

Chapter 2

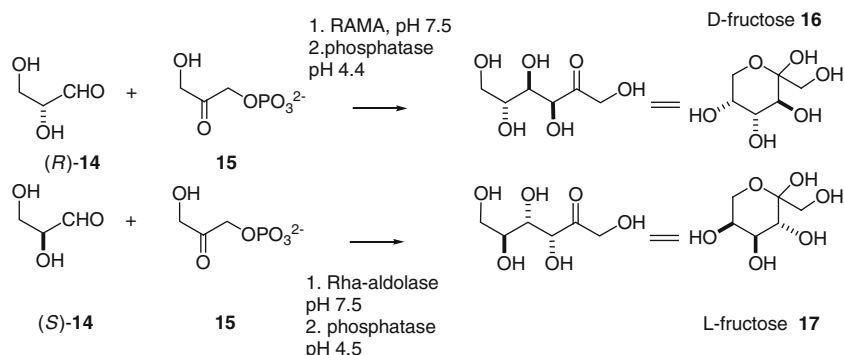
Total Synthesis of Carbohydrates

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

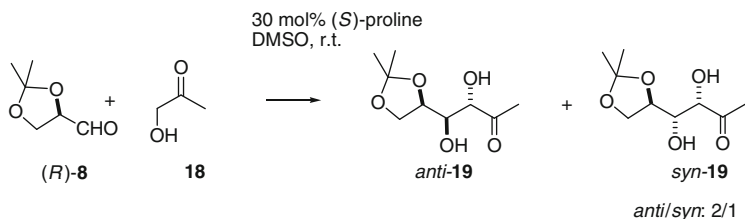


Scheme 2.1 C₃+C₃ enzyme-catalyzed approach to D-fructose **16** and L-fructose **17** (RAMA: rabbit muscle aldolase; Rha: rhamnulose aldolase)

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—type I aldolase and type II aldolase [10]. These enzymes stereospecifically 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 enzyme-catalyzed transformations. 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 C₃-unit for these biomimetic reactions. Several reports were published describing aldol additions of unprotected dihydroxyacetone with unprotected hydroxyaldehydes (C₃+C₂-strategies give an access to pentoses, while C₃+C₃-strategies yield hexoses) [18–25]. Also, aldol additions of unprotected hydroxyaldehydes were studied (C₂+C₂+C₂-strategies yield hexoses, C₂+C₂ strategies yield tetroses, C₃+C₁+C₁ 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 C₃+C₃ 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).

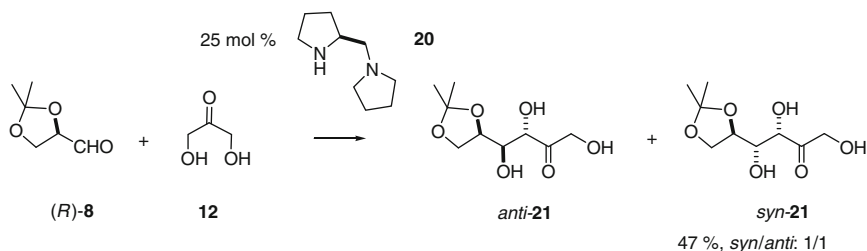
This publication was the go-ahead of a strong, still ongoing development of the so-called organocatalysis [35, 36] and represents the most promising and direct approach to carbohydrates so far. This easy and direct aldol reaction imitates nature in an elegant way [37, 38].

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.

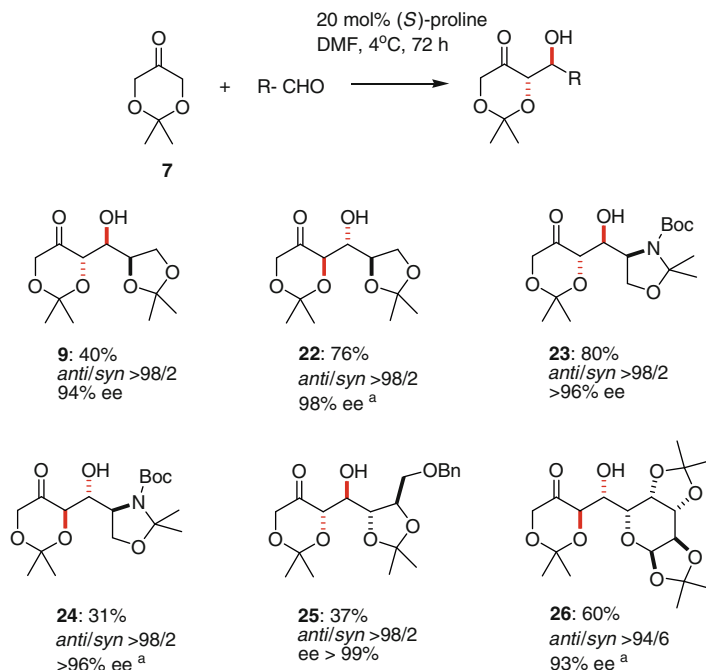
By comparing results of **9** and **23** ((*S*)-proline) with those obtained in the (*R*)-proline series (**22** and **24**), matched- and mismatched-situations becomes propable.

The *anti*-preference of (*S*)-proline-catalyzed aldol reactions provides an additional and efficient tool for enantioselective synthesis. Enantiopure *anti*-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].

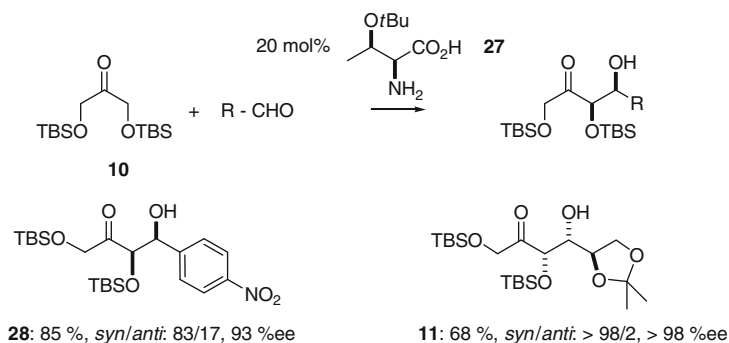
To test further amino acids as catalysts in direct aldol additions Barbas et al. have demonstrated the utility of threonine-derivatives in asymmetric organocatalyzed aldol additions with TBS-protected dihydroxyacetone **10** [47]. Under these reaction conditions the authors were able to isolate aldol 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

