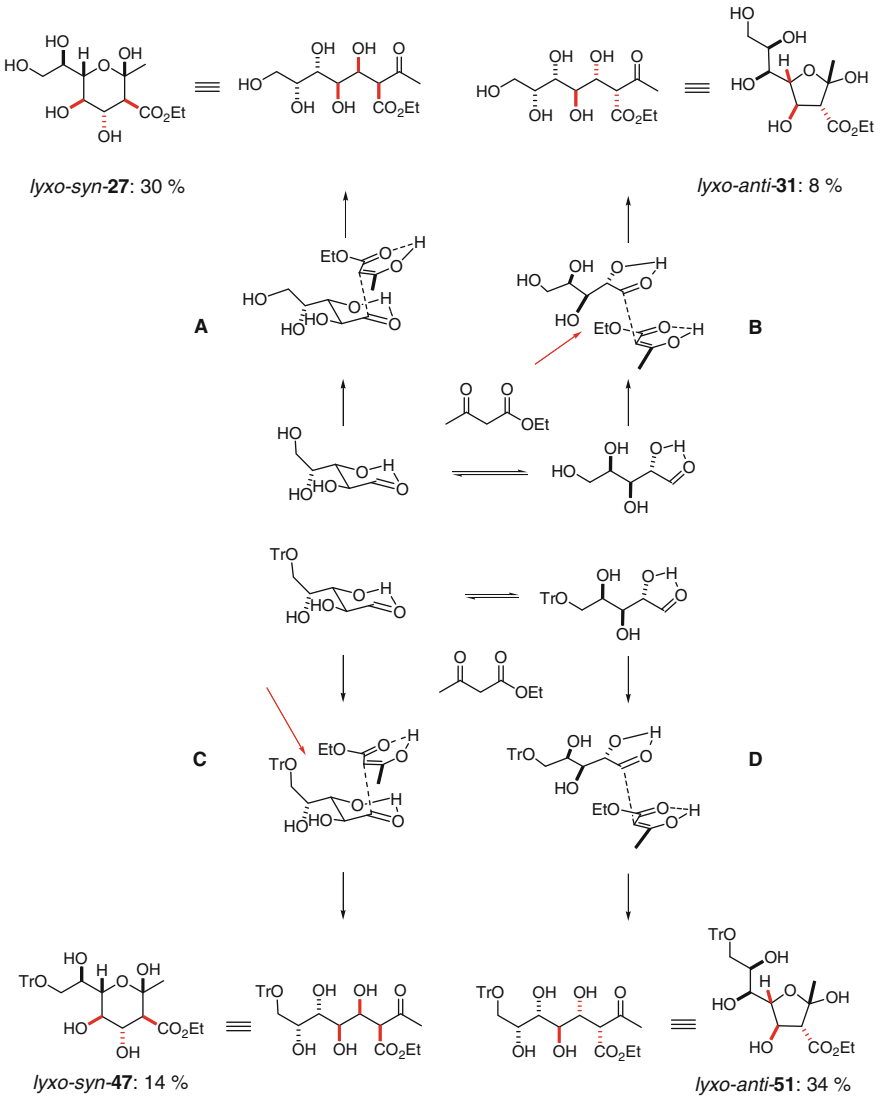
- A *Z*-enolate of acetoacetic ester **19** is the only reactive species. This configuration is stabilized by a hydrogen bond.
- Furthermore, the installation of *syn*-configuration during the C–C bond formation is a consequence of a *like*-approach (*Re*-side attack of acetoacetic ester to the *Re*-side of carbohydrate aldehyde or *Si*-side attack of acetoacetic ester **19** to the *Si*-side of carbohydrate aldehyde).

The correlated proposed stereochemical models are shown in Scheme 3.9 (**A** and **B** for lyxose) and in Scheme 3.10 (**E** and **F** for arabinose). The transition state models (**A/B** and **E/F**), which result in the different internal stereochemical outcome, differ in the ring size of hydrogen bond stabilized cycles of pentoses (**A** and **E** → 6-membered rings; **B** and **F** → 5-membered ring). As a result of that, two transition state models are proposed. For reasons of stereochemical repulsion models **A** and **E** are assumed to be the favored ones (follow red arrows in model **B** and **F**).

As mentioned above, an overall reversal of the internal diastereoselectivity was observed by the deployment of 5-tritylated pentoses (deoxyribose **38**, ribose **39**, arabinose **40**, xylose **41** and lyxose **42**). These findings indicate a general steric shielding caused by the trityl group, which works in addition to and independently of possible hydrogen bonds. In contrast to results of unprotected carbohydrates (Scheme 3.6) the formation of the 5-membered ring is favored due to the bulky trityl group, which assembles in a maximum distance to the C–C bond-formation site. This is demonstrated in Schemes 3.9 and 3.10. When used with 5-tritylated arabinose **40** the bulky trityl substituent directs the acetoacetic ester **19** to a *Si*-side access. As a consequence, *syn*-configured product **49** was detected as the main product (model **H** in Scheme 3.10). Similar considerations hold true for the preference of model **D** in the lyxose-series (Scheme 3.9).

With further experiments we have expanded this amine-catalyzed reaction of ribose **4** to several different β-keto esters. The results of this investigation are depicted in Scheme 3.11. The findings suggest that the internal diastereoselectivity and yield are influenced by the steric demand of the substituents of the acetoacetic esters deployed (**52**–**56**). Moreover, the results demonstrate that this new transformation can be extended to further 1.3-dicarbonyl compounds.

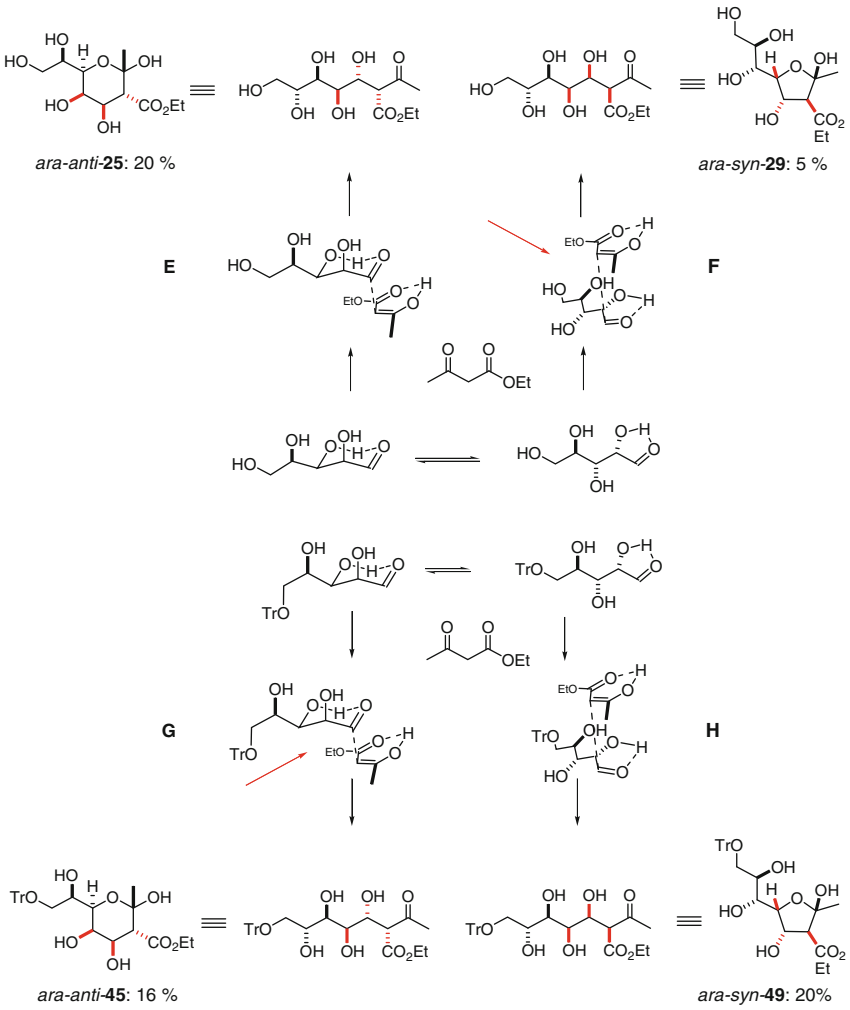
By tweaking the reaction conditions slightly—20 mol% proline instead of 20 mol% 2-pyridone—a completely different reaction sequence is observed. The corresponding C-glycoside **73** was isolated as a single stereoisomer instead of elongated carbohydrate **24**, isolated in reactions of ribose with acetoacetate. This compound was formed by a Knoevenagel condensation/ketalization/oxa-Michael cascade reaction. These different results are demonstrated in Scheme 3.12 [81].



Scheme 3.9 Configurative course of chain-elongation of lyxose **23** and 5-tritylated lyxose **42** with acetoacetic ester **19**

A subsequent optimization yielded the following protocol. When used with 10 mol% DBU and 20 mol% proline the highly functionalized hemiketal, fused tetrahyrofuran **73** was isolated in good to high yields (Scheme 3.13). The reactions were carried out in DMF at room temperature.

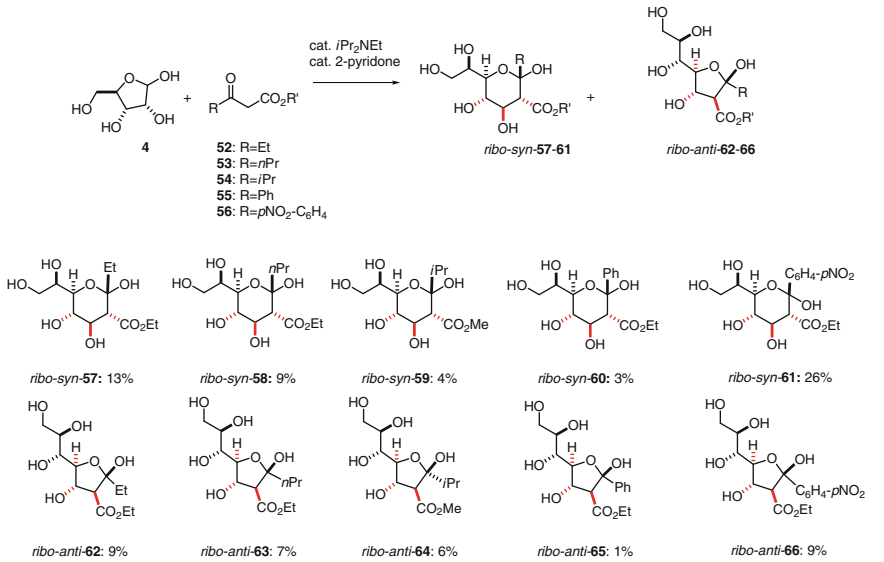
Inspired by these results—achieved by a simple changing of the catalytic system—we have tested the scope and limitations of this new organocatalyzed



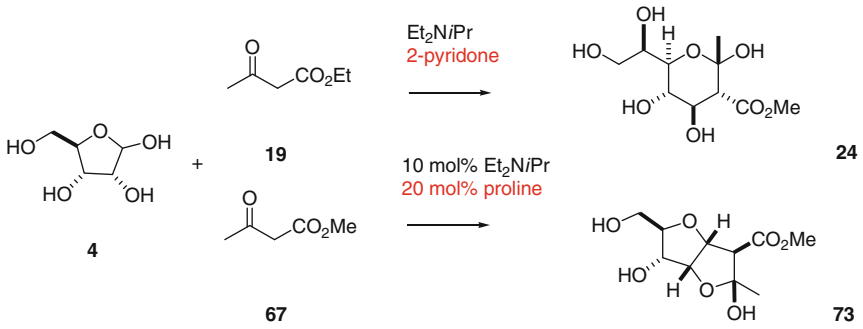
Scheme 3.10 Configurative course of chain-elongation of arabinose **21** and 5-tritylated arabinose **40** with ethyl acetoacetate **19**

cascade reaction. In a first series we reacted unprotected ribose with different substituted
β-keto esters **67–72**. The results of these investigations are depicted in Scheme 3.13. All products, **73–78**, were isolated as single stereoisomers in their furanoid form and were found to be α-configured at the anomeric carbon atom. Byproducts or other stereoisomers were not detected.

The yields of the reaction depend on both, steric demand of the substituent R^1 of the 1.3-dicarbonyl compounds as well as the electronic nature of this substituent. Very good yields were obtained by employing dimethyl 3-oxoglutarate **68** or



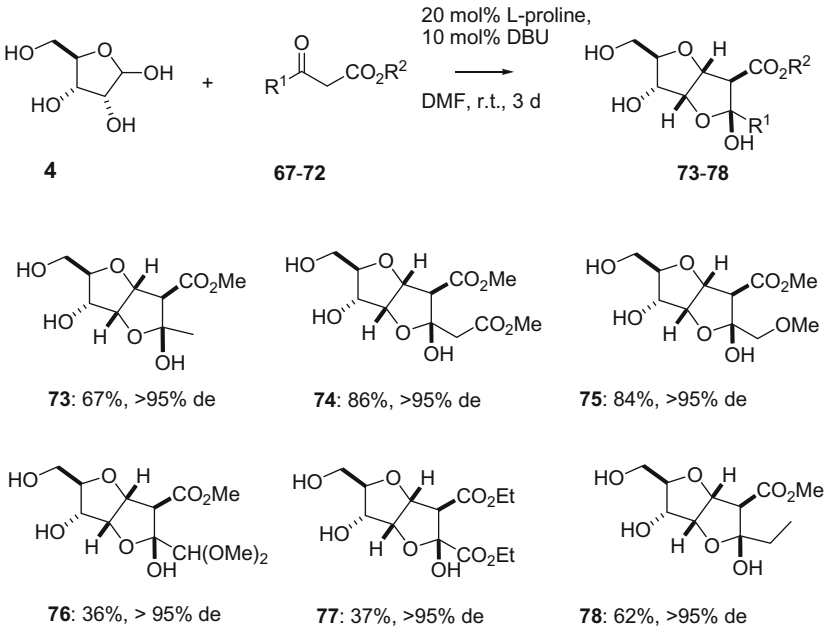
Scheme 3.11 Chain elongation of D-ribose with different substituted acetoacetates



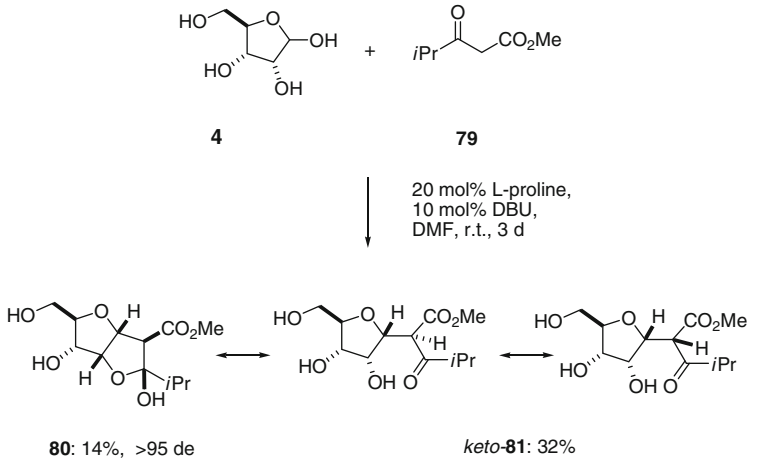
Scheme 3.12 Different cascade reactions of D-ribose with acetoacetates

methyl 4-methoxy-3-oxobutanoate **69**. The lowest yields were observed while using with methyl 4.4-dimethoxy-3-oxobutanoate **70** or diethyl 2-oxalacetate **71** (Scheme 3.13).

