2.7 Degradations and Rearrangement Reactions

Jianbo Zhang
Department of Chemistry, East China Normal University,
200062 Shanghai, China
jbzhang@chem.ecnu.edu.cn

In: *Glycoscience*. Fraser-Reid B, Tatsuta K, Thiem J (eds)
Chapter-DOI 10-1007/978-3-540-30429-6_9:

Abstract

This section deals with recent reports concerning degradation and rearrangement reactions of free sugars as well as some glycosides. The transformations are classified in chemical and enzymatic ways. In addition, the Maillard reaction will be discussed as an example of degradation and rearrangement transformation and its application in current research in the fields of chemistry and biology.

Keywords

Degradation; Rearrangement; Hydrolysis; Double bond shift; Ring transformation; Ring-contraction; Ring-expansion; Ferrier carbocyclization; Anomerization; Aromatization; Maillard reaction; Amadori reaction

Abbreviations

AGEs	advanced glycation end products
DAST	diethylaminosulfur trifluoride
DMDO	dimethyldioxirane
DMF	dimethylformamide
EFC	ethanol-from-cellulose
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HMF	5-(hydroxymethyl)-2-furaldehyde, 5-hydroxymethylfuraldehyde
IDCP	iodonium dicollidine perchlorate
LTMP	lithium 2,2,6,6-tetramethylpiperidide
m-CPBA	3-chloroperoxybenzoic acid, *meta*-chloroperoxybenzoic acid
PTC	phase transfer catalysis
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TMSCN	trimethylsilyl cyanide
TMSOTf	trimethylsilyl triflate
TMU	*N*,*N*-tetramethylurea

1 Overview

Degradation and rearrangement reactions in carbohydrate chemistry are described in the standard organic chemistry textbooks [1,2]. Recent books [3,4,5] contain informative surveys of developments in this area. This chapter dealing with degradation and rearrangement reactions of carbohydrate systems covers literature published in the last few years. Degradation reactions are classified into two main categories: hydrolysis from glycosides or polysaccharides into free sugars, and the degradations from free sugars into useful building blocks or chiral synthons for organic synthesis. The rearrangement reactions described herein are classified into four groups: double bond shifts, ring rearrangements associating with a double bond, ring isomerizations (contraction and expansion), and other processes. Current results on the Maillard reaction initiated by the Amadori reaction, which are so intimately associated with degradation and rearrangement reactions, are also discussed in this chapter.

2 Hydrolysis of Glycosides and Polysaccharides

Among all the degradation patterns for glycosides and polysaccharides, hydrolysis is the most important process in carbohydrate chemistry, either in nature or in biological systems. Before long, it became a process important in the food industry for production of free sugars and is now gaining more and more attention because of the present energy crisis. This is because petroleum is not an ideal chemical feedstock for industry, due to its intractability, while glycosides and polysaccharides—which are abundant and recyclable—can be utilized in the production of fuel and chiral synthons to be used instead of traditional petroleum [6].

2.1 Chemical Hydrolysis

Chemical hydrolysis is a very familiar reaction for the sugar industry. However, it may generate an array of possible degradation products. For example, very low rate constants for the spontaneous hydrolysis of nonactivated methyl β-D-glucopyranoside **1** have been determined at 220 °C [7], (*Fig. 1*). At pH > 7, the rate constants approach a constant value. On hydrolysis at pH 10 in the presence of $H_2{}^{18}O$, the results show that the reaction occurs almost exclusively by cleavage of the C1/O1 bond. The β-anomer **1** is roughly twice as reactive as the α-anomer **2**, as are also the anomeric pair of methyl D-ribofuranosides **3** and **4**. Unlike the hydrolysis at pH < 7, the hydrolysis of **1** without catalysts proceeds with a negative entropy of activation. This is consistent with bimolecular attack of water on **1**.

Acid hydrolysis of isopropenyl α-D-glucopyranoside **5** at pH 3.0 and 25 °C occurs by *C*-protonation followed by cleavage of the alkenyl ether C/O bond. The α-anomer **5** is hydrolyzed 4.5-times faster that its β-anomer **6**. Spectroscopic evidence indicates greater conjugation of O1 with the double bond, and hence a greater basicity of the β-carbon of the double bond, in **5** compared to **6** [8].

An accelerating effect by the intramolecular nucleophilic catalysis of a phosphate anion upon hydrolysis of the phosphate **7** at 80TT °C and pH 6–9, in comparison with the unsubstituted **8** and its 2-*O*-methyl derivatives **9**, has been observed [9]. The reaction of **8** is base-catalyzed down almost to pH 7, while that of **9** is pH-independent up to pH 9–10 The hydrolysis of **7** proceeds about 100-times faster than that of **9** at pH ~9 and 80 °C. In comparison, the hydrolysis of **10** is pH-independent down to pH 7 and ~20-times slower than that of **7** at pH 9 and 80 °C [10].