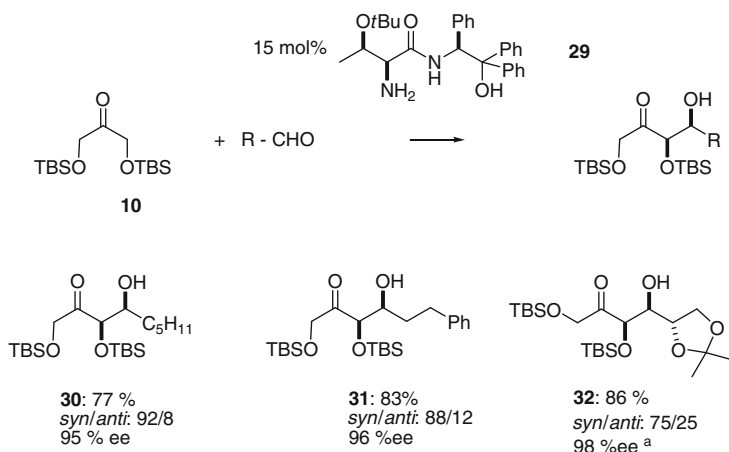


Scheme 2.4 Proline-catalyzed aldol additions of protected dihydroxyacetone (*R*)-proline was used as catalyst

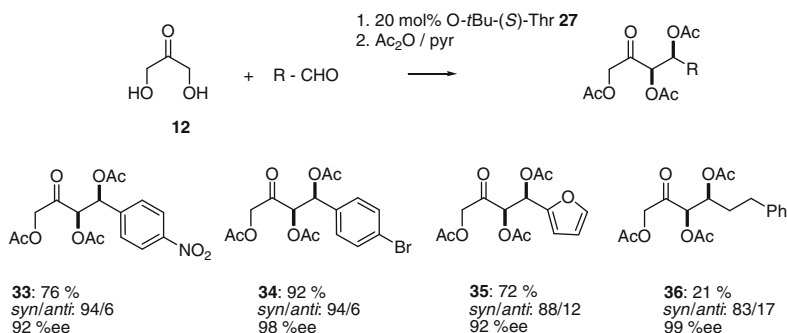


Scheme 2.5 *Syn*-selective aldol additions of protected dihydroxyacetone

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

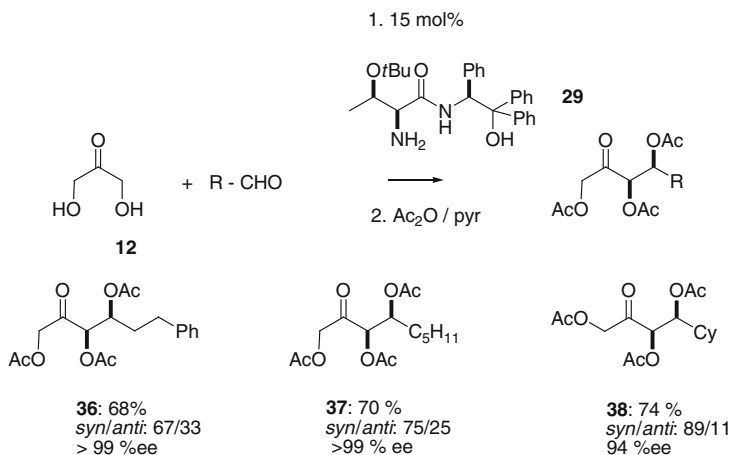
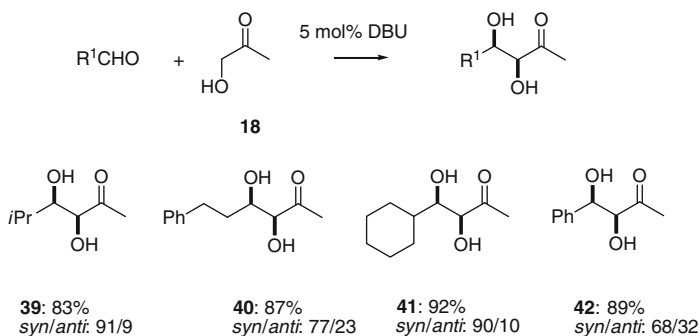
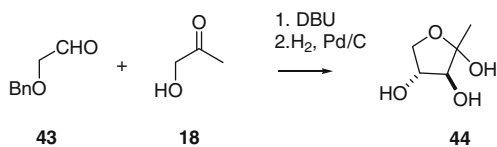


Scheme 2.7 *Syn*-selective aldol additions of unprotected dihydroxyacetone (*S*)-configured glyceraldehyde was used

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).

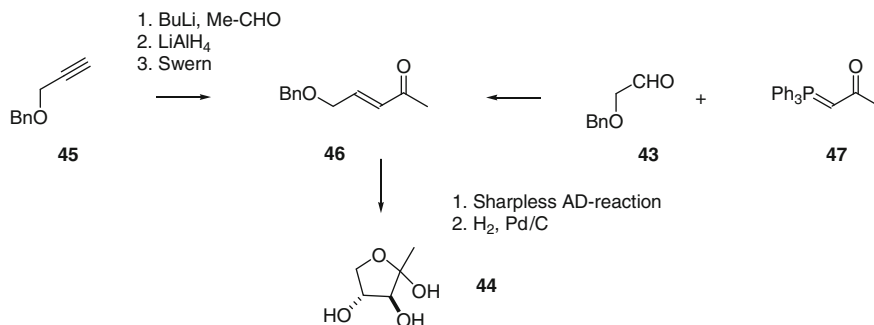
During this development it was found that aldehydes react in the presence of catalytic amounts of tertiary amines with hydroxyacetone **18** to give the corresponding aldol adducts. High *syn*-diastereoselectivities were observed during this aldol-step [50].

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

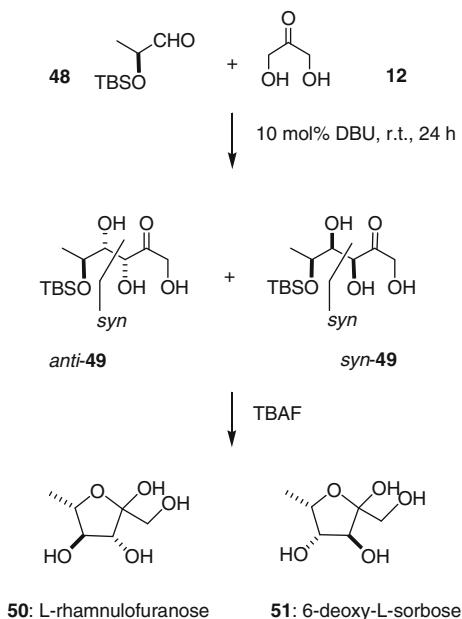


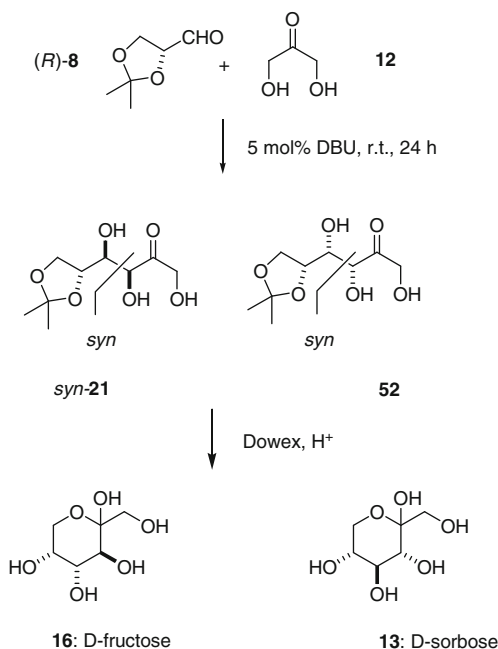
Scheme 2.11 Classical routes to 1-deoxy-D-xylulose