Only a single diastereoisomer was detected in all reactions we performed. Remarkably, the configurative course of this reaction is exclusively dictated the configuration at C-2 position of the carbohydrate deployed. This is achieved by a stereoselective formation of the corresponding hemiketal **K** of the intermediately formed Knoevenagel-condensation product **I** during the reaction (see Scheme 3.16). Support for this consideration is not only obtained from NMR characterization of intermediate **K**, but is also given by the reaction of ribose with substituted

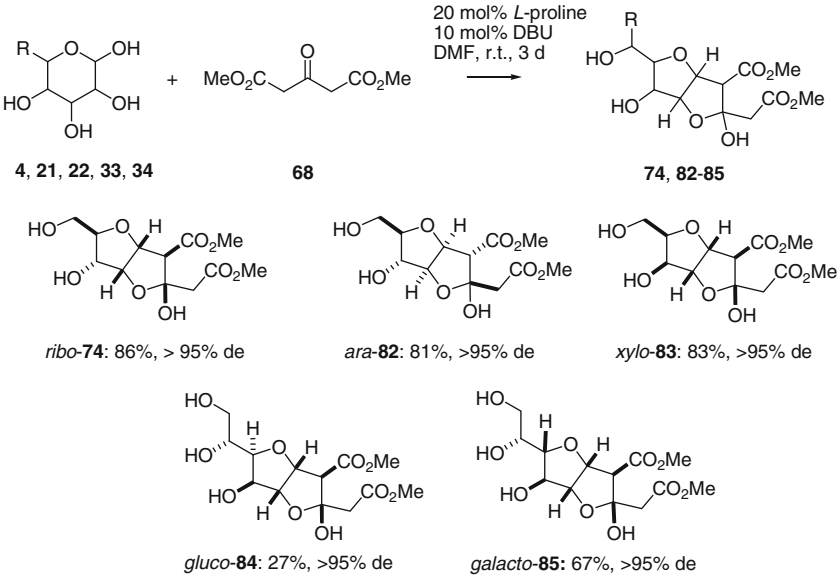


Scheme 3.13 Amine-catalyzed reactions of different β-keto esters with D-ribose



Scheme 3.14 Reaction of D-ribose with acetoacetate **79**

acetoacetates. When used with methyl 4-methyl-3-oxovalerate **79** three products, **80** and two epimers of *keto*-**81** were obtained as an inseparable mixture with an overall yield of 46 %. The formation of this equilibrium, due a retro-ketalization process, cannot be prevented. The laboriously isolated product **80** yield the same

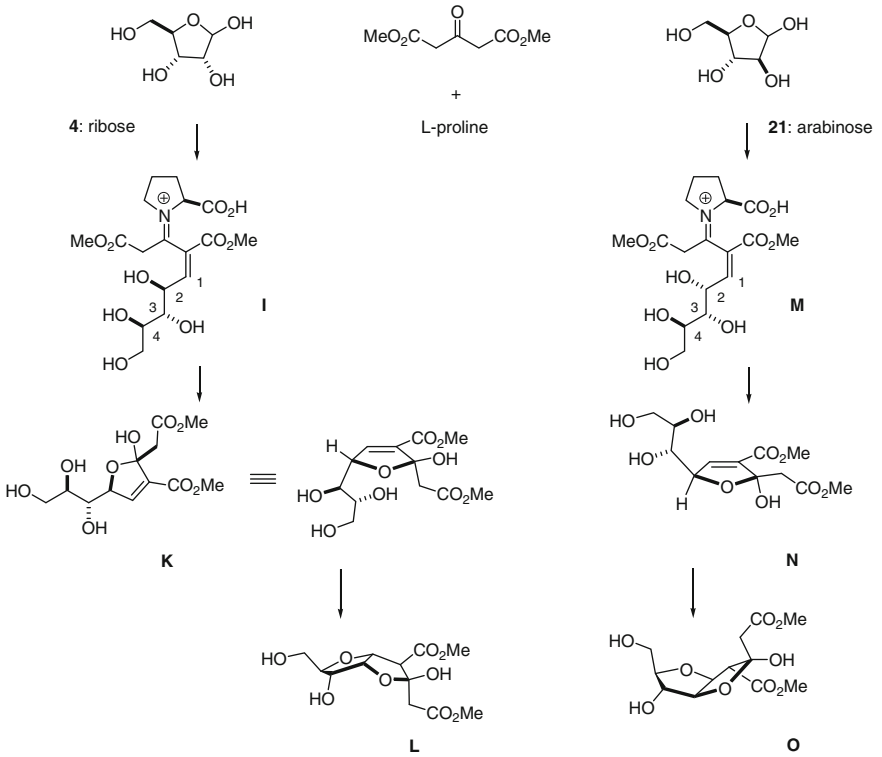


Scheme 3.15 Reactions of dimethyl-3-oxoglutarate with ribose **4**, arabinose **21**, xylose **22**, glucose **33** or galactose **34**

equilibrium within 2 h at room temperature. Independent of this observation, all three products (**80** and two epimeric *keto*-**81**) are formed with the same furanoid α-anomeric configuration.

In further experiments we tested various pentoses and hexoses in these reactions. Dimethyl 3-oxoglutarate **68** was used as standard 1,3-dicarbonyl compound in these transformations. The results of these studies are depicted in Scheme 3.15. The expected tetrahydrofurans **74** and **82–85** were isolated with good to high yields (with the exception of **84**: 27 %). Again, only a single stereoisomer was detected in all our reactions (de > 95 %). Independent of the structure of the carbohydrates deployed—pentoses (ribose **4**, arabinose **21** or xylose **22**) or hexoses (glucose **33** or galactose **34**)—products were isolated exclusively in their furanoid form (compare structures of **74**, **82** and **83** with those of **84** and **85**). On the other hand, the installation of configuration at the anomeric carbon atom and the two new stereogenic centers is dictated by the C-2 configuration of carbohydrates deployed. When used with ribose, xylose, glucose and galactose α-configured anomers were obtained. In contrast to that, in reaction of arabinose **21** (β-configured hydroxyl group at C-2), the β-configured product **82** with inversed configurations at the two new created stereogenic centers was isolated as a single stereoisomer.

Based on these findings obtained, a Knoevenagel/ketalization/oxa-Michael cascade reaction can be assumed (Scheme 3.16). In the first step of the reaction cascade an *E*-selective Knoevenagel reaction of the carbohydrate takes place (**I** in Scheme 3.16). It is supposed that DBU stabilizes the intermediately formed proline enamine. Support for this consideration is given by analysis of corresponding



Scheme 3.16 Configurative course of Knoevenagel condensation/ketalization/oxa-Michael cascade reactions

NMR-experiments [82]. This condensation process is followed by a stereoselective ketalization dictated by the configuration of the 2-hydroxy group of the carbohydrate (**K**). Subsequent *Re*-side attack of the 4-hydroxy group gives an access to fused tetrahydrofuran structure **L**. Structure **L** is identical with that of compound (**74**), which is obtained when used with ribose. In reactions with arabinose a *Si*-side attack of 4-hydroxy group determines the configuration of structure **O**, which is identical to the configuration of compound **82**. During this process two new stereogenic centers are formed with defined configuration in a highly selective manner.

To date, several protocols for Knoevenagel-additions to protected carbohydrates or carbohydrate derived molecules have been reported in the literature [83–94]. For a manganese(III)- or cerium(IV)-mediated radical addition of malonates to protected carbohydrates see reference [95–97]. For early reactions of protected carbohydrates with malonic acid in basic medium (pyridine) see reference 26.

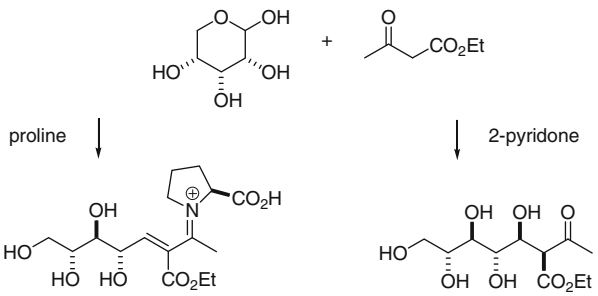
Furthermore, investigations into reacting even unprotected carbohydrates with 1,3-dicarbonyl compounds have been published in the literature. Controlled by the reaction conditions the formation of substituted furans or C-glycosides was observed. By application of acidic reaction conditions multi-condensation processes

were obtained. As a consequence of that the formation of polyhydroxylated furans was noticed [98–110]. These transformations are connected with the loss of stereogenic centers of the carbohydrates deployed. Under basic conditions a Knoevenagel-condensation occurs. Subsequent retro-Claisen aldol reaction yields the corresponding C-glycosides. This transformation involves the elimination of an acetate-unit of the starting 1.3-dicarbonyl compounds, when used with acetylacetone (Lubineau-reaction) [111–121], for an overview see [122].

A completely different situation is observed under the reaction conditions we describe herein. The two new methods described above enable an organocatalytic, stereoselective synthesis of the desired structural motifs without the loss of functionalities or stereogenic centers of the deployed substrates.

Both new cascade reactions were carried out in basic medium (tertiary amines). However, the key difference of this two cascade processes is as follows. The initial reaction step in the C-glycoside formation process is a Knoevenagel condensation, whereas the chain elongation cascade starts with a Knoevenagel-addition reaction of the acyclic form of the carbohydrates. This difference is dictated by the application of either 2-hydroxypyridine (Knoevenagel-addition reaction) or proline (Knoevenagel condensation). The intermediately formed Knoevenagel-addition or condensation products determinate the subsequent reaction steps. Based on that, a different outcome of these cascade reactions is observed (Scheme 3.17).

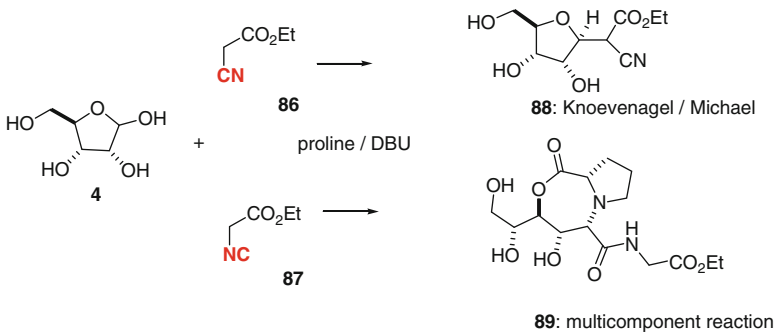
A further small tweaking of the reaction conditions involves great changes—a further new cascade channel is breaking. This is accomplished by modulation of the nucleophilicity of the activated methylene compounds applied. When used with isocanyoacetate **87** instead of cyanoacetates **86** as methylene activated component, an Ugi-like multicomponent cascade reaction is observed. This reaction was first detected by deployment of ethyl isocyanoacetate **87** in reactions of ribose and proline. In these experiments proline—once the catalyst in the Knoevenagel condensation/ketalization/oxa-Michael cascade reactions—is directly incorporated into the product. As a result of that 7-membered lactone **89** is formed. This sharp difference is demonstrated in Scheme 3.18 [123].



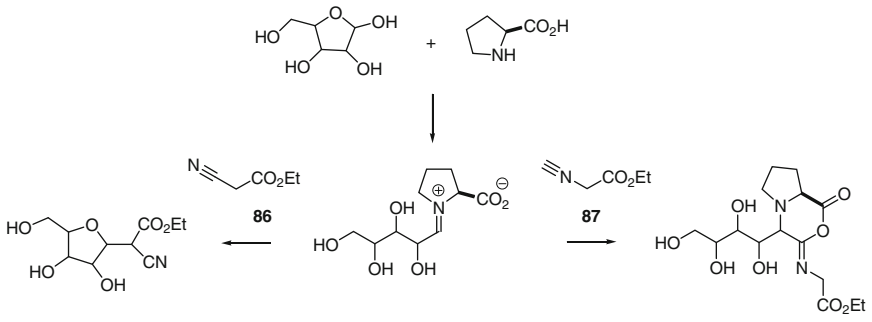
Scheme 3.17 Different key intermediates in DBU-catalyzed Knoevenagel cascade reactions of ribose (not isolated)

It is assumed that both reactions start with the formation of the imine of the acyclic structure of carbohydrates with proline. After this initial step the cyanoacetate **86** dictates a Knoevenagel/Michael cascade, whereas by employment of isocyanoacetate **87** a nucleophilic addition of the carbon atom of the isocyano group and subsequent rearrangement reaction are observed. An explanation for this different behavior of the isostructural compounds (ethylesters **86** and **87**) shown above is given by the different sites of highest nucleophilicity as described by Mayr et al. [124, 125]. These mechanistic considerations are depicted in Scheme 3.19.

Further investigation of this Ugi-type cascade reaction and optimization revealed a broad application of this multicomponent cascade. This transformation works without any catalyst or reagent at room temperature. For shortening reaction times and increasing yields catalytic amounts of tertiary amines and working in boiling methanol proved to be the most successful conditions. These reaction conditions do not only influence the selectivity of the reaction but also increase the yield slightly in much shorter reaction time.

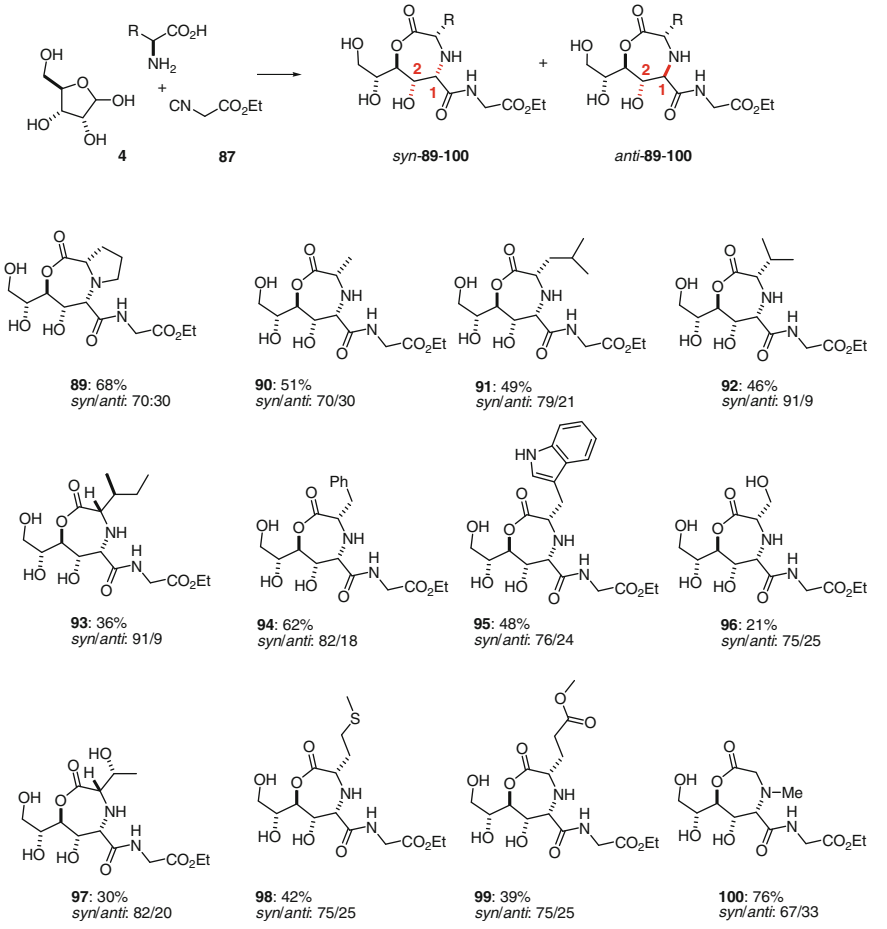


Scheme 3.18 Comparison between organocatalyzed reactions of ethyl isocyanoacetate **87** or cyanoacetate **86** with ribose in the presence of L-proline



Scheme 3.19 Mechanistic similarities and differences of Knoevenagel cascades and multicomponent cascades