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-deoxy-sorbose **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



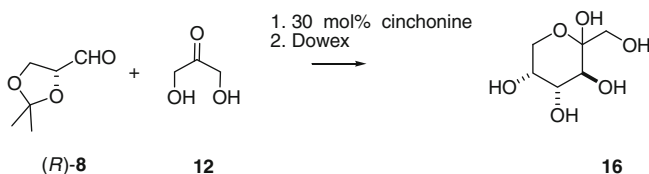
Scheme 2.13 *Syn*-selective aldol additions to D-fructose and D-sorbose

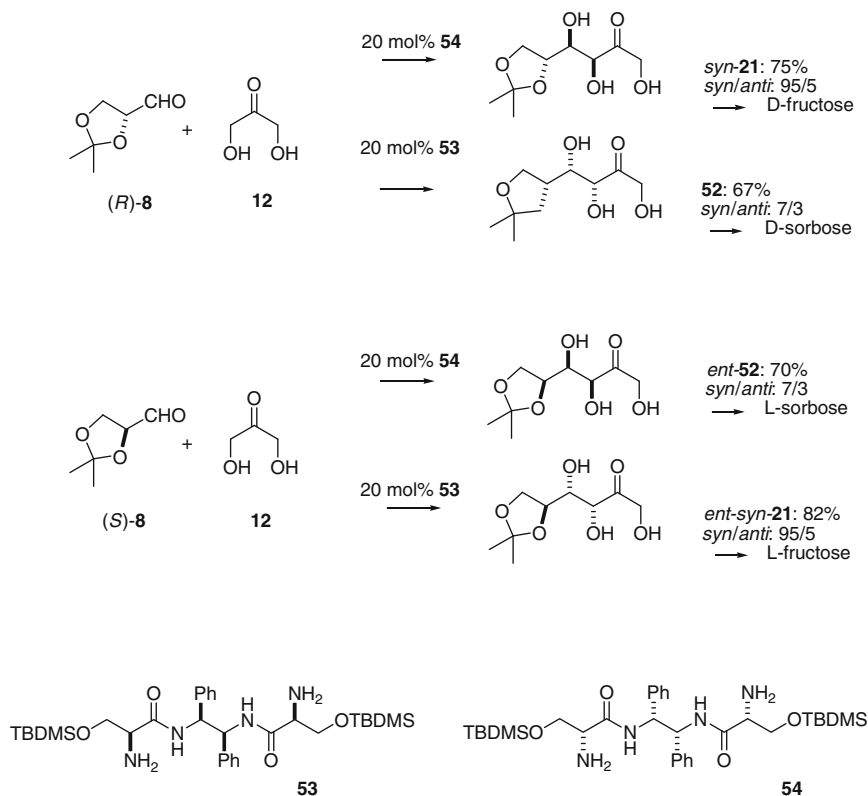
syn-**21** and protected D-sorbose **52** were identified with a ratio of 1/1 (Scheme 2.13). Similar ratios were obtained by deployment with other tertiary amines.

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

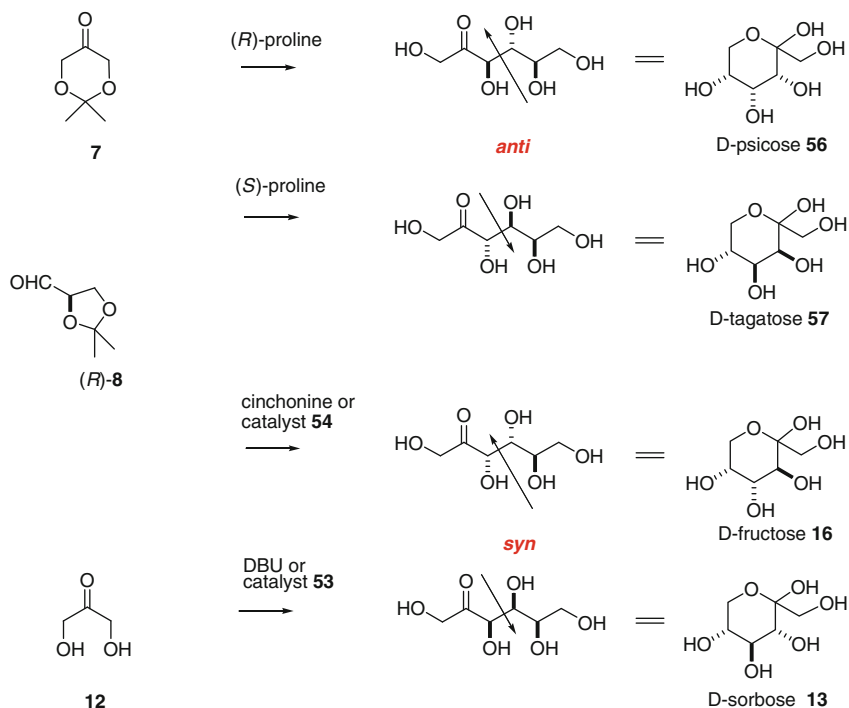
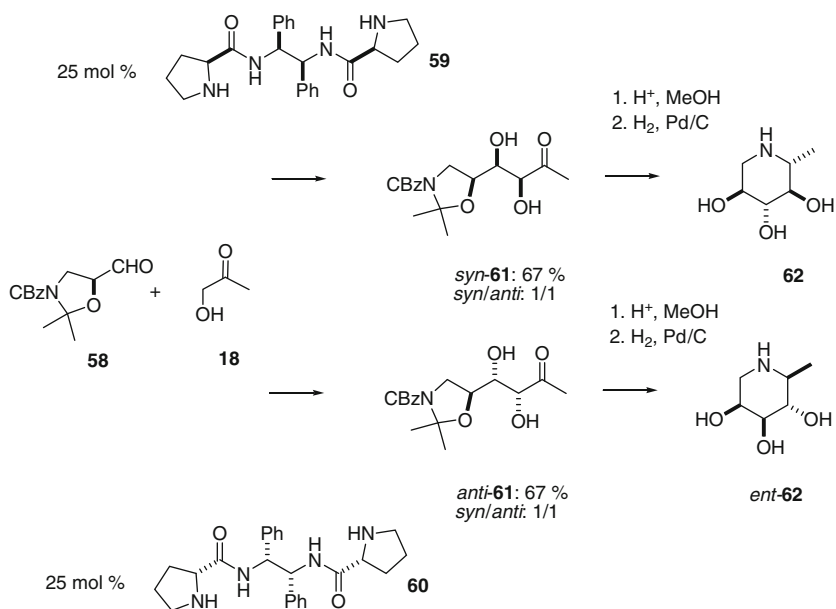