To test the general application of this transformation, we expanded these preliminary findings in a first series to reactions of D-ribose with ethyl isocyanoacetate **87** and a wide range of proteinogenic amino acids (Scheme 3.20). 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. Furthermore, a general trend to installed configuration and diastereoselectivity was observed. By application of L-configured amino acids 1.2-*syn*-configured structures 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. Highest degrees of diastereoselectivity resulted from the use of valine or isoleucine (**92** and **93**, *syn*/*anti*: 91/9). It is assumed

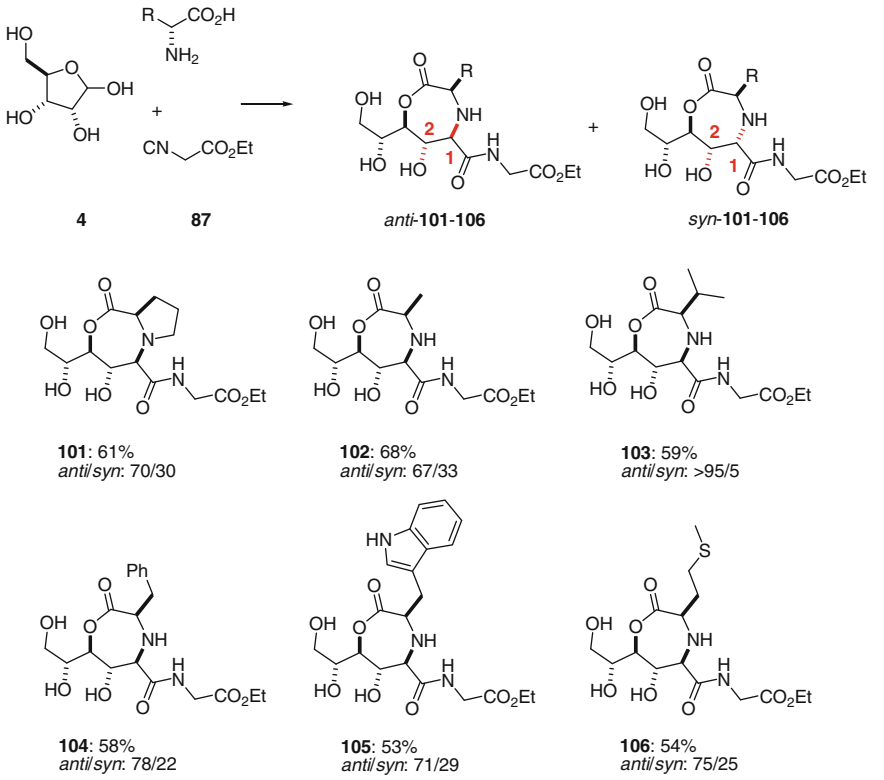


Scheme 3.20 Multicomponent reactions of D-ribose and ethyl isocyanoacetate with L-amino acids

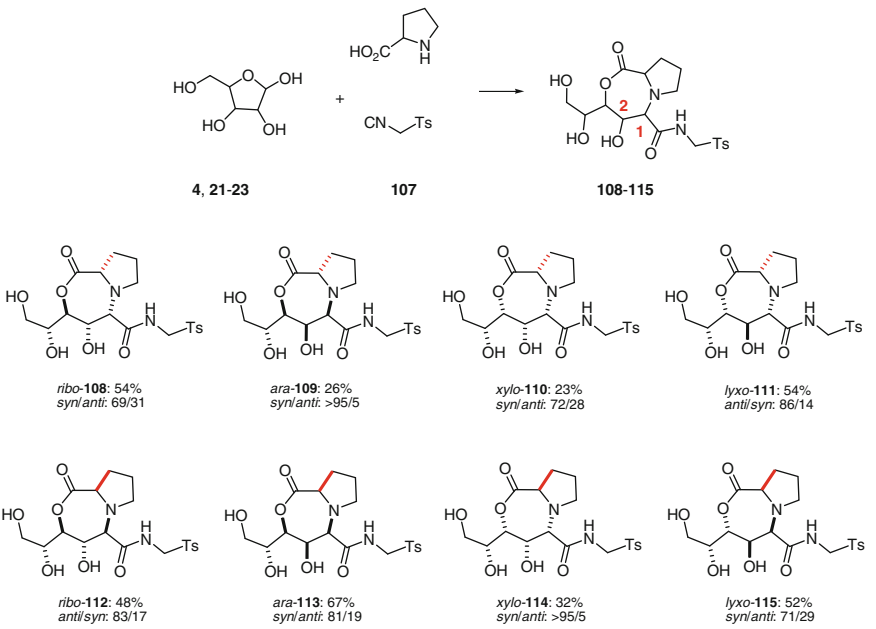
that this high selectivity is caused by the β-branching of valine or isoleucine. Hence, incorporating unbranched amino acids (R=H, Scheme 3.20) should lower the selectivity. These considerations were supported by results of reactions with sarcosine. Product **100** was found with a ratio of 67/33 (*syn*/*anti*), though with good yields (76 %). Results of these studies are depicted in Scheme 3.20.

The observation of different diastereoselectivities with L-amino acids with varying steric demand of the side chain suggests, that the configuration of the amino acid employed, dictates the installation of configuration at the anomeric carbon atom. Thus, when used with naturally configured L-amino acids 1.2-*syn* configured products are detected. In contrast, by applying D-configured amino acids a preferred formation of 1.2-*anti* configured products is observed (Scheme 3.21).

By comparison of the results of reactions of naturally configured amino acids (Scheme 3.20) with those of D-configured amino acids (Scheme 3.21) a matched or mismatched situation cannot be discussed. Nearly identical results with regard to yields and selectivities were obtained in both series, but with an inverted configuration at the former anomeric carbon atom.



Scheme 3.21 Multicomponent reactions of D-ribose and ethyl isocyanoacetate with D-configured amino acids



Scheme 3.22 Multicomponent reaction of pentoses with D- and L-proline

To evaluate the influences of the configuration of carbohydrates and amino acids on the stereoselective course of this multicomponent reaction, different pentoses were reacted with both, D- and L-proline in the presence of p-toluenesulfonylmethyl isocyanoacetate **107**. Results of these investigations are depicted in Scheme 3.22.

From inspection of these results a correlation of the formation of 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 deployed can be identified.

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 **108** as the major diastereoisomer, whereas by reaction with D-proline the 1.2-*anti*-configured product **112** 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, but an inverted relative configuration for C-1 and C-2. Based on these results and considerations in conjunction with the observed diastereoselectivities, a mismatched situation for *ribo*-**108**/*lyxo*-**115** and a matched case for *lyxo*-**111**/*ribo*-**112** can be discussed.

In contrast to that, the installation of the configuration at the former anomeric center (C-1) is not influenced by the configuration of the amino acid deployed, 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 formation of this 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 for the installation of absolute and relative configuration is based on different modes and influences as discussed above.

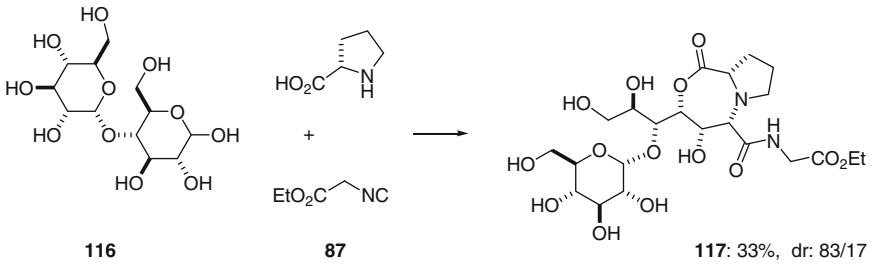
In general, a mismatched case is observed if both the configuration of the carbon atom C-2 of the carbohydrate and the configuration of the amino acid are the same (*ribo*-**108**/*lyxo*-**115** and *xylo*-**110**/*ara*-**113**). In reactions where the absolute configuration of the amino acid contrasts the configuration at C-2 of the deployed carbohydrates a matched case can be discussed (*ara*-**109**/*xylo*-**114** and *lyxo*-**111**/*ribo***112**). This rule of thumb holds true for reactions of proline with several different carbohydrates.

This elaborated methodology should provide an easy access to glycopeptide mimetica. To demonstrate that we reacted maltose **116** as an example for the deployment of disaccharides in these cascade reactions (Scheme 3.23). The expected lactone **117** was isolated with 33 % yields after 3 h in refluxing methanol. These yields are comparable with those obtained in reactions of glucose with L-proline and ethyl isocyanoacetate (36 %). But an increase of *syn*-selectivity was detected, indicating further supporting hydrogen bonds (compare glucose: *syn*/*anti* = 60/40 with **117**: *syn*/*anti* = 83/17).

In a further experiment we demonstrated the utility of dipeptides in these reactions. To this end we reacted ß-aspartame **118** with ribose and ethyl isocyanoacetate **87**. The expected lactone *syn*-**119** was isolated with 42 % yield and high levels of diastereoselectivity (Scheme 3.24).

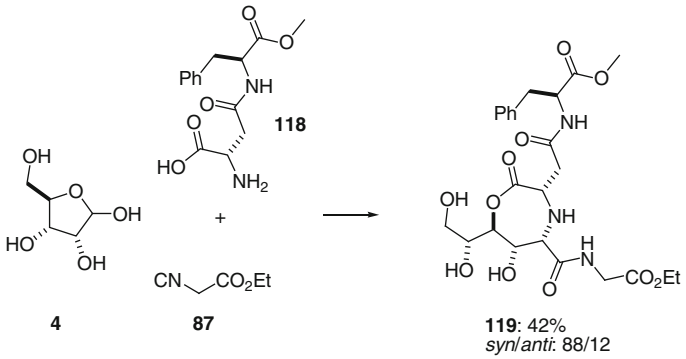
These multicomponent reactions are novel. Multicomponent-reactions of aldehydes and isonitriles with amino acids have been described in the literature (for reviews see the following references [126–133]) but the utilization of the carbonyl function of carbohydrates instead of aldehydes has not been reported previously.

So far, we have demonstrated, that the carbonyl functionality of aldoses can successfully be used in several cascade reactions (aldehyde in the acyclic structure).



116 **87** **117**: 33%, dr: 83/17

Scheme 3.23 Cascade reaction of maltose with L-proline and ethyl isocyanoacetate

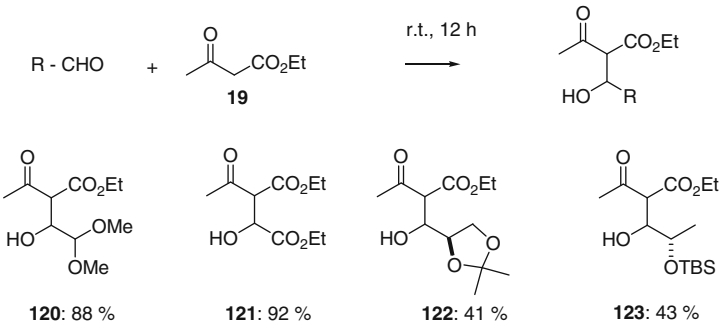


Scheme 3.24 Multicomponent reaction of ribose with aspartame and ethyl isocyanoacetate

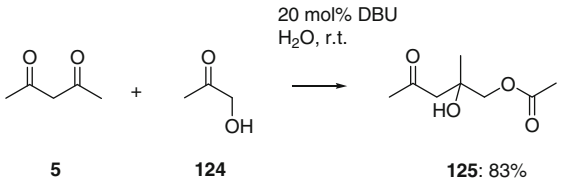
Also, ketoses proved to be useful substrates in cascade reactions with 1.3-dicarbonyl compounds (ketone in the acyclic structure). In these reactions several unusual and highly substituted carbohydrates were formed with high degrees of chemo- as well stereoselectivity.

The starting point of this study were observations that have been made in aldol additions of aldehydes with 1.3-dicarbonyl compounds [134]. These reactions proceed without any reagent or catalyst. A condensation was not observed under these conditions. The products were isolated with quantitative yields in part. Some examples are depicted in Scheme 3.25.

At this point we wondered whether ketones instead of aldehydes can be deployed in these reactions. As expected, a reaction is not observed in the absence of a catalyst or reagent. After a systematical optimization the following cascade reaction was detected. For reasons of simplification and comparability these transformations were conducted with acetylacetone **5** as the enol component and hydroxyacetone **124** (Scheme 3.26). After 24 h at room temperature acetate **125** was isolated in good yields.



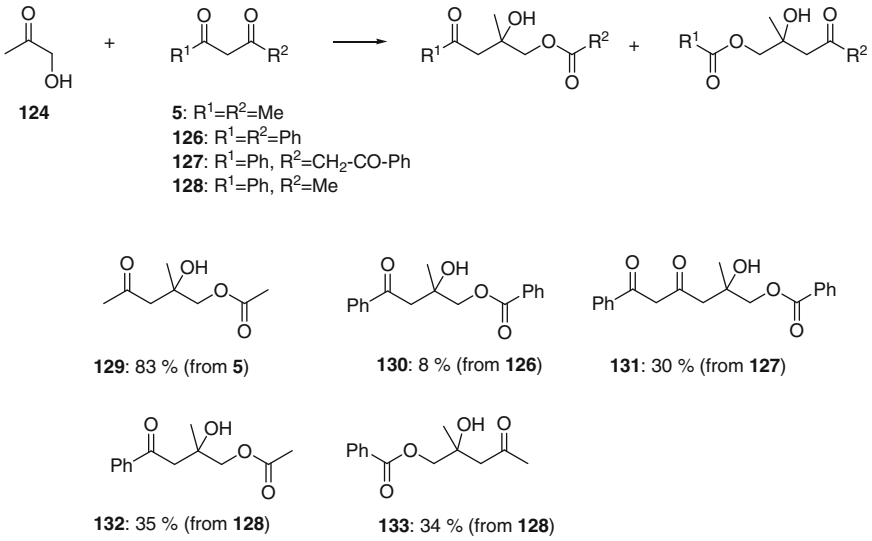
Scheme 3.25 Catalyst-free aldol additions of aldehydes with 1.3-dicarbonyl compounds



Scheme 3.26 Amine-catalyzed cascade reactions of hydroxyacetone with acetylacetone

The best results with regard to solvents were obtained in water. The reaction is catalyzed by tertiary amines. The most efficient catalyst concerning to yields, clear reaction and selectivity is DBU (20 mol%). This transformation was expanded to several 1.3-dicarbonyl compounds. Due to the symmetry of acetylacetone **5** or dibenzoylacetone **126** only one product was formed by the intermediately ketalization step (**5**: R_1=R_2=Me; **126**: R_1=R_2=Ph, Scheme 3.27). When used with unsymmetrical 1.3-dicarbonyl compounds, different products were formed via a regioisomeric ketalization step. Reactions of benzoylacetone **128** yield two different esters (**132** and **133**, Scheme 3.27) [135].

Similar to the mechanism described in Scheme 3.16 a Knoevenagel reaction/ketalization cascade of hydroxyacetone with 1.3-dicarbonyl compounds is assumed. In Scheme 3.16 a Knoevenagel condensation/ketalization reaction is depicted. This sequence allows a subsequent oxa-Michael addition, which yields the corresponding



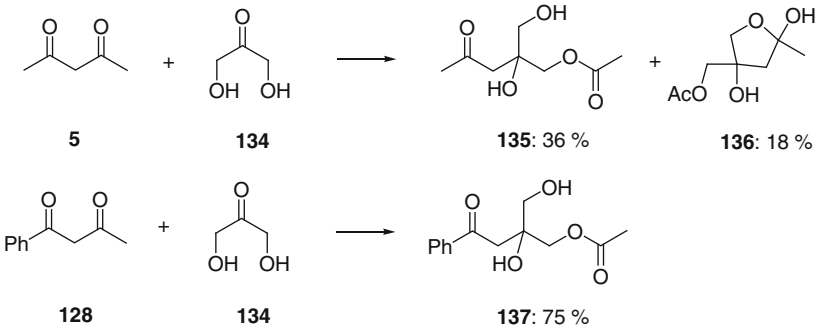
Scheme 3.27 Amine-catalyzed cascade reactions of hydroxyacetone with 1.3-dicarbonyl compounds

C-glycosides. In contrast, a Knoevenagel addition/ketalization occur under the reaction condition described in Scheme 3.26, which is followed by an intramolecular retro-aldol type step. As a result of that the corresponding esters were obtained (Scheme 3.27).

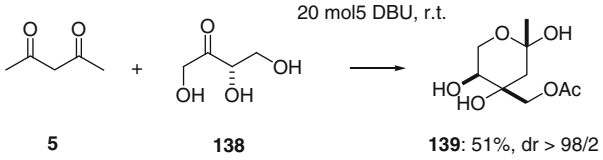
This transformation was successfully extended to reactions of unprotected dihydroxyacetone **134** with acetylacetone **5** or benzoylacetone **128**. The expected products derived from a Knoevenagel/ketalization/retro-aldol type cascade were isolated in high yields (Scheme 3.28).

In further experiments we expanded this cascade to the deployment of optically active hydroxyketones. This was successfully realized by reactions of acetylacetone with L-erythrulose **138**. Again a Knoevenagel/ketalization/retro-aldol type cascade was observed. The 1-deoxy-ketose **139** was isolated with extremely high degrees of stereoselectivity. Thus an access to unusually substituted, optically pure ketoses is given (Scheme 3.29).

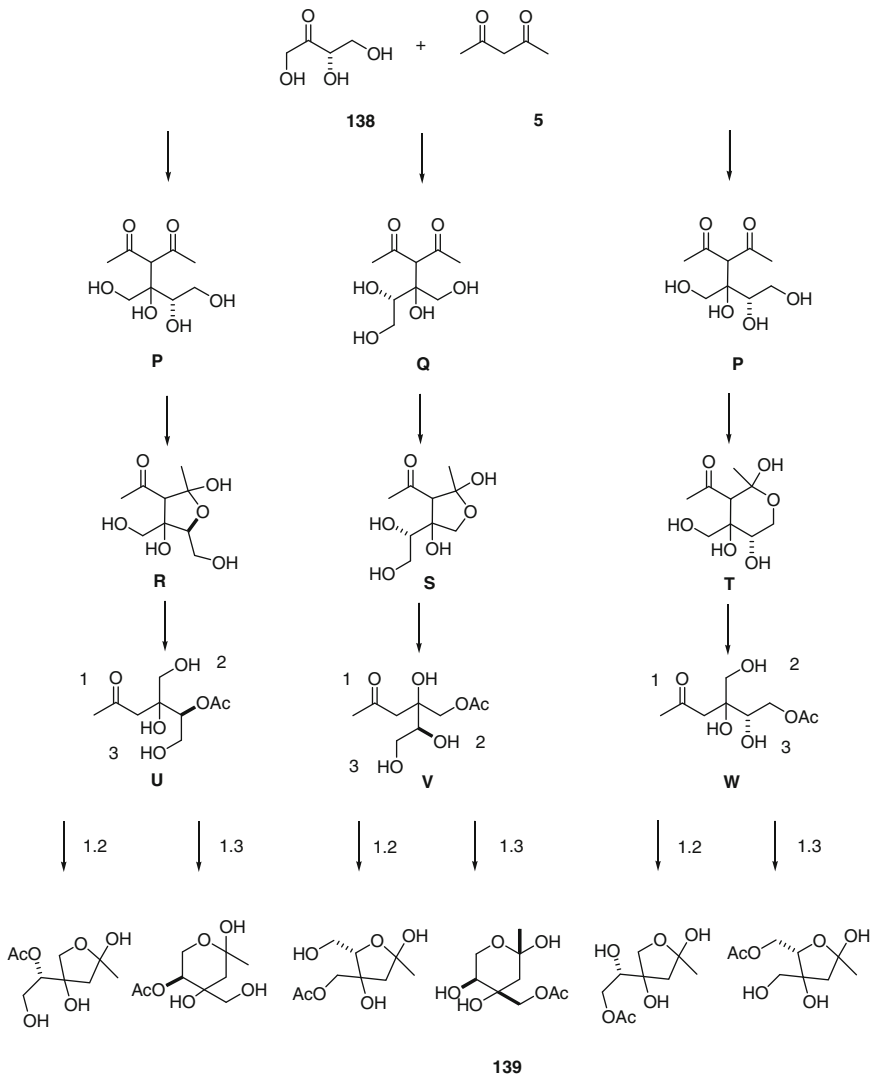
To explain the high selectivity, which is detected in these cascade reactions, the possible products and reaction paths for reaction with L-erythrulose **138** and acetylacetone **5** are depicted in Scheme 3.30. The stereoselective Knoevenagel-addition to intermediate **Q** is favoured and determines simultaneously the configuration of the tertiary alcohol. A subsequent ketalization step to ketone **S** followed by the final intramolecular retro-Claisen step yields the isolated product **139** as a single stereoisomer.



Scheme 3.28 Cascade reactions of dihydroxyacetone with 1.3-dicarbonyl compounds



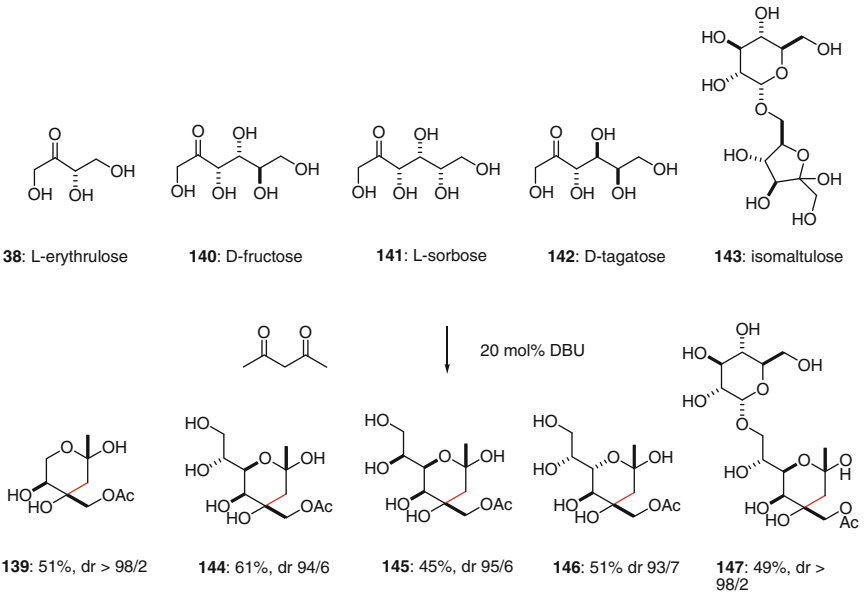
Scheme 3.29 Cascade reactions of L-erythrulose with acetylacetone



Scheme 3.30 Amine-catalyzed reaction pathway of acetylacetone and L-erythrulose

These results were expanded to several other hexoses. To this end fructose, sorbose, tagatose and isomaltulose were reacted with acetylacetone in the presence of 20 mol% DBU. Extremely high diastereoselectivities were observed. Only one single stereoisomer was detected in these transformations. Results of these investigations are depicted in Scheme 3.31.

These results differ considerably from those obtained by Lubineau-reactions. In the Lubineau-series a Knoevenagel condensation followed by an oxa-Michael/

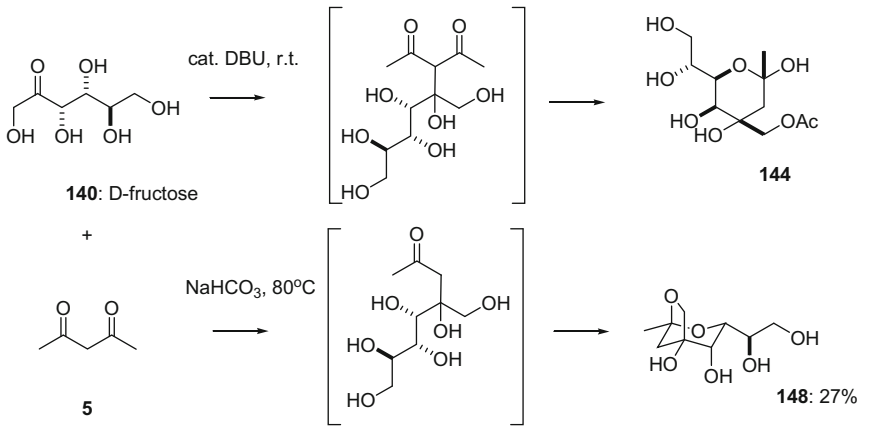


Scheme 3.31 DBU-catalyzed cascade reactions of acetylacetone and ketoses; new formed C–C bonds are indicated in *red* colour

intermolecular retro-aldol type-process is proposed. As a result of the Lubineau-sequence the loss of an acetate-fragment occurs in reactions with acetylacetone.

In the amine-catalyzed reactions a Knoevenagel addition/ketalization/intramolecular retro-aldol type cascade is detected (Scheme 3.30). The retro-aldol type step is enabled by the ketalization of the Knoevenagel addition product **Q**. The ketalization of the Knoevenagel product (**Q** → **S**) is initiated by the hydroxyl groups of the carbohydrate moiety, as in-house NMR-experiments suggest (formation of intermediate ketal structure **K** in Knoevenagel condensation/ketalization/oxa-Michael cascade reaction, Scheme 3.16). Products derived from this reaction-sequence (Scheme 3.16) were not obtained in these amine-catalyzed transformations. The fundamental difference between these two cascade transformations is the Knoevenagel-condensation, which is obtained as the initial reaction in the Lubineau series and in Knoevenagel condensation/ketalization/oxa-Michael cascade reactions. In contrast, a Knoevenagel addition is observed as the starting reaction in the amine-catalyzed cascade reactions (Scheme 3.30). This main difference dictates the course of these two cascade channels. A comparison of these two cascades is given for the reaction of fructose **140** with acetylacetone (Scheme 3.32). The product **148** formed under Lubineau-conditions was isolated with 27 % yield [136].

The extensive and extremely strong development of organocatalysis over the last years provided versatile methodologies for convenient utilization of the carbonyl function of unprotected carbohydrates in C–C-bond formation processes.



Scheme 3.32 Comparison of DBU-catalyzed cascade reaction with Lubineau-reaction

These biomimetic amine-activated mechanisms enable multiple cascade-protocols for the synthesis of a large scope of carbohydrate derived compound classes.

Several, only slightly different protocols have been developed for the application of 1.3-dicarbonyls in stereoselective chain-elongation of unprotected carbohydrates and the synthesis of highly functionalized C-glycosides of defined configuration.

Furthermore, the latter class of compounds can also be accessed by the use of methyl ketones. So a high substrate scope is available for the installation of desired functionalities in C-glycosides.

By a one-pot, operationally simple cascade reaction of isocyanides with unprotected aldoses and amino acids an access to a broad range of defined glycosylated pseudopeptides is given.

The elaborated organocatalyzed cascade-reactions provide defined access to highly functionalized carbohydrate derivatives.

Depending on the reaction conditions different origin to control the installation of configuration during the bond-formation process were observed.

The demonstrated organocatalyzed cascade sequences indicate the great potential of unprotected carbohydrates in the synthesis of highly functionalized biomimetic structure motifs by operationally simple, one-pot protocols.

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Chapter 4
Organocatalyzed Glycosylation Reactions of Carbohydrates

Abstract Several different organocatalyzed glycosylation processes of carbohydrates will be discussed. The results clearly support the concept of the application of unactivated and unprotected carbohydrates in glycosylation processes. By generating hydrogen bridges, which are working during the reaction, the configuration at the anomeric carbon atom can be controlled. Extremely high degrees of stereoselectivities were obtained, depending on the configuration of the carbohydrates deployed.

Keywords Unprotected carbohydrates · Unactivated carbohydrates · Metalcatalyzed methods · Organocatalyzed methods · Michael additions · Amine-catalyzed glycosylation

Glycosylation is a fundamental chemical transformation in both nature as well as in chemical laboratories. The natural process is realized with the aid of enzymatic catalysis [1] and references cited in [2–4]. Polysaccharides or glycosides are synthesized directly in the absence of any protective groups under physiological conditions. For a selective execution of the glycosylation the enzyme has to differentiate between different chemical and configured hydroxyl groups of the carbohydrates. But this differentiation of the extremely high number of different hydroxyl group poses a big challenge. Many methods and concepts have been developed to overcome these problems. Most of these protocols are realized by the following general strategy:

- protection of hydroxyl groups (PG = protective group) followed by an
- activation of the anomeric carbon atom (X = halogen, trichloroacetimidate, -SR, -OR, -$OSiR_3$, -$OP(=O)OR_2$ etc.)
- glycosylation of an acceptor (R-OH) and
- final deprotection step (Scheme 4.1; For current and comprehensive overviews in this field, see: [5–12]).

This sequence of Scheme 4.1 shows the classical and most reliable methodologies. To avoid these tediously multi-step approaches to defined glycosides demonstrated in Scheme 4.1, several attempts have been made to increase and thus to utilize the differences of reactivity between the hemiacetal hydroxyl group and the

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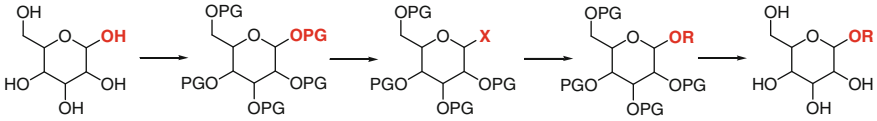
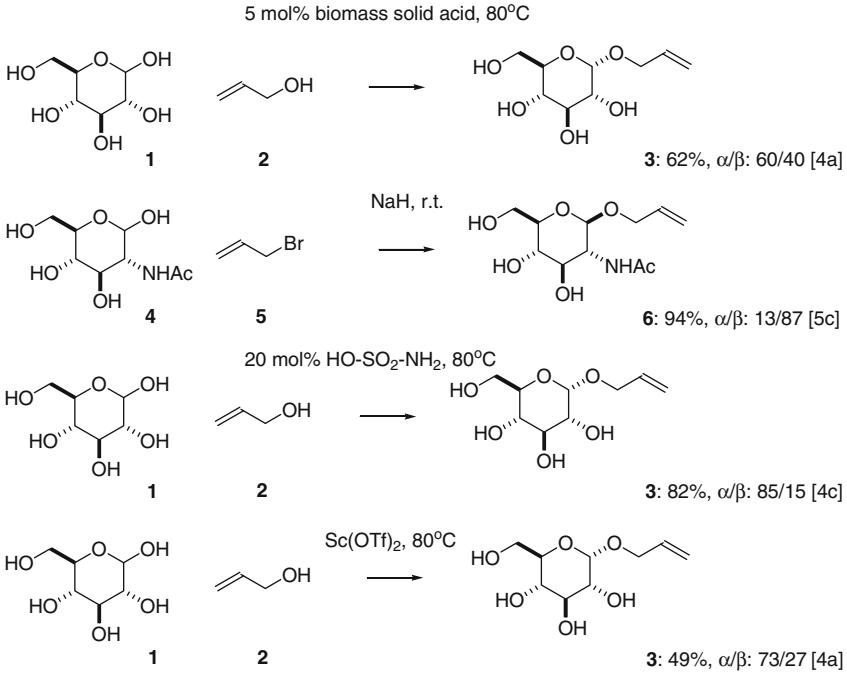


Scheme 4.1 Schematic overview of classical glycosylation methods

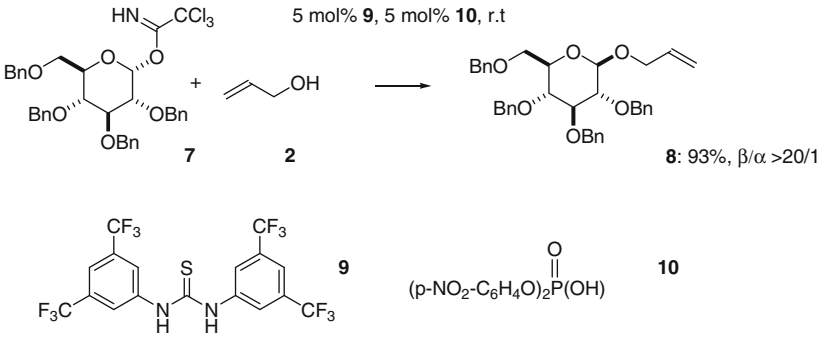
remaining unprotected hydroxyl groups of carbohydrates [13, 14]. Furthermore, methods have been developed to deploy unprotected and unactivated carbohydrates in direct glycosylation processes. These transformations are associated with high reaction temperatures [15–18] and/or the deployment of strong bases [19–21], strong acids (Fischer-glycosylation) [22–42] or Lewis acids [43–52] as catalysts. Representative examples of these methodologies are depicted in Scheme 4.2.