Scheme 2.15 Optional access to D- or L-ketoses

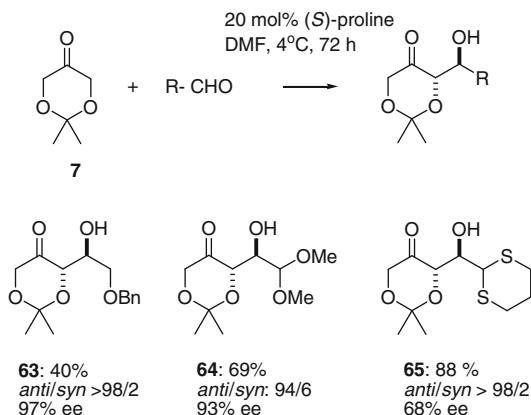
approach to the four D-ketohexoses appears to be solved by the methods described above. As discussed, there exist several different possibilities to synthesize psicose, tagatose, fructose and sorbose. This can be easily accomplished by the C_3+C_3 strategy for the de novo carbohydrate synthesis. Additionally, 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 C₂-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.

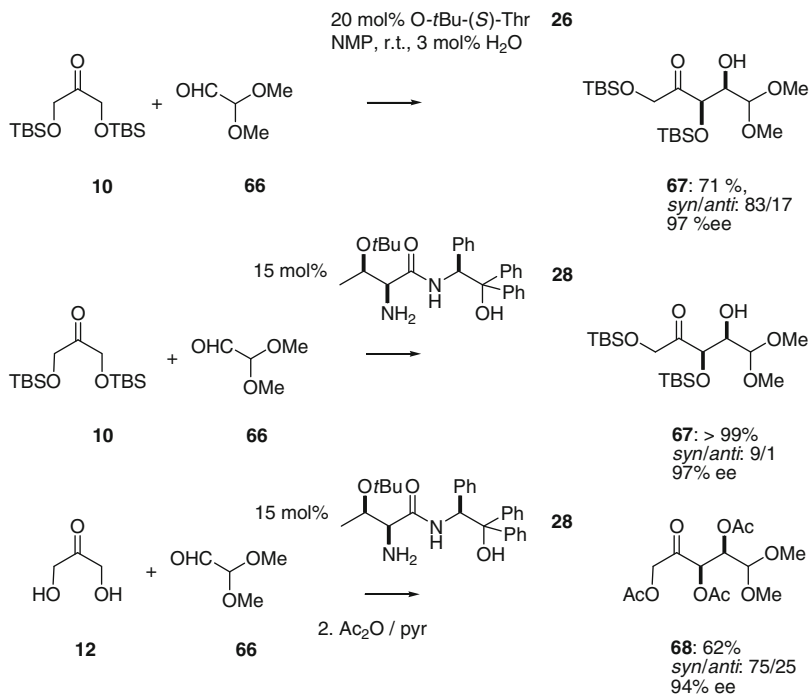
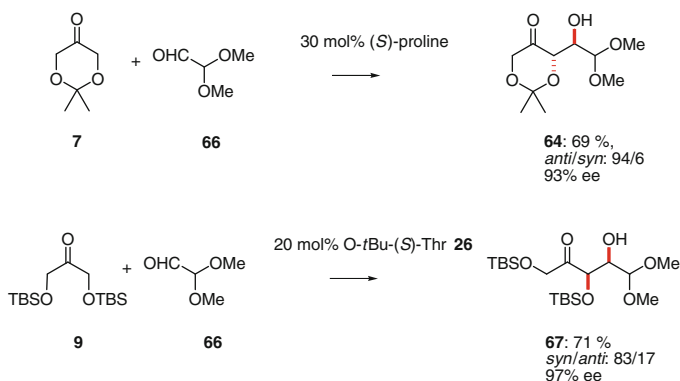
The C₃+C₂ strategy promises to be a valuable synthetic tool for the total synthesis of pentoses. Enders and Grondal have highlighted the utility of this concept [55]. Aldol adduct **63**, **64** or **65** were isolated with high degrees of enantio- as well as *anti*-diastereoselectivity in reactions of protected DHA **7** (C₃-unit) with dimethoxyacetaldehyde or benzyloxy acetaldehyde (C₂-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].

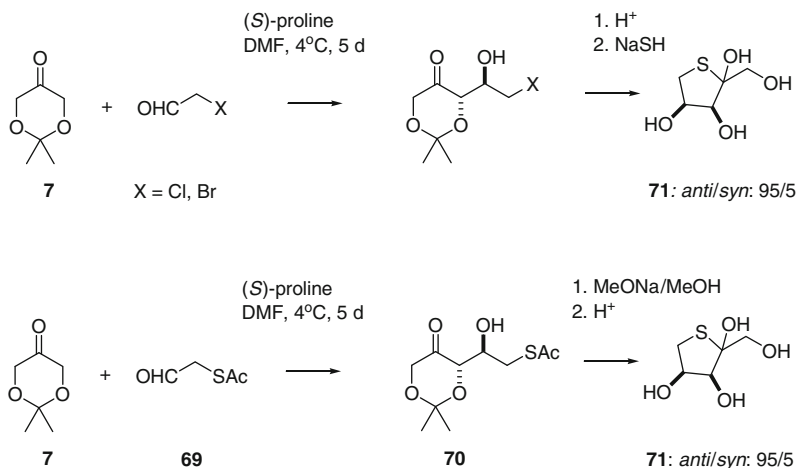
An access to *syn*-configured aldol adducts of protected DHA with protected glycolaldehyde has recently been reported by the group of Barbas (**67** and **68**, Scheme 2.19) [47, 48]. Substoichiometric amounts of derivatives of threonine were used as catalysts in these aldol transformations. Even unprotected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

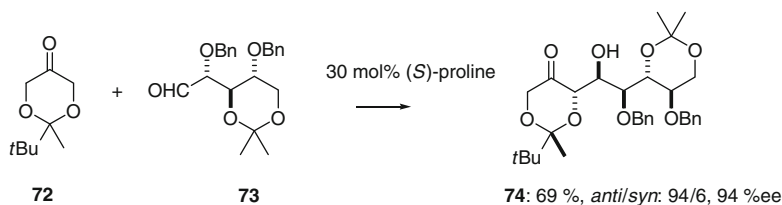
The totalsynthesis of thioketoses can be realized via C₃+C₂ strategy through aldol additions of protected dihydroxyactone with acetylmercatocetaldehyde **69** by means of proline [57]. Alternatively, same authors have synthesized thioketose **71** by aldol additions of protected DHA with halogen acetaldehyde 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 C₃+C₂ approach to L-threo-pentuloses**Scheme 2.20** Comparison between *anti*- and *syn*-selective C₃+C₂ approach to pentoses

By proline-catalyzed aldol reactions of protected dihydroxyacetone **72** with chiral hydroxylated aldehyde (**73**: C₅-unit) an access to “higher” carbohydrates is given (C₃+C₅ → 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

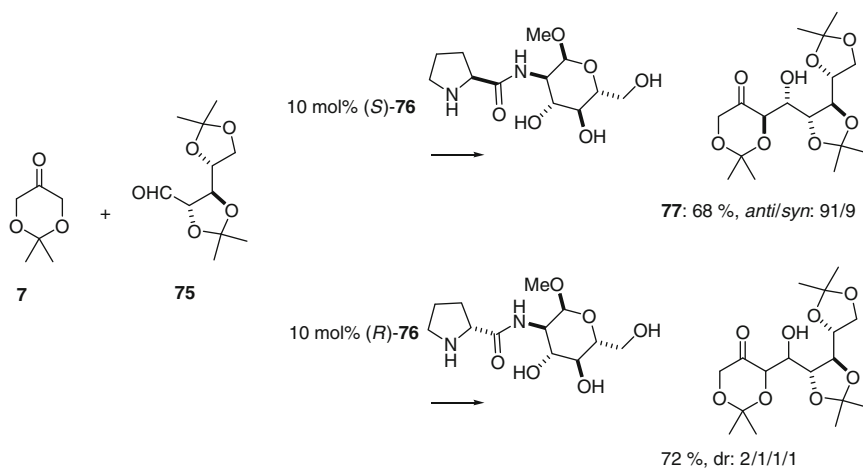
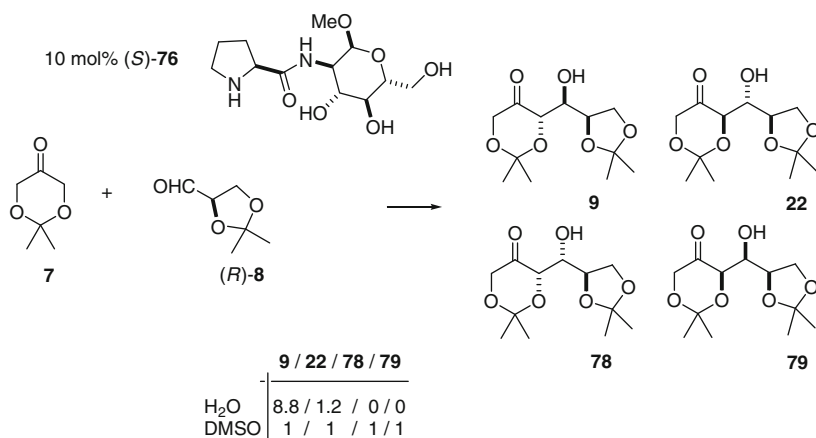


Scheme 2.22 C_3+C_5 strategy to precursor of *manno*-octulose

When prolinamide-derived catalyst (*S*)-**76** was used in this strategy ($\text{C}_3+\text{C}_5 \rightarrow \text{octulose}$) *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.

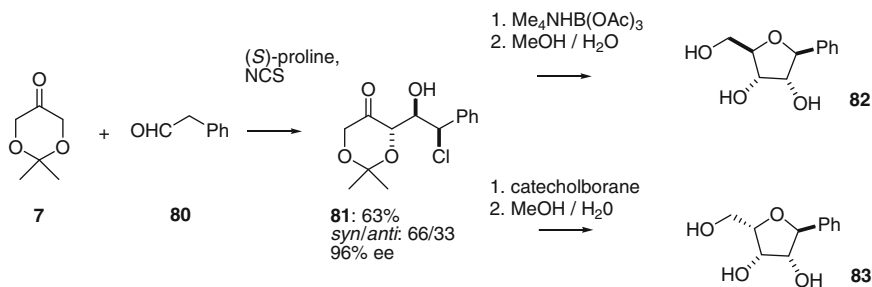
During these investigations the authors detected a strong influence of the solvent on the configurative outcome of this aldol reaction. High stereoselectivities were obtained with water as the solvent. In strong contrast to that, a completely unselective reaction was observed with DMSO as the solvent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

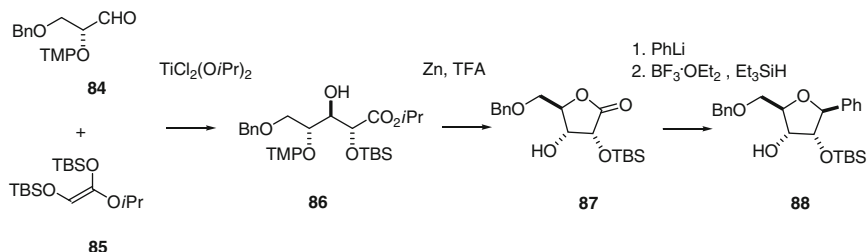
**Scheme 2.23** Gluco-octulose by C₃+C₅ strategy**Scheme 2.24** Solvent dictates the configurative outcome

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 organo-catalyzed 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



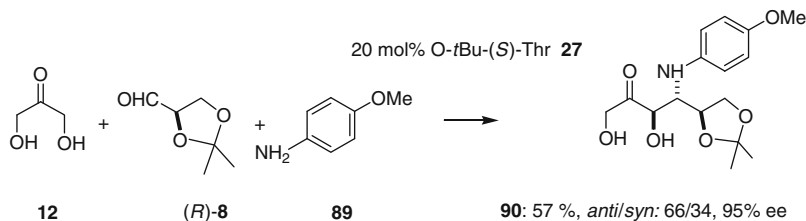
Scheme 2.25 Proline-catalyzed access to C-glycosides



Scheme 2.26 MacMillan organocatalyzed approach to pentoses TMP = 2,2,6,6-tetramethylpiperidiny1

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).

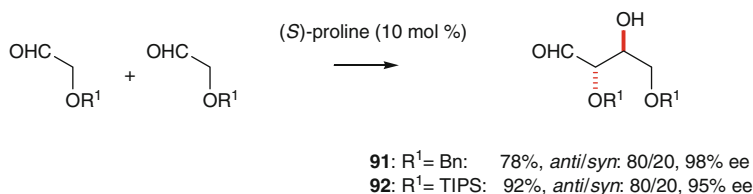
Depending on the conditions of a subsequent stereocontrolled Mukaiyama-reaction an access to protected L-allose **95**, L-mannose **96** or L-glucose **97** is possible. Following this protocol, protected carbohydrates were isolated with high degrees of stereoselectivities (Scheme 2.29).