In addition there are several glycosylation reactions of unprotected carbohydrates. These are glycosylation with amines [53–56], direct glycosylations of aromatic compounds [57] and glycosylation processes, where the corresponding glycals were deployed (For reviews in this field see [58–61]). These reactions do not follow the general sequence of Scheme 4.1. They are bound to special substrates and reaction conditions.

Moreover, some reports have been published describing organocatalyzed glycosylation processes. There have been several attempts to react fully protected and



Scheme 4.2 Direct glycosylations of unprotected and unactivated carbohydrates

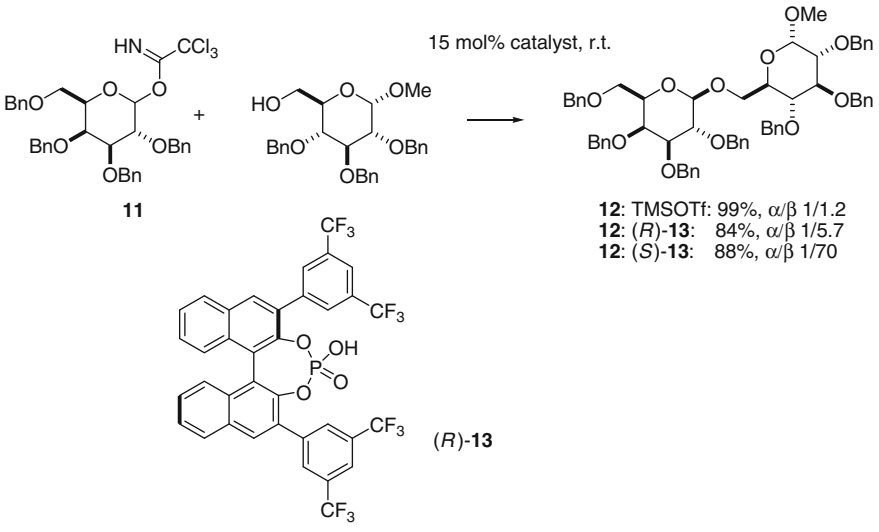


Scheme 4.3 Thiourea-catalyzed glycosylation of protected carbohydrates

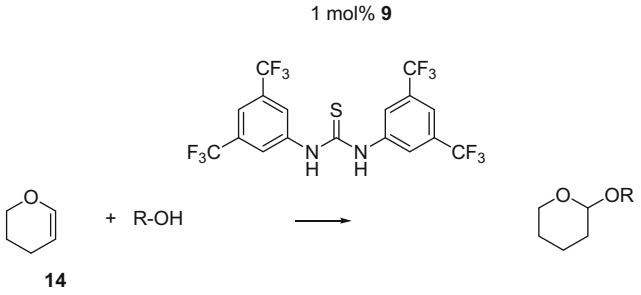
activated carbohydrates with alcohols or glycosyl acceptors in the presence of organocatalysts. Schmidt et al. have demonstrated that trichloroacetimidate of protected carbohydrates can be transformed into the corresponding glycosides by catalytic deployment of thiourea. ß-Anomers of glycosides were obtained with high degrees of stereoselectivity [62] (Scheme 4.3).

When used with the same substrates a glycosylation can be achieved in the presence of catalytic amounts of BINOL-derived phosphoric acid. The configuration of the deployed BINOL-phosphoric acid influences the degree of stereoselectivity of the installation of configuration at the anomeric carbon atom, as demonstrated by the formation of disaccharide **12** (Scheme 4.4) [63].

In 2007 Kotke und Schreiner reported a thiourea-catalyzed addition of alcohols to enol ether, particular dihydropyran, which for several reasons is a valuable one.



Scheme 4.4 Brønsted acid-catalyzed glycosylation



Scheme 4.5 Thiourea-catalyzed addition of alcohols to cyclic enol ethers

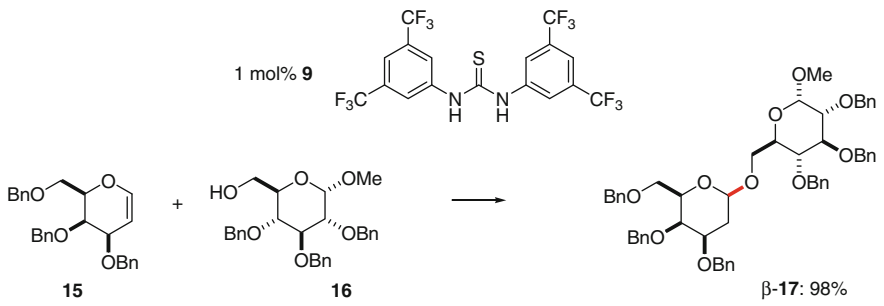
The classical addition of alcohols to enol ethers is realized by acid-catalysis. When used with thiourea-catalysis even acid-sensitive substrates can be reacted with quantitative yields. Furthermore, the reaction can be successfully accomplished with catalyst loadings as low as to 0.001 mol% (Scheme 4.5) [64–66].

These results inspired the group of McGarrigle to transfer this method to thiourea-catalyzed glycosylation of glycals. By deploying 1 mol% of thiourea-derived catalyst **9** the authors succeeded in glycosylations of protected glycal **15**. 2-Deoxyglycoside **17** was obtained with high yields (Scheme 4.6) [67, 68].

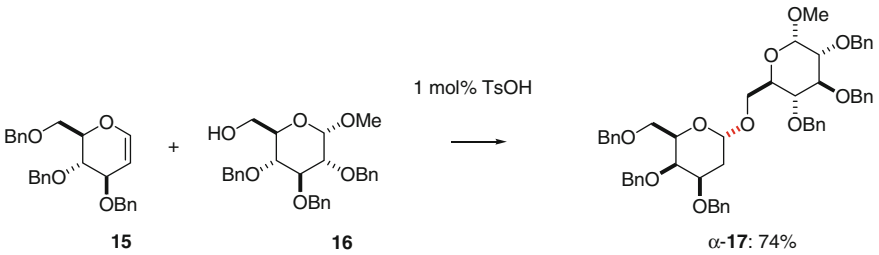
Interestingly, using the same substrates under acidic conditions (**15** and **16**, 1 mol% p-toluenesulfonic acid) the same reaction occurs, but with inverted stereoselectivity. In contrast to thiourea-catalyzed glycosylation the α-configured disaccharide **17** is detected with high degrees of stereoselectivity (Scheme 4.7) [69].

To demonstrate the power of this new methodology the synthesis of trisaccharide **21** has been accomplished in a one-pot procedure (Scheme 4.8). The formation of the disaccharide **19** was realized by a thiourea-catalyzed glycosylation. This initial glycosylation-step was followed by the activation of the thioglycoside **19** with NIS and catalytic TMSOTf. Subsequent glycosylation yields the protected trisaccharide **21** in high yields and stereoselectivity.

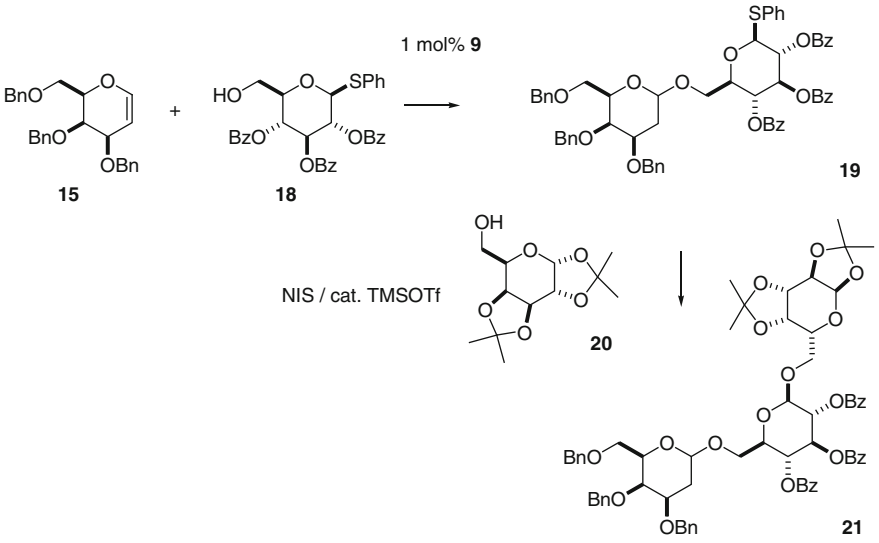
A further report on organocatalyzed glycosylations of glycals was published by the Liu group. The authors describe an acylanion addition to protected 2-nitroglycals



Scheme 4.6 Thiourea-catalyzed glycosylation of glycals



Scheme 4.7 Acid-catalyzed glycosylation of glycals

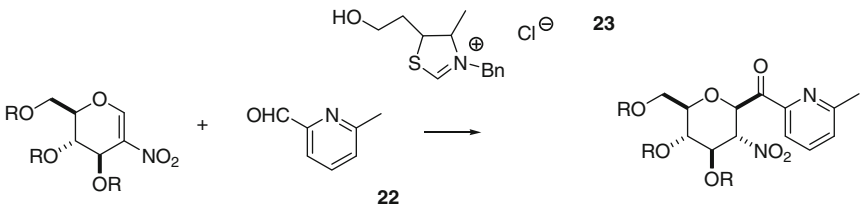


Scheme 4.8 One-pot synthesis of trisaccharides

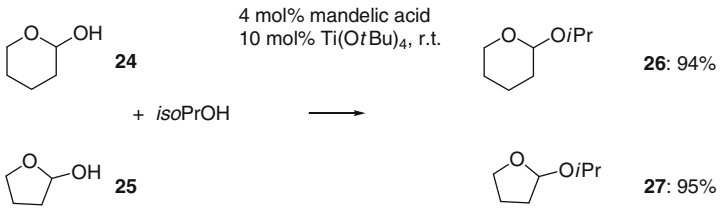
in the presence of N-hetereocyclic carbene catalyst **23** (Scheme 4.9) [70]. This approach yields a stereoselective access to C-glycosides, providing the opportunity to produce new classes of C-glycosides.

During our ongoing studies in organocatalysis we became interest in catalytic systems for glycosylation processes. The starting point of our investigations was to differentiate between the different chemical reactivities of hydroxyl groups of carbohydrates. A successful catalytically system has to differentiate between the anomeric hydroxyl group (hemiacetal) and the remaining hydroxyl groups of the carbohydrate deployed. In contrast to the methods described above, this approach is similar to a naturally occurring one, in which enzymes realize the glycosylation processes.

By investigations of ligand-exchange mediated C–C bond formation processes we detected substantial amounts of products that derived from acetalisation. These reactions were performed in the presence of titanium(IV)-alkoxides and α-hydroxy



Scheme 4.9 Carbene-catalyzed glycosylation



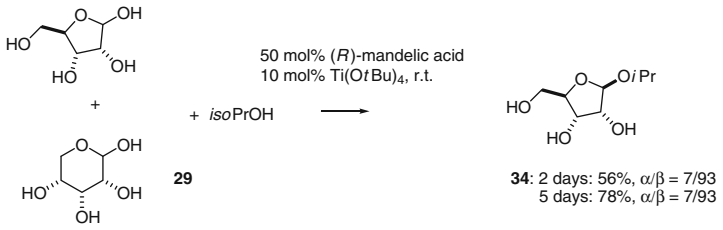
Scheme 4.10 Titanium(IV)-alkoxide catalyzed acetalization of hemiacetals

acids [71–73]. After further optimization, we were able to achieve quantitative acetalization of hemiacetals in the furan- as well as pyran-series under neutral reaction conditions (Scheme 4.10).

This acetalization of hemiacetals was observed only by application of a combination of titanium(IV)-alkoxides and α-hydroxy acids. An acetalization was not detected with titanium(IV)-alkoxides or mandelic acid alone (even in equimolar amounts). The corresponding isopropyl acetals **26** and **27** were isolated in quantitative yields at room temperature within 24 h.

Encouraged by these results we tested this catalytic system in the glycosylation of unprotected carbohydrates. For this purpose D-ribose **28** was reacted with isopropanol under the following reaction conditions. When titanium(IV)-*tert*-butoxide (10 mol%) and D-mandelic acid (50 mol%) are employed at room temperature the corresponding isopropylriboside **34** is isolated in good yield and with a high β-selectivity (Scheme 4.11).

Further investigations revealed that primary as well as secondary alcohols can be successfully applied in reactions with D-ribose [74]. A ratio of 5/1 (mandelic acid/$Ti(OtBu)_4$) for pentoses and a ratio of 1/2 for deoxyribose was identified by optimization of glycosylation conditions of D-pentoses with isopropanol. Preformed titanium(IV)-alkoxide/mandelic acid complexes are unable to form glycosylation products under these reaction conditions. Competitive glycosylation by D-mandelic acid could be ruled out. A substantial glycosylation is observed when used with 100 mol% mandelic acid (48 h, r.t., yield <5 %) (with the exception of deoxyribose: glycosylation is observed in the presence of 10 mol% mandelic acid after 48 h, r.t. yield <5 %). These optimized reaction conditions were applied to glycosylation reactions with isopropanol for pentoses **27**–**31** as mentioned in Table 4.1.