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].

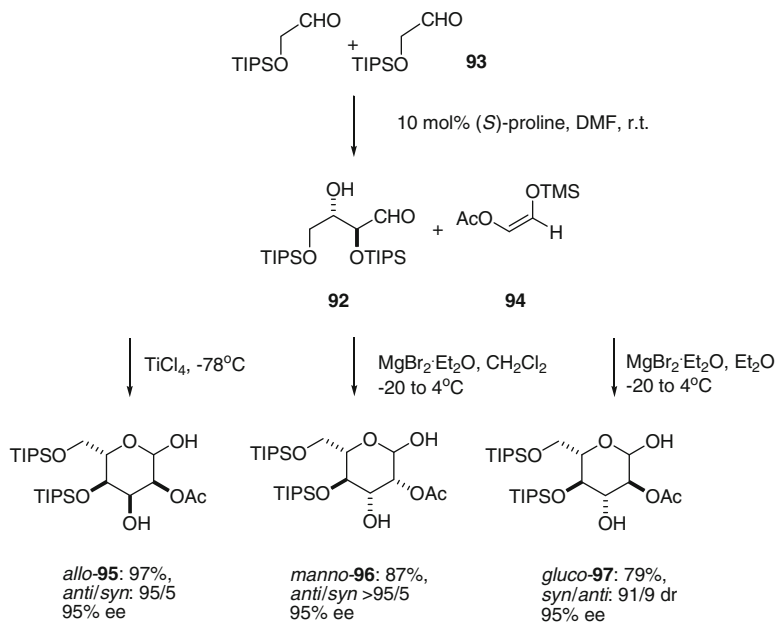
A further application of this methodology was reported by Mainkar et al. [76]. The authors used this Mukaiyama/proline approach for the synthesis of O-spiro-C-aryl glycosides.

A full proline-catalyzed approach to carbohydrate derivatives 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.

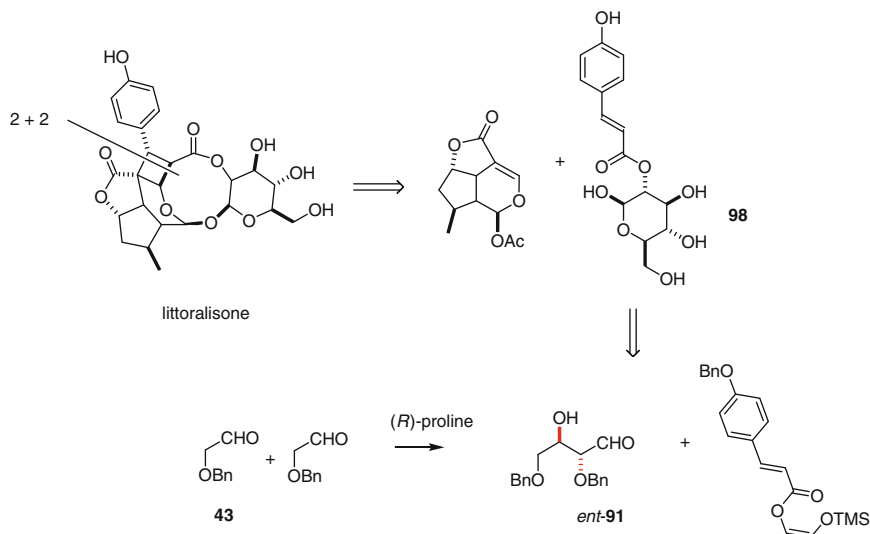
When used with (*R*)-proline followed by (*S*)-proline-catalysis, D-configured carbohydrates can be accessed. In contrast to that, by the deployment of (*S*)-proline followed by a (*R*)-proline-catalysis, L-configured carbohydrates were obtained (compare **101** and *ent*-**101** in Scheme 2.31). As 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].



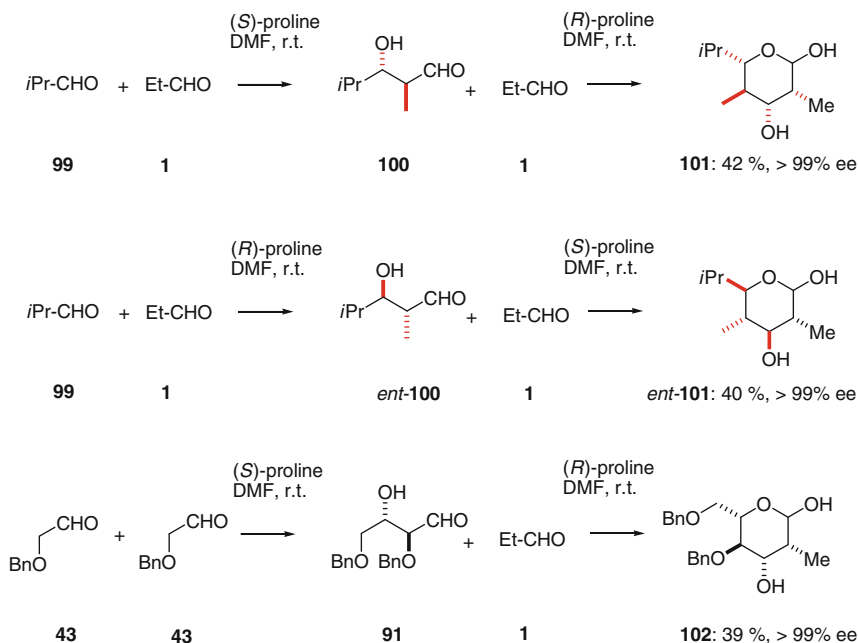
Scheme 2.28 (*S*)-Proline-catalyzed homodimerization of oxygen-substituted acetaldehydes



Scheme 2.29 Organocatalyzed aldol /Mukaiyama-aldol $\text{C}_2+\text{C}_2+\text{C}_2$ 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

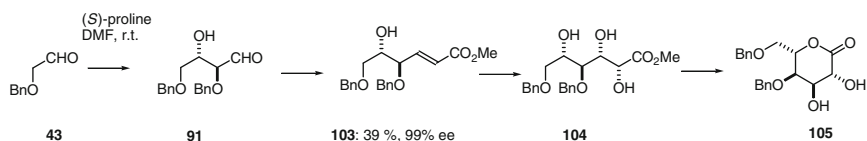
Zinc-proline-complex catalysis gives a nonselective access to all eight aldohexoses. This catalyst was tested in aldol reactions of hydroxyacetaldehyde ($\text{C}_2+\text{C}_2+\text{C}_2$ strategy) [79–81].

The $\text{C}_2+\text{C}_2+\text{C}_2$ -strategy, utilizing nitroolefines as C_2 -building blocks, gives an access to a precursor of carbohydrate derivatives by intermolecular Michael/Henry cascade reactions [82].

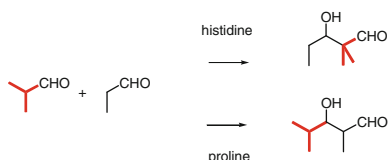
Several reports were published for the total synthesis of tetroses by the C_2+C_2 strategy. These transformations were realized by the deployment of catalytic amounts of proline amide [83] or *N*-Me leucine ethylester [84].

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 C₂+C₂ aldol /Horner sequence to aldohexoses

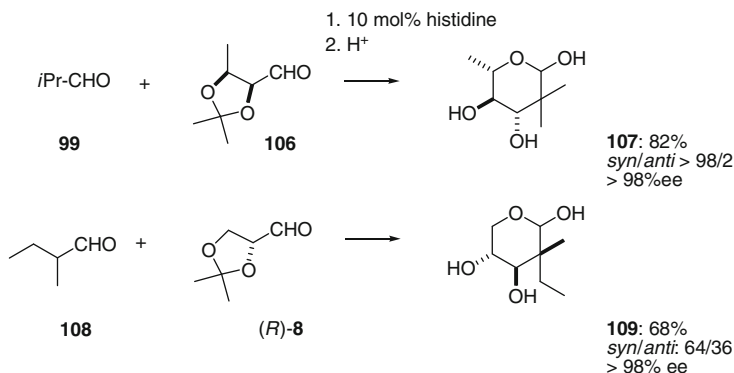


Scheme 2.33 Chemoselectivity of proline- and histidine-catalyzed aldol reactions of enolizable aldehydes

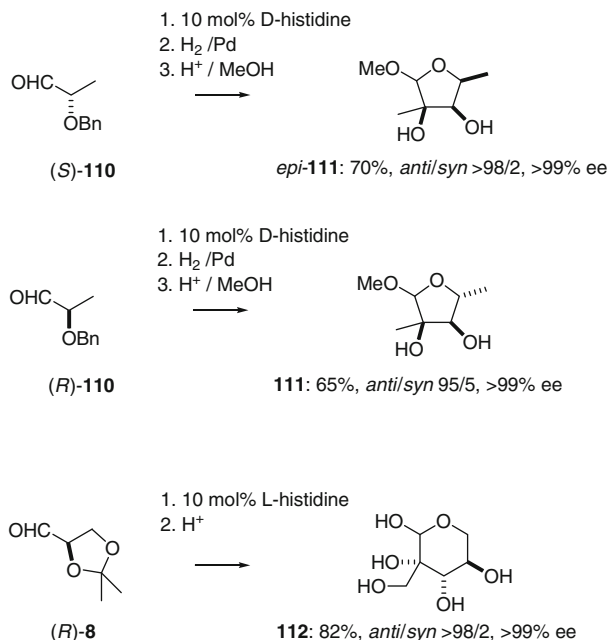
group [86]. α -Substituted aldehydes cannot act as enol-component in proline-catalyzed reactions. This different reaction behavior of proline and histidine is demonstrated in Scheme 2.33.

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 C₄+C₂ approach to 2-dimethyl D-*xyl*-boivoinose and to 2-methyl-2-ethyl-2-deoxy-xylose by the C₃+C₂ approach

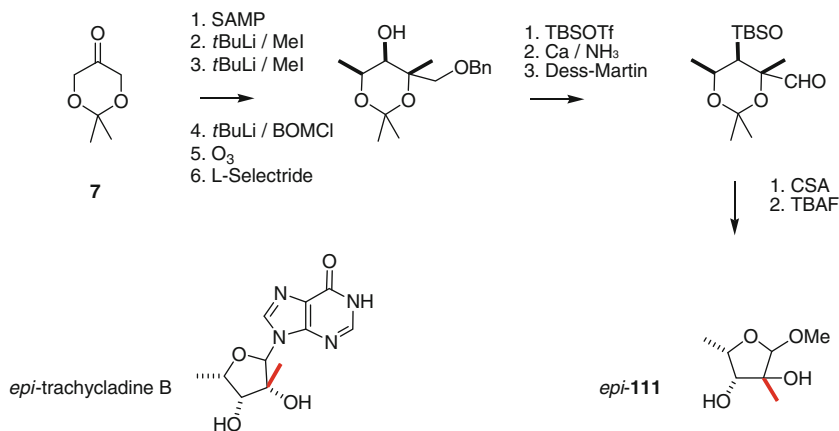


Scheme 2.35 Histidine-catalyzed aldol addition in total synthesis of branched carbohydrates

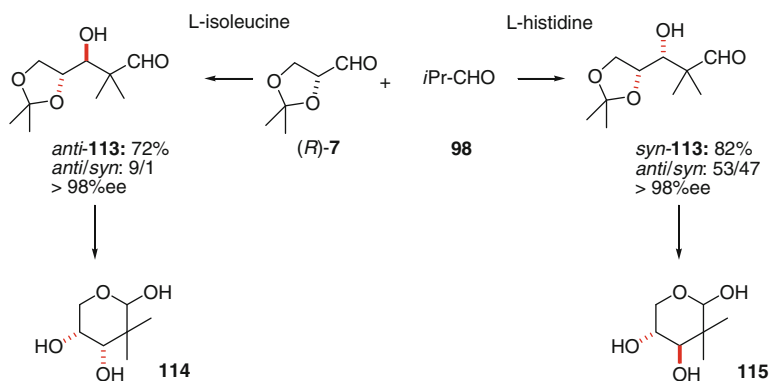
histidine deployed: *S*-configured aldehydes need D-histidine for a matched case, whereas L-histidine is needed for a matched case when using with *R*-configured aldehydes [87, 88].

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*-diastereoselectivity 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

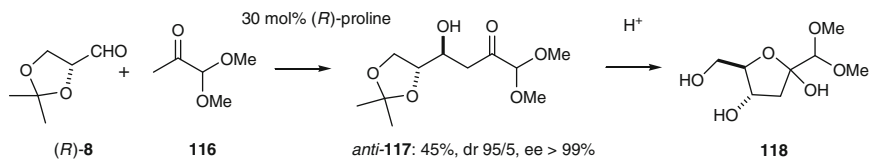


Scheme 2.37 Comparison of isoleucine- and histidine-catalyzed aldol additions with protected glyceraldehyde