Scheme 4.11 Catalytic glycosylation of unprotected and unactivated ribose (Ribose consists at room temperature in a ratio of about 8/2 (pyranose/furanose). This ratio was determined by in-house NMR-experiments (*i*PrOH-d_8))

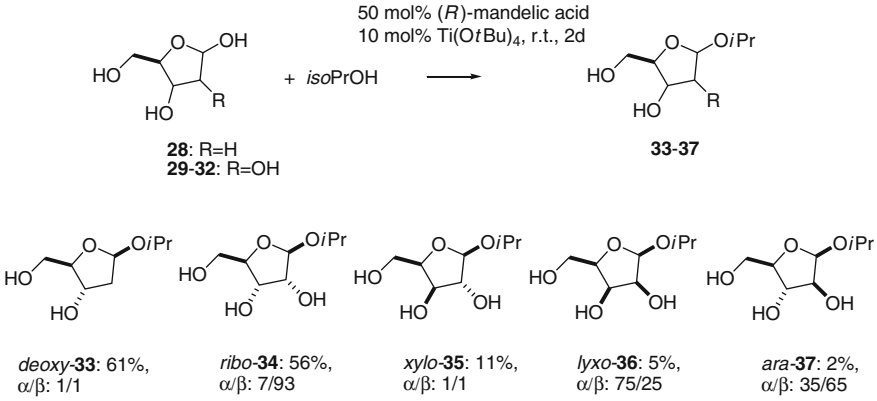


Table 4.1 Yields and anomeric ratios of isopropylglycosides of D-pentoses

Entry	Compound	Yield (%) 2 days	Yield (%) 5 days	Yield (%) 12 days	Ratio α/β (%)[a]
1	*deoxy*-**33**	61	78	62	50/50
2	*ribo*-**34**	56	78	73	7/93
3	*xylo*-**35**	11	13	28	50/50
4	*lyxo*-**36**	5	9	23	75/25
5	*ara*-**37**	2	5	20	35/65

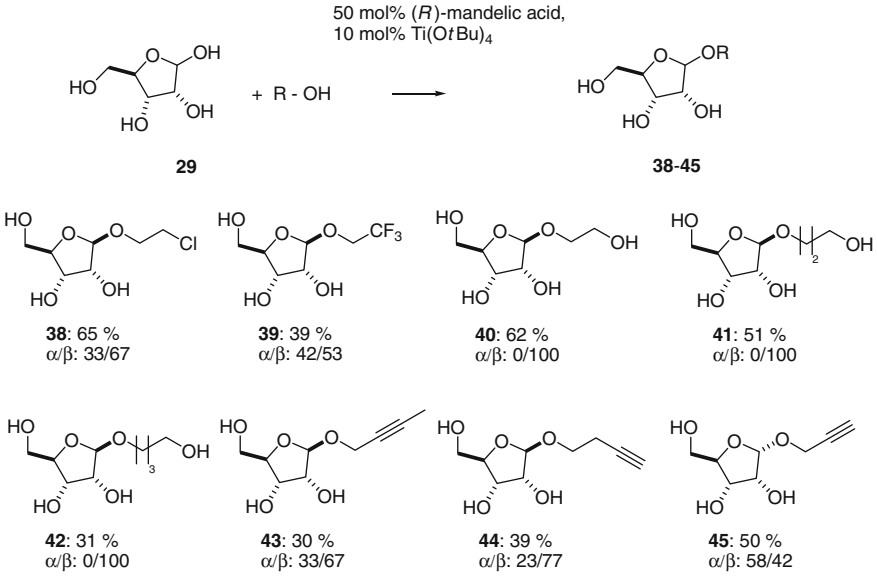
[a]2 d reaction time

The highest yields were obtained by deployment of deoxy-D-ribose (**33**: 61 %) and D-ribose (**34**: 56 %), while the lowest yields were detected with D-lyxose **31** or D-arabinose **32** (<10 %). The yields can be improved by longer reaction times. Isopropylglycosides of D-xylose, D-lyxose and D-arabinose were isolated after 12 days at room temperature, with max. 30 % yield (**35**:28, **36**:23, **37**:20 %,

Table 4.1). Under these conditions the exclusive formation of furanoid isopropyl-glycosides is observed (kinetic control). Moreover, substantial amounts of pyranoid glycosides could not be detected even after 12 days at room temperature. These findings contrast results obtained by Fischer- or other acid-mediated glycosylation method. Different ratios of pyranoid/furanoid glycosides were detected under Fischer-conditions depending on reaction times [75]. The following anomeric ratios were detected for isolated furanoid isopropylglycosides: α/β ratio for lyxose (**36**: 75/25), ribose (**34**:7/93), arabinose (**37**:35/65), deoxyribose and xylose (**33** and **35**:1/1). This strong substrate-selectivity is not consistent with results obtained by Fischer-glycosylations with methanol [76, 77]. Both, yields and anomeric ratios of glycosides were dictated by configuration of hydroxy groups of pentoses deployed.

To demonstrate the efficiency of this direct glycosylation several functionalized alcohols were reacted with unprotected ribose **29** under these conditions. Again, only furanoid ribosides were observed after 2 days reaction time. A preference for the formation of β-configured ribosides was observed. Solely β-configured anomers were detected in the diol series (**40**–**42**, Scheme 4.12). The results demonstrate that under these reaction conditions both the aglycon as well as the unprotected carbohydrate influence the anomeric ratio of glycosides formed.

Several attempts have been made to decrease the described lengthy reaction times. To this end different additives were tested. As a result of this optimization work lithium salts, especially lithium bromide, were found to be the favorite in these transformations (Lithium salts are known to promote and to direct glycosylation processes [78–88]). The results of these investigations are depicted in Table 4.2. A strong increase of yields was noticed for all D-pentoses used.



Scheme 4.12 Titanium(IV)-alkoxide catalyzed glycosylation of ribose

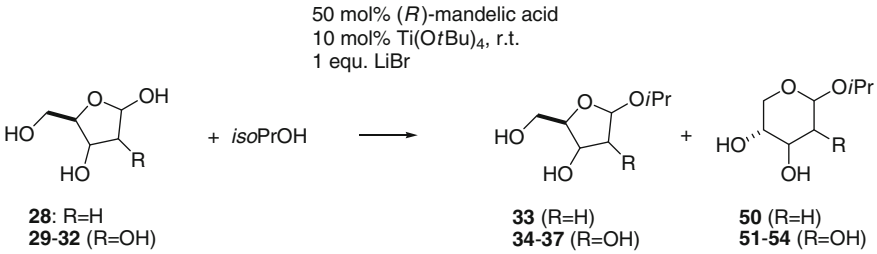


Table 4.2 Glycosylation in the presence of 1 equivalent lithium bromide

Entry	Compound	Yield (%) 2 days (*f/p*)[a]	Yield (%) 5 days (*f/p*)[a]	Yield (%) 12 days (*f/p*)[a]
1	*deoxy*-**33** + **50**	79 (76/24)	85 (47/53)	95 (30/70)
2	*ribo*-**34** + **51**	81 (90/10)	90 (84/16)	90 (76/34)
3	*xylo*-**35** + **52**	26 (93/7)	42 (87/13)	73 (46/54)
4	*lyxo*-**36** + **53**	24 (75/25)	33 (83/17)	65 (34/66)
5	*ara*-**37** + **54**	13 (96/4)	32 (93/7)	64 (77/23)

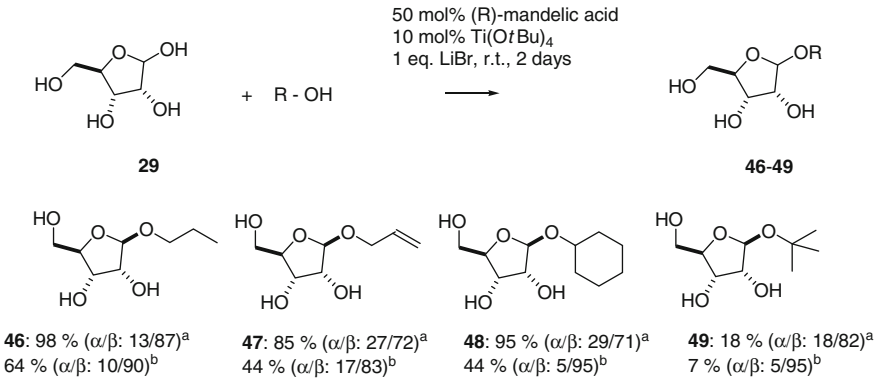
[a]ratio of furanoid/pyranoid structures

In contrast to the reactions without addition of lithium bromide, longer reaction times are associated with a clear increase of pyranoid structures of glycosides. Furanoid glycosides are the major products after 2 days at room temperature. (80–100 %). Pyranoid glycosides were detected by longer reaction times (for detailed ratio see supporting informations of reference 74).

To demonstrate this property of lithium bromide several alcohols were reacted under the described reaction conditions for 2 days (Scheme 4.13). These results clearly emphasize the yield-increasing feature of LiBr.

So far, experiments with liquid aglycons have been described, which were used in excess as solvents. In further experiments the application of solvents was studied to reduce the amount of aglycons and thus enabling the application of solid aglycons. Reactions were not observed in the presence of DMSO or DMF (This might be due to chelating effect of these solvents). The favoured solvent in these reactions proved to be propylene carbonate. Comparable yields to results of Table 4.1 (excess of isopropanol) were obtained when used with propylene carbonate and reduced amounts of isopropanol (5 equivalents of isopropanol). Exclusively furanoid glycosides were detected.

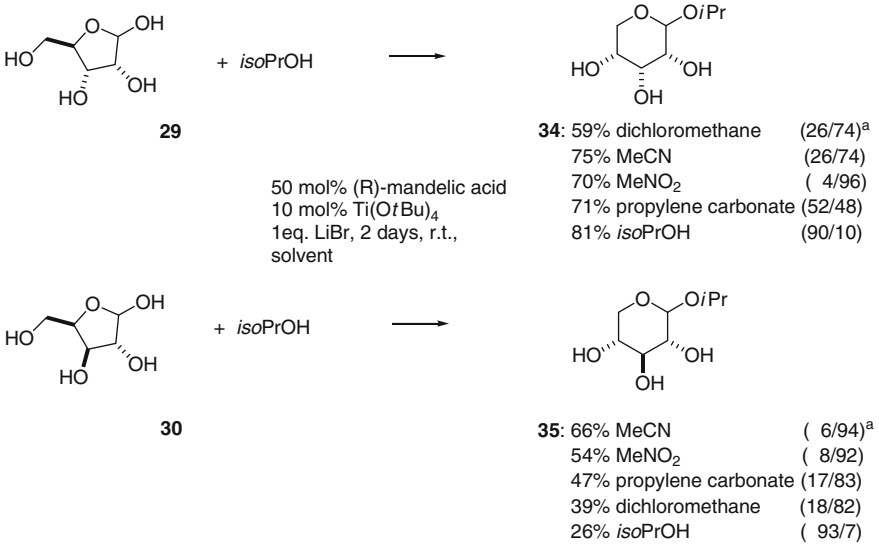
To study the influence of lithium bromide under these reaction conditions the most qualified solvents were used in a next series of glycosylation reactions of D-ribose and D-xylose. A preferred formation of thermodynamic-controlled pyranoid glycosides was observed (**34** and **35**, Scheme 4.14). These findings strongly



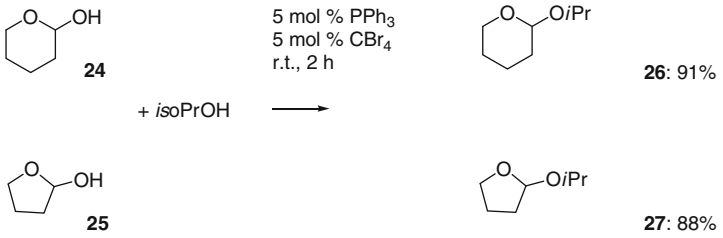
Scheme 4.13 Catalytic glycosylation of ribose in the presence of lithium bromide. [a]presence of LiBr; [b]absence of LiBr

contrast results observed in the absence of solvents (compare with the results obtained in isopropanol—Table 4.2—with those described in Scheme 4.14).

To realize a real organocatalytic execution, we tested by further experiments the utility of different organic base/acid pairs in direct glycosylation processes in further experiments. During these investigations we observed a rapid and quantitative formation of acetals of enolizable aldehydes or cyclic hemiacetals at room temperature. These transformations were catalyzed by catalytic amounts of triphenylphosphine



Scheme 4.14 Yields of glycosylation of ribose and xylose as a function of solvents. [a]ratio of (furanoid/pyranoid) structure



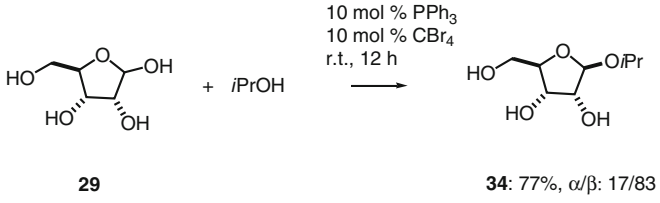
Scheme 4.15 Organocatalyzed acetalisation of hemiacetals

and substituted trihalomethanes. After optimizing the process, we obtained the best results by deployment of catalytic amounts of tetrabromomethane and triphenylphosphine for both yields and reaction time (Scheme 4.15) [89].

Similar results have been reported for acetalisation of aromatic aldehydes [90]. A cleavage of acetals was not detected under these conditions, as is known for Appel conditions [91–94].

Encouraged by these findings we tested this protocol for the glycosylation of ribose **29** with isopropanol. We obtained the corresponding isopropylriboside **34** in high yield and with high degrees of diastereoselectivity (Scheme 4.16). The reactions were carried out directly in isopropanol in the presence of catalytic amounts of triphenylphosphine/tetrabromomethane (10 mol%) at room temperature. A clean and rapid reaction with no side products was observed. The reaction proceeds under genuinely catalytic and neutral reaction conditions.

By extending these initial results to the glycosylation of other pentoses, unexpected and differing results were obtained. Clean reactions were detected when used with deoxyribose **28** and ribose **29** under the described conditions (**33**: 75 and **34**: 77 % in *iso*PrOH, 10 mol% PPh_3/10 mol% CBr_4, room temperature). In contrast, only low reaction rates and yields were observed when used with xylose **30**, lyxose **31** or arabinose **32**. The expected glycosides **35–37** were detected only in traces, even after 2 days at room temperature (A similar tendency has been observed in glycosylations using a mandelic acid / titanium(IV) alkoxide catalyst. See reference 74). To increase the yields of this direct glycosylation process, several different solvents and additives were tested in subsequent optimization works. Nitromethane, acetonitrile or propylene carbonate proved to be optimal solvents for this direct glycosylation process.

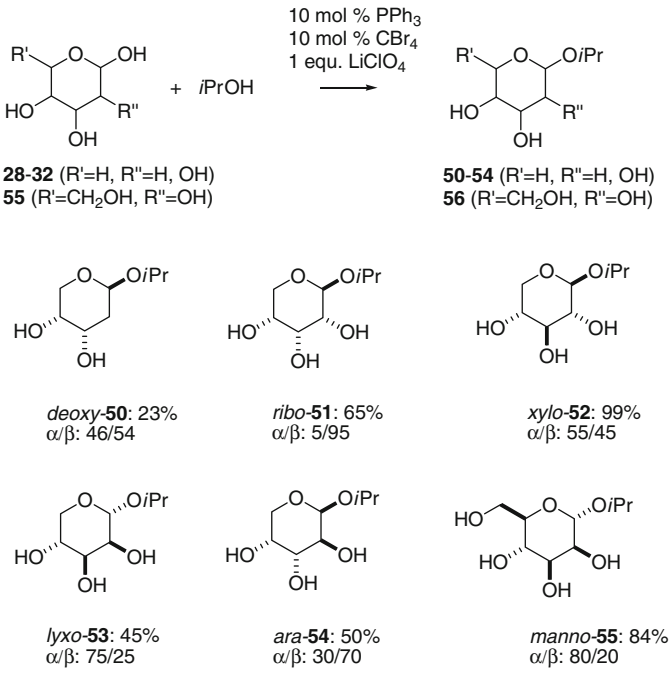


Scheme 4.16 Organocatalyzed glycosylation of unprotected ribose

In addition, several lithium salts were analyzed as additives. Lithium perchlorate is known to promote glycosylation processes (Lithium salts are known to promote and to direct glycosylation processes [78–88]). As a consequence, its effects were examined under these reaction conditions. Thus, a direct catalytic glycosylation of unprotected carbohydrates was achieved in another very clean reaction with no byproducts. The best results were obtained in acetonitrile in the presence of 2 equivalents of lithium perchlorate as an additive. The isopropyl glycosides **50**, **51**, **52**, **53** and **54** were obtained mostly in the pyranoid form, indicating thermodynamic control of these transformations. Support for this consideration is provided by the glycosylation of D-mannose **55**. In direct glycosylation reactions of mannose **55**, the α-configured isopropyl glycoside **56** was isolated as the main product, which is the thermodynamically favoured anomer in the mannose series (Scheme 4.17) [95, 96].

An insight of the stereochemical course of this reaction is given by X-ray structure analysis of an isopropylriboside (**51**)—sodium perchlorate complex (Fig. 4.1). Suitable crystals were collected during reactions of ribose with isopropanol and sodium perchlorate. The complexation of the hydroxyl groups with sodium perchlorate provides a full and temporary protection of one side of ribose. As a consequence the attack of isopropanol takes place exclusively at the opposite side of the anomeric carbon atom (**51**: α/β: > 5/95).

Furthermore, scope and limitations of this new glycosylation methodology were explored by reactions of several different aglycones with D-ribose **29** under the



Scheme 4.17 Organocatalyzed direct glycosylation in the presence of lithium perchlorate

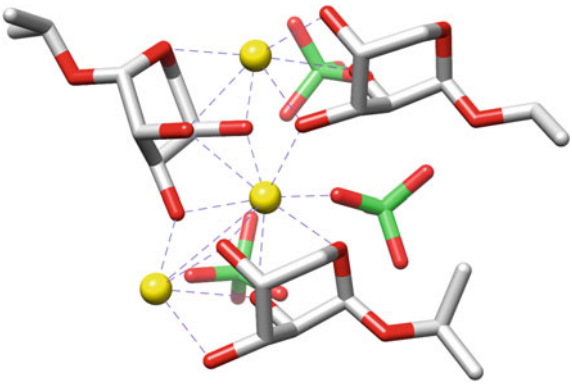
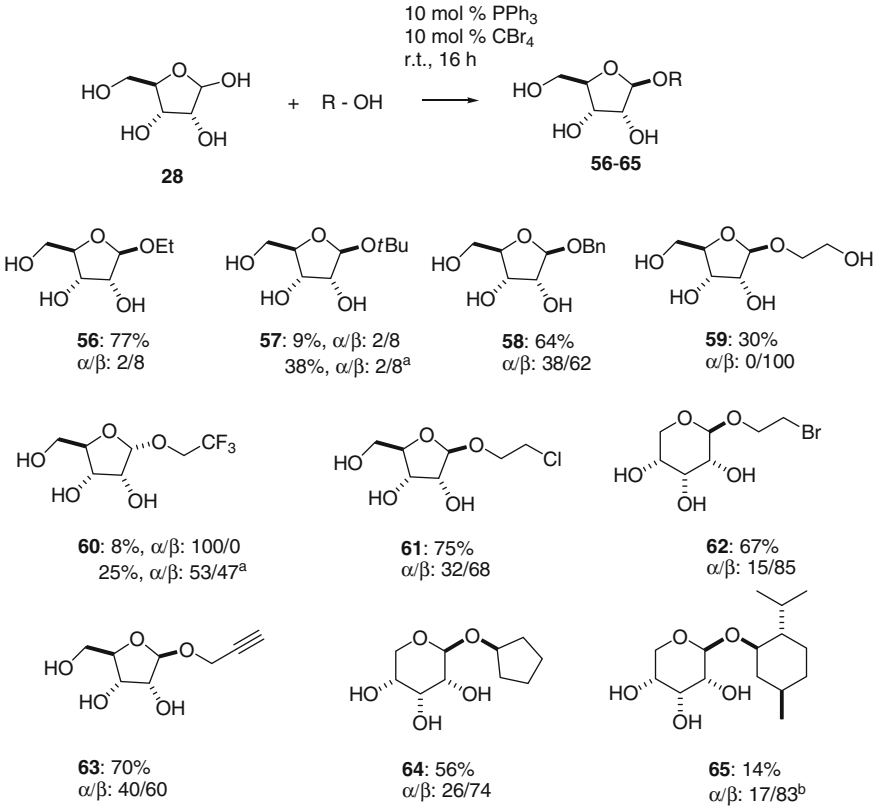


Fig. 4.1 Isopropylriboside (**51**)—sodium perchlorate complex. (The author thanks Dr. B. Braun for the x-ray structure analysis. *green* chlorine; *yellow* sodium)

standard conditions (Scheme 4.18). These glycosylation reactions were performed in the presence of catalytic system PPh_3/CBr_4 (10 mol% of each) at room temperature without additional solvent. The corresponding ribosides **57**–**66** were isolated in moderate-to-high yields, with the exceptions of the reactions of ribose with *tert*-butanol (**58**:9 %) and trifluoroethanol (**61**:8 %). These results indicate extreme influences of both, an electronic effect (**61**) and a steric effect (**58**) of the deployed aglycons on the outcome of this glycosylation. These yield-minimizing effects can be overcome by the additional application of lithium salts, especially lithium perchlorate (Also, quantitative yields were obtained by increasing the catalyst system up to 50 mol %). Furthermore, a moderate to high β-selectivity was noticed in these glycosylation reactions. Excellent diastereoselectivities were obtained with oxygen containing aglycones (**60**: de > 99 %). When used with solid aglycones (e.g. menthol) propylene carbonate was deployed as solvent.

The application of triphenylphosphine and tetrabromomethane in glycosylation processes has been described in the literature [97–103]. These conditions were applied to glycosylation of fully protected 1-hydroxy carbohydrates. In these reactions triphenylphosphine and tetrabromomethane were used in an excess (up to 9 equivalents) under inert and dry reaction conditions to intermediately generate the corresponding protected 1-bromo glycosyl derivative. The following glycosylation was achieved by the addition of amines or DMF.

The present reaction conditions cannot be compared with those described in literature. Water generated during the reaction is tolerated. Also, alterations to the yields and selectivities were not noticed when adding one or two equivalents of water. The formation of 1-bromo glycosyl intermediates was not observed. Additional bases or DMF are not necessary for this glycosylation. These results contrast to reactions carried out in the presence of excess of triphenylphosphine and tetrabromomethane. Also, the formation of triphenylphosphine oxide cannot be the driving force of this catalytic procedure. This consideration is not consistent with the high yields of compounds **53** (99 %) or **55** (84 %) by deployment of 10 mol% catalyst system (see Scheme 4.17).

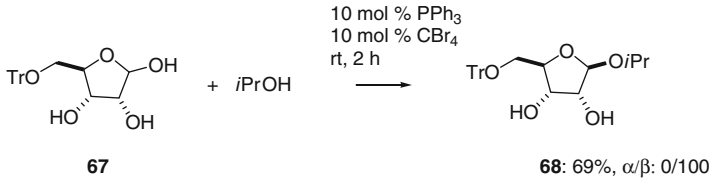


Scheme 4.18 Organocatalyzed glycosylation of ribose with several different aglycones. [a]2 equiv. of $LiClO_4$ were added; [b]reactions were carried out in propylene carbonate

Furthermore, this catalytic reaction proceeds in an essentially neutral medium. To demonstrate the neutral reaction medium, we have reacted 5-tritylated ribose **67** under the described standard reaction conditions. A very rapid, clear and selective glycosylation was observed. Cleavage of trityl group was not detected as would be expected in the presence of the Appel-reagent (For cleavage of triyl ethers under Appel-conditions see [104]). After 2 h at room temperature 5-protected isopropylriboside **68** was isolated with high yields as a single stereoisomer (Scheme 4.19).

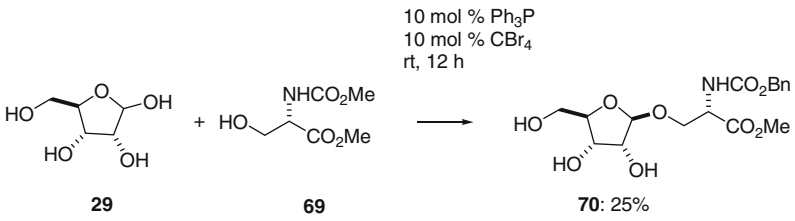
To demonstrate the utility of this operationally simple protocol we reacted Cbz-protected serine methyl ester **69** with unprotected ribose **29** under the reported standard conditions (Scheme 4.20). After 12 h at room temperature the riboside **70** was isolated with 25 % yield. For a comparison with the classical synthesis (protection—glycosylation—deprotection) of Cbz-protected serine methyl ester glycoside in the xylose series see reference [105, 106].

In further investigations into direct glycosylation processes we elaborated an organocatalyzed direct glycosylation based on an oxa-Michael-addition. We



67 **68**: 69%, α/β: 0/100

Scheme 4.19 Organocatalyzed glycosylation of 5-tritylated ribose

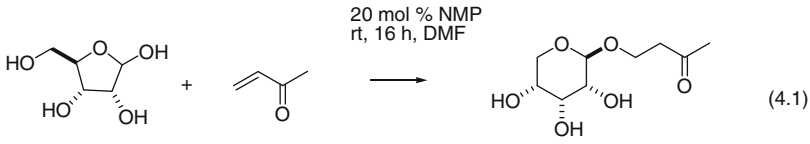


29 **69** **70**: 25%

Scheme 4.20 Organocatalyzed glycosylation of protected serine ester

observed an intramolecular oxa-Michael addition of unprotected carbohydrates during several cascade reactions **(see Schemes 3.3 and 3.16**, Chap. 3**)**. Based on a Knoevenagel/intramolecular oxa-Michael cascade we elaborated a protocol for the stereoselective synthesis of C-glycosides [107]. Adapted from these results we envisioned a direct glycosylation of unprotected carbohydrates with α,β-unsaturated carbonyl compounds.

To verify a glycosylation by an oxa-Michael reaction with unprotected carbohydrates we reacted ribose with methyl vinyl ketone in the presence of catalytic amounts of different bases. Initial experiments were carried out under the conditions that were elaborated for the Knoevenagel/oxa-Michael cascade of carbohydrates. These conditions proved to be unsuccessful. After extensive optimization of the process, however, we were able to realize an oxa-Michael process. In reactions carried out in the presence of 20 mol% N-methyl pyrrolidine (NMP) at room temperature we succeeded in isolating the unprotected riboside **72** with 46 % yield. Only the β-anomer was detected (dr > 95/5), proving the reaction to be highly stereoselective (Eq. 1).



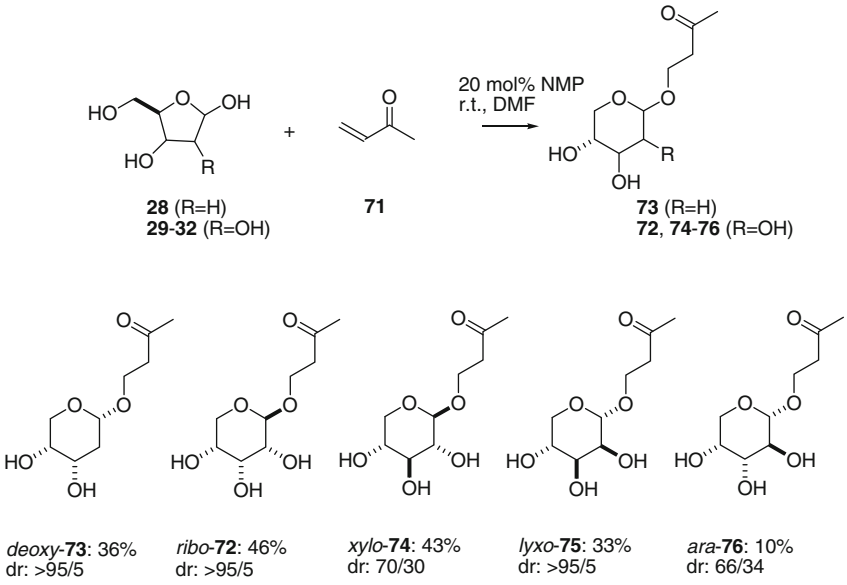
29 **71** **72**: 46%, dr: >95/5

Furthermore, this transformation is highly chemoselective. The Michael-acceptor reacts only with the anomeric hydroxyl group of the carbohydrates deployed. Further oxa-Michael reactions with additional hydroxyl groups of carbohydrates were not detected. Finally, substantial amounts of acetyl-methyl-dihydropyran were detected as a byproduct (dimer of starting methyl vinyl ketone) [108, 109].

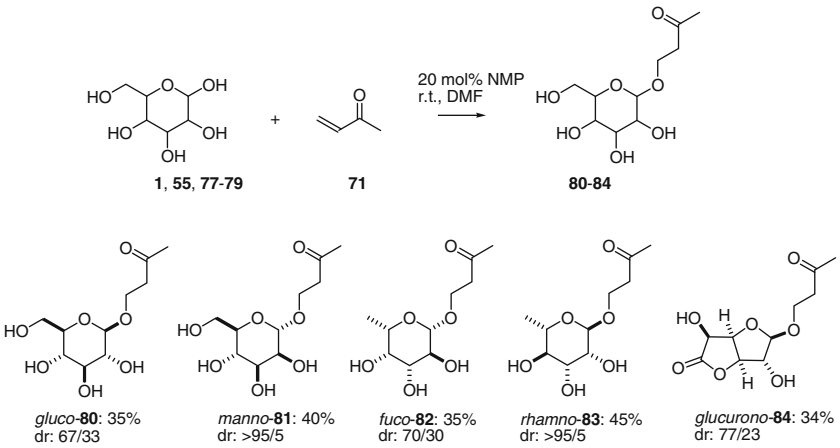
Oxa-Michael additions have been reported using common and typical alcohols as substrates in various, different catalytic systems. For an overview of these investigations see reference [110–116]. Recently, amine-catalyzed oxa-Michael additions have been increasingly deployed in several useful and highly selective cascade reactions [117–126]. In contrast to that, oxa-Michael additions of carbohydrates, in particular unprotected carbohydrates, are unknown so far.

To obtain more information on this oxa-Michael process and expand on it, we tested several different D-pentoses in a next series. Pentoses as well hexoses were reacted with methyl vinyl ketone **71** under the optimized reaction conditions described above (Eq. 1). The results of these investigations are depicted in Schemes 4.21 and 4.22.

The glycosides of the pentose-series **72**–**76** and of the hexoses-series **80**–**84** were isolated with high degrees of stereoselectivity. The installation of configuration at



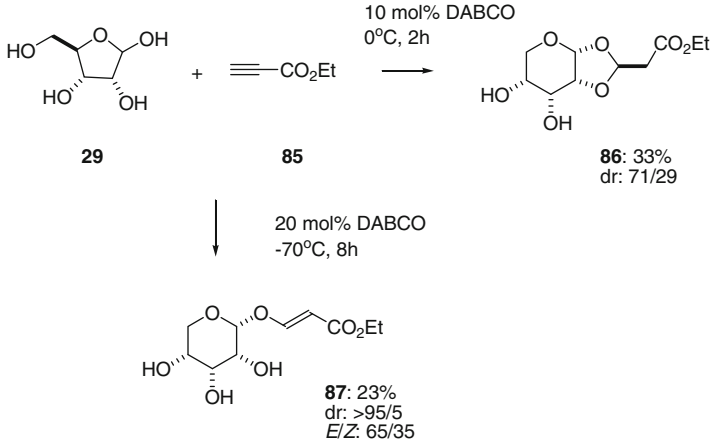
Scheme 4.21 Amine-catalyzed oxa-Michael additions with various D-pentoses



Scheme 4.22 Amine-catalyzed oxa-Michael additions with various D-hexoses

the anomeric carbon is dictated by the configuration of C-2 of the input carbohydrates. Based on steric hindrance, a highly selective *trans*-glycosylation is detected. This observation holds true for both series, oxa-Michael additions of hexoses as well as pentoses.