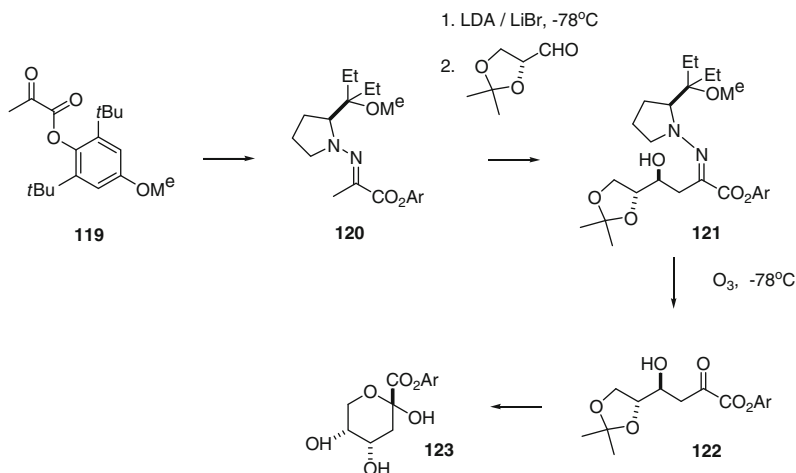
2.3 Aldol Reactions with Pyruvic Derivatives: Access to Ulosonic Acid Derivatives

Ulosonic acids are carbohydrates involving an α -keto acid structure. Precursors of ulosonic acid are easily 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

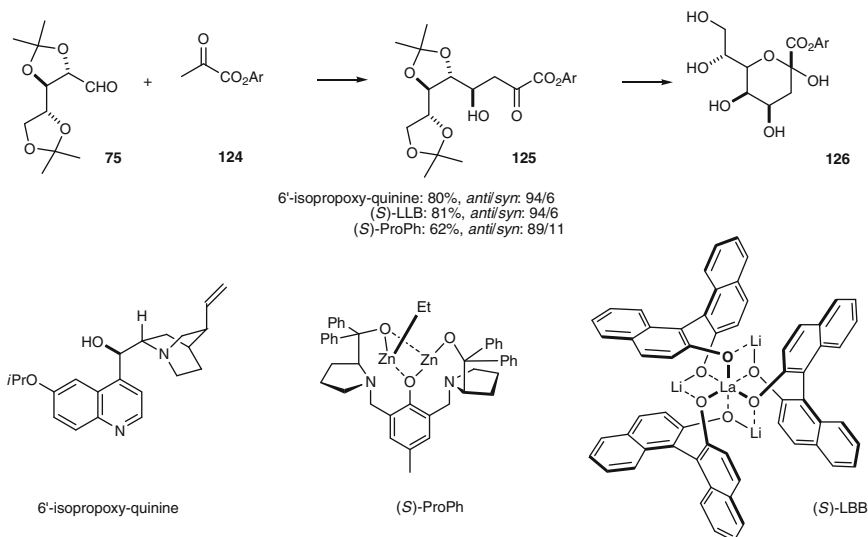


Scheme 2.39 Enantioselective access to ulosonic acid derivatives by the SAEP-method SAEP: (*S*)-1-amino-2-(1-ethyl-1-methoxypropyl)pyrrolidine

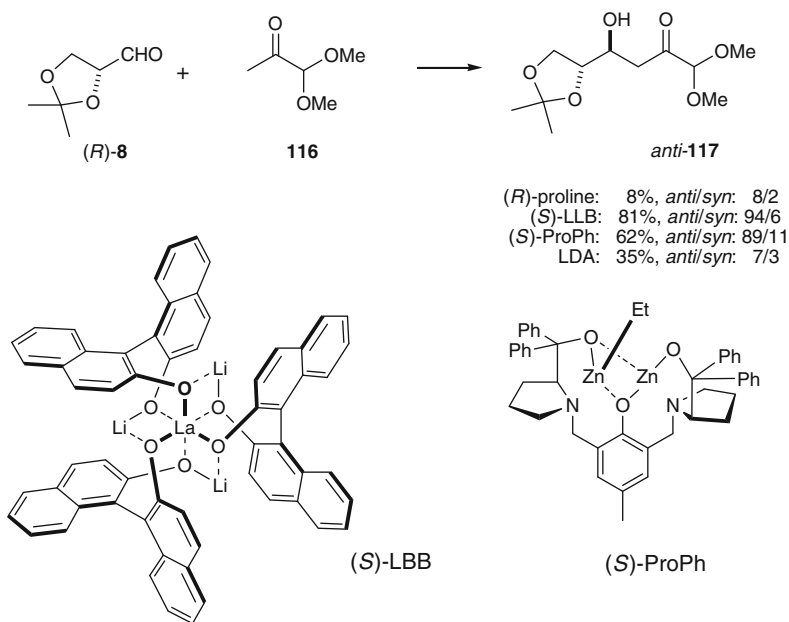
To underline the tremendous progress of organic chemistry made by the development of organocatalysis this auxiliary-based sequence is depicted in Scheme 2.39. The authors used the sterically more demanding SAEP-auxiliary instead of the SAMP-group in this sequence to increase the stereoselectivity of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



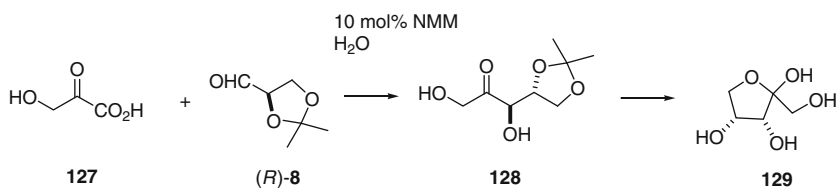
Scheme 2.41 C_3+C_3 strategy to ulosonic acid precursor

2.4 Miscellaneous

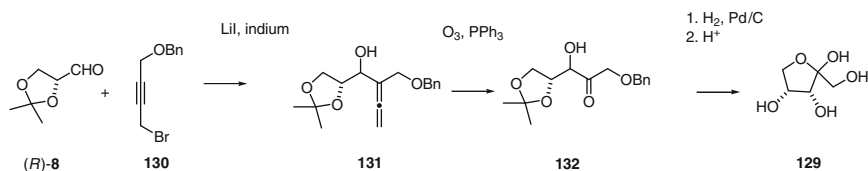
A further useful tool for the total synthesis of carbohydrates is the decarboxylative aldol reaction. For an overview of this development see reference [98–101]. During our investigations in this field we have developed several protocols for amine-catalyzed decarboxylative aldol additions using α -keto 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].

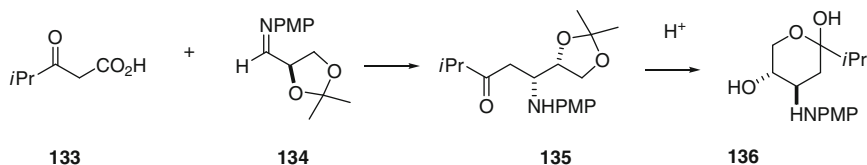
A decarboxylative approach to aminocarbohydrates has been opened, by the utilization of β -keto acids as enol component and the readily available imines of aldehydes deployed [104]. This decarboxylative Mannich-reaction proceeds catalyst-free. The basicity of the imine used proved strong enough to induce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



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



Scheme 2.43 Total synthesis of *erythro*-pentulose



Scheme 2.44 Organocatalytic 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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