Next, based on the success of oxa-Michael additions with methyl vinyl ketone, we investigated activated terminal as well internal alkynes as substrates in these addition reactions. Initial experiments with ribose **29** and ethyl propiolate **85** yielded a complex mixture of compounds, when the reaction conditions of the enone-series were applied (20 mol% NMP, r.t.). After subsequent extensive

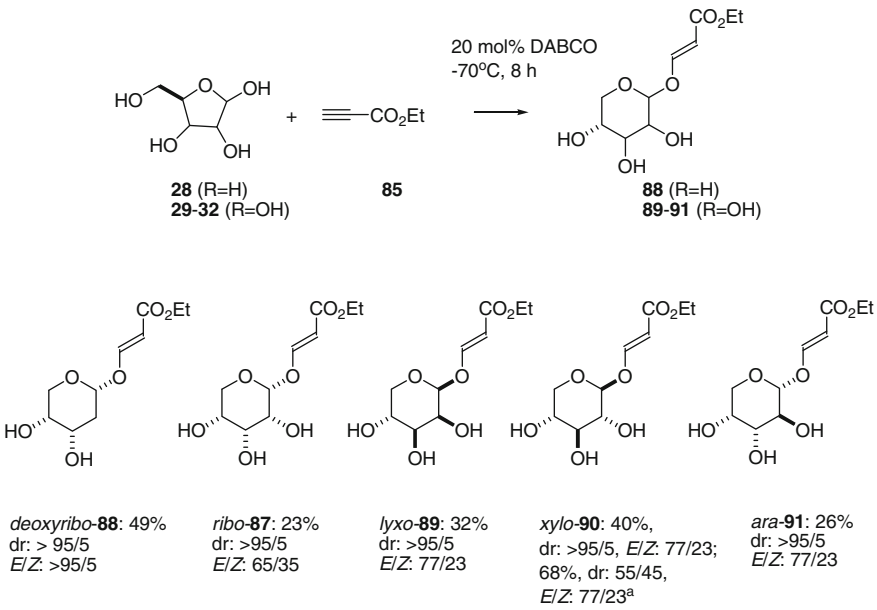


Scheme 4.23 DACO-catalyzed oxa-Michael addition of ribose to ethyl propiolate **85**

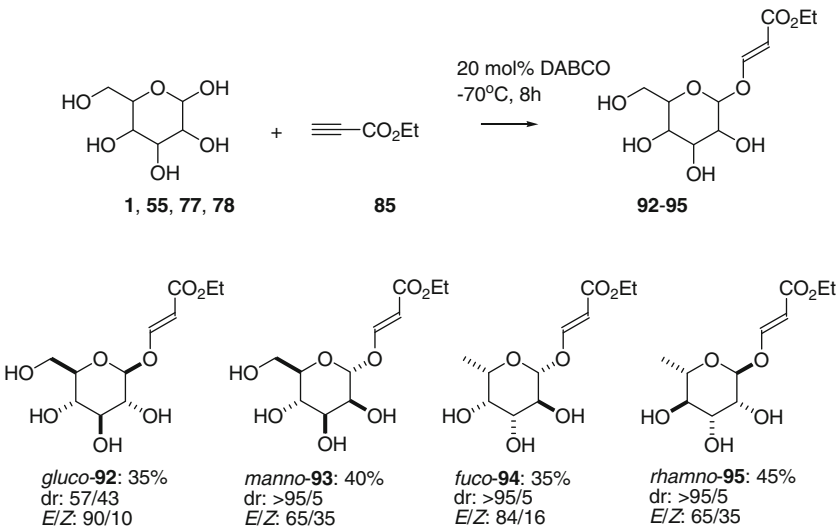
optimization a general protocol was elaborated. With a reduced reaction temperature of 0 °C a double oxa-Michael addition (dihydroalkoxylation) was observed. As a result a mixture of diastereomeric acetals **86** was isolated (dr ~ 70/30) (for a similar observation see [127–129]). A clear and selective formation of the corresponding enol riboside **87** was observed at −70 °C (Scheme 4.23). Under these conditions the riboside **87** was detected 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 allenes during the reaction.

Using this optimized protocol we were able to elaborate a general oxa-Michael addition of unprotected carbohydrates to activated alkynes. To this end we reacted pentoses as well hexoses with ethyl propiolate **85** in the presence of 20 mol% DABCO at −70 °C. The results of these investigations are depicted in Schemes 4.24 and 4.25. The reaction again proceeds with an extremely high degree of stereoselectivity (dr: > 95/5), with the exception of reactions with glucose **1**. Enol glucoside **92** was isolated with a diastereomeric ratio of 57/43 (Scheme 4.25).

The enol glycosides **87**–**91** were formed with mostly high degrees of *E*-configured double bonds. These results agree with the stereochemical rules of base-catalyzed oxa-Michael additions to activated alkynes established by Winterfeldt [130–132].



Scheme 4.24 Oxa-Michael addition of ethyl propiolate with different pentoses . [a]2.0 equiv of xylose were used



Scheme 4.25 Oxa-Michael addition of ethyl propiolate with different hexoses

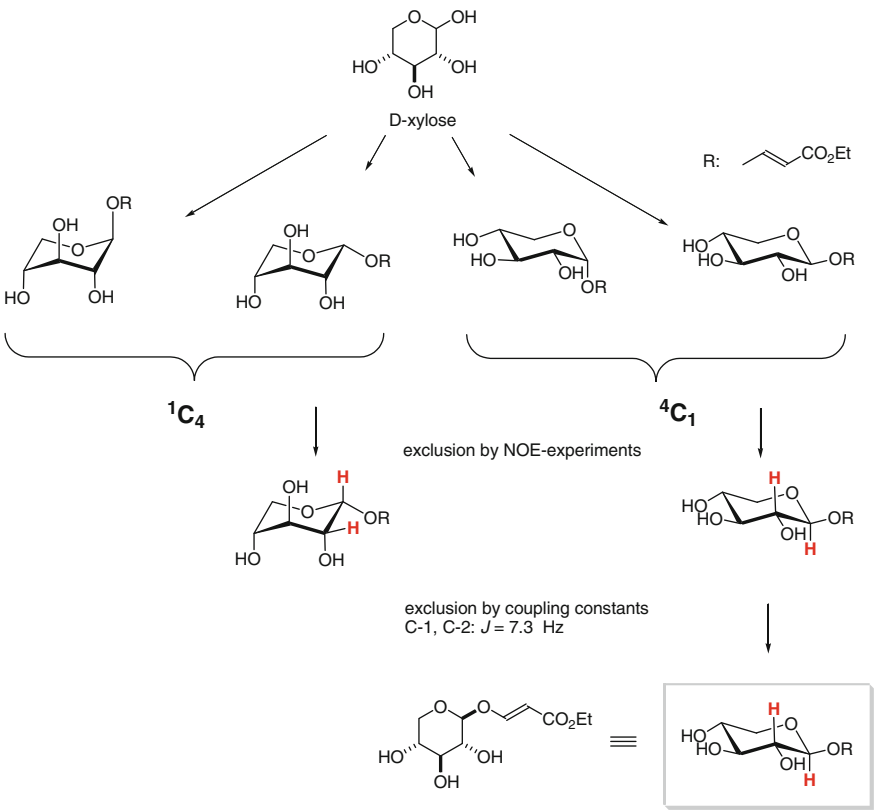
The formation of exlusively pyranoid glycosides and the observed configuration at the anomeric carbon atom indicate a thermodynamic reaction control. Based on that, a preliminary explanation for the extremely high stereoselectivity is given by comparison of potential conformations. These considerations have been exemplarily depicted for compound *xylo*-**90** in Scheme 4.26.

In a further series we tested several different alkynes with ribose and xylose as substrates (Schemes 4.27 and 4.28). The results indicate that even internal alkynes can be employed in oxa-Michael reactions with unprotected carbohydrates, albeit at higher reaction temperatures (−40 °C).

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 **100** 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 with regard to stereoselectivity were obtained under these conditions. For example *xylo*-**90** is observed with 40 % yield (dr: > 95/5) when used with one equivalent of xylose. By application of two equivalents of D-xylose yield increases (68 %), but the stereoselectivity drops and *xylo*-**90** is observed with a diastereomeric ratio of 45/55 (α/β, Scheme 4.24). On the other hand, when used with D-xylose and phenylpropargyl aldehyde **99** the yield of enol xyloside **108** increases from 18 to 40 %. However the same high stereoselectivities were detected in both reactions (Scheme 4.28).

An instructive comparison is derived from the application of butyn-one and the corresponding 4-trimethylsilyl-butyn-one as substrates. The same high diastereoselectivities and high *E*/*Z*-ratios were detected in both series, using D-ribose **29** as



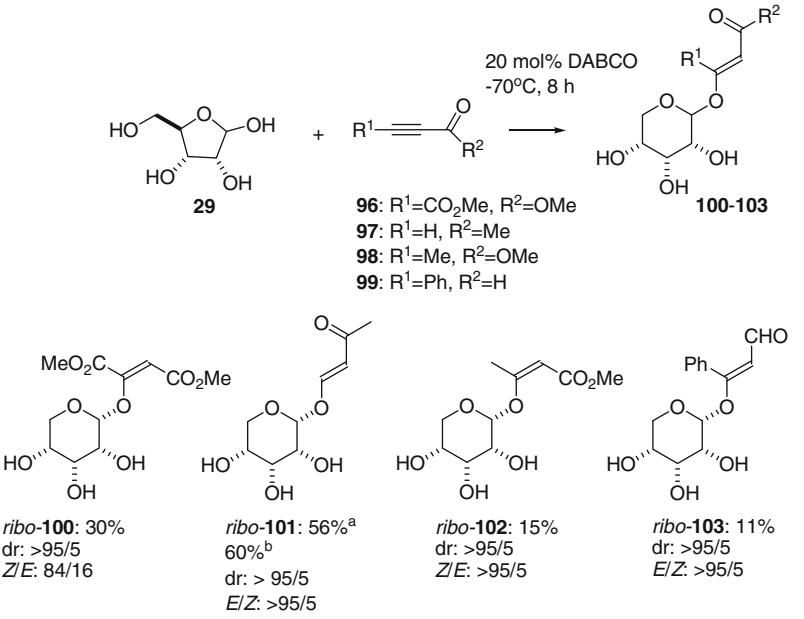
Scheme 4.26 Structural assignment by nO-experiments and analysis of coupling constants

well D-xylose **30**. However, yields differ significantly, with higher yields in the xylose series (compare *ribo*-**101** with *xylo*-**106** in Scheme 4.29).

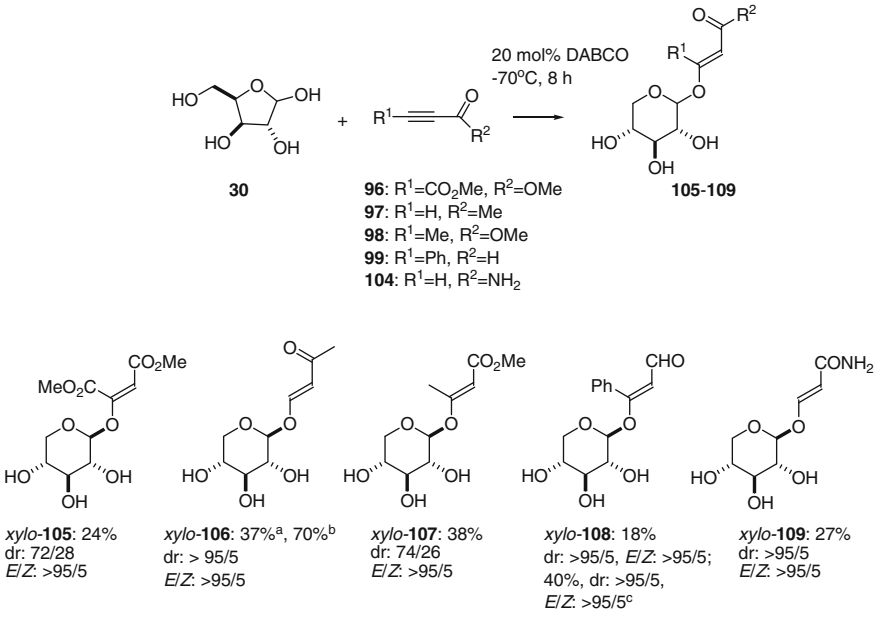
The intermolecular addition of alcohols to terminal and activated alkynes has been reported before [133–138] and has been used extensively in radical cyclization of β-alkoxyacrylates [139–154], in reductive cyclizations of β-alkoxyacrylates (Maitotoxin total synthesis [155–159]) and palladium-catalyzed cyclization in the presence of CO [160]. For an overview of the application of alkynes in organocatalysis see reference [161]. Oxa-Michael additions of unprotected carbohydrates to alkynes have not been reported so far.

To test the utility of this new synthetic method, the acrolein derived xyloside **108** was reacted with phosphonium salt **110** to yield the *E*,*E*-configured diene **111** (Scheme 4.30).

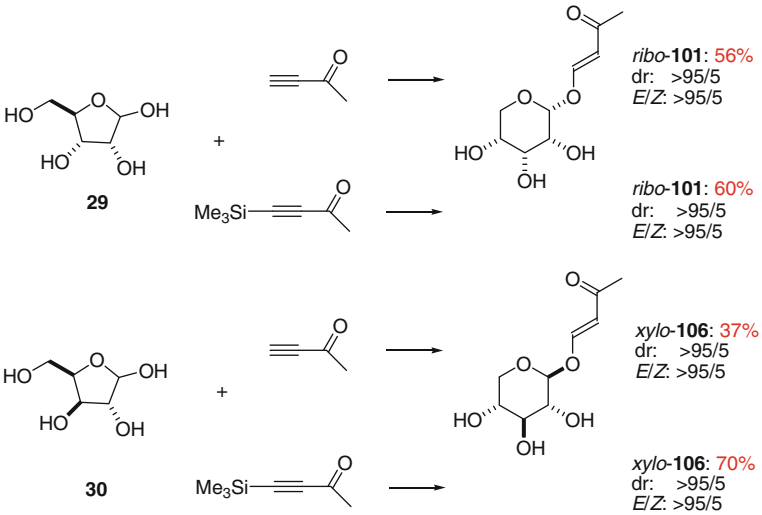
Similar compounds, like dienoic acid ethylester **111**, represent valuable starting products in Diels-Alder reactions in total synthesis of optical active non-proteinogenic amino acids [162, 163] or anthracyclines [164–166]. The existing techniques for the synthesis of carbohydrate-modified dienes like **111** [167], carbohydrate-modified



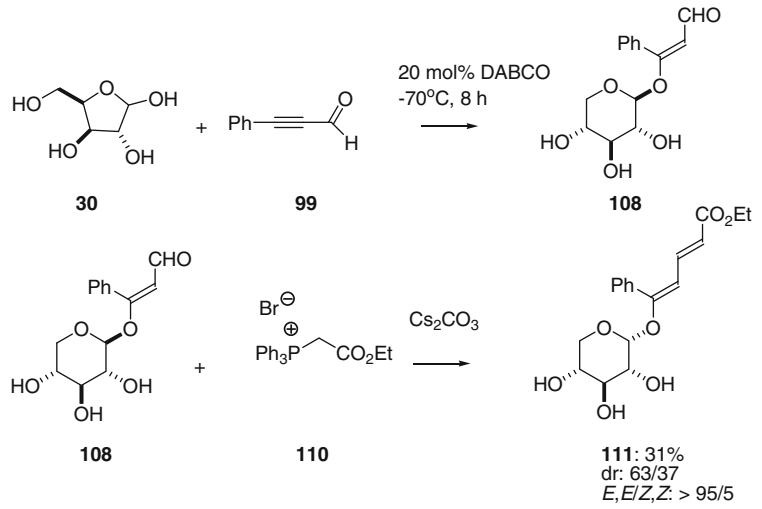
Scheme 4.27 DABCO-catalyzed oxa-Michael additions with ribose. [a] TMS-≡-COMe was used; [b] H-≡-COMe was used



Scheme 4.28 DABCO-catalyzed oxa-Michael additions with xylose. [a]TMS-≡-COMe was used; [b]H-≡-COMe was used; [c]2 equiv xylose were used



Scheme 4.29 Comparison of oxa-Michael additions to butyn-one and to trimethylsilyl-butyn-one



Scheme 4.30 Synthesis of glycosyl dienoic acid esters

aldehydes **103/108** [168–171] or ketones **101/106** [172–176] 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 reference [177].

Several different organocatalyzed glycosylation processes of carbohydrates have been discussed. The results clearly support the concept of the application of unactivated and unprotected carbohydrates in glycosylation processes. By utilizing

hydrogen bridges, which are working during the reaction, the configuration at the anomeric carbon atom can be controlled. Extremely high degrees of stereoselectivities were obtained, dependent on the carbohydrates deployed.

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