A kinetic study of the acyl migration reaction of the 1-*O*-acyl β-D-glucopyranuronic acid **11**, a model drug ester glucuronide, employing a directly coupled stop-flow HPLC/600 MHz ^{1}H-NMR system at pH 7.4 and 25 °C, has been carried out [11]. The acyl migration rate of the β-1-*O*-acyl group of **11** is greater than any other regio-isomers. The simulating mutarotation rates for the 4-*O*-acyl isomers **12** are in good accord with the experimental values.

The fructofuranosyl cation **13** is the first formed product of the acid-catalyzed melt thermolyses of sucrose **14** (*Scheme 1*). This reacts with hydroxy nucleophiles co-existing in the melt to give fructose-grafted products. Rigorous thermolysis of **14** itself at 170 °C furnishes a fructosylglucan with an average dp ~25 together with the known sucrose thermal oligosaccharides from **14**, such as **15** (3.9%) and **16** (4.1%) [12].

Mechanistic studies on acid hydrolysis of glycosides often encounter the *endo*/*exo*-cyclic cleavage problem [13]. For instance, the sulfuric acid (1%)-catalyzed acetolysis of the

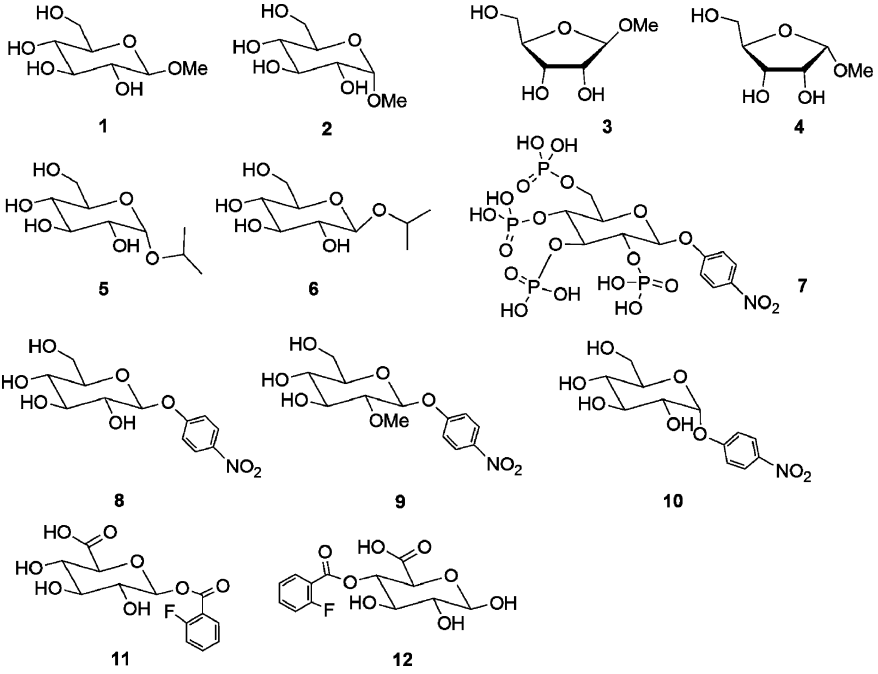
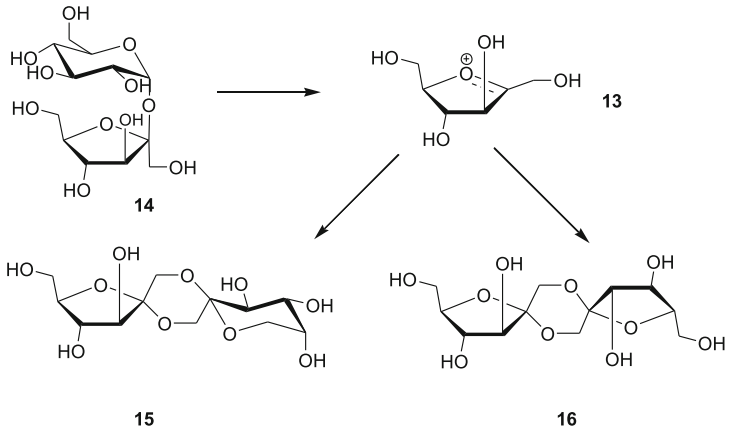


Figure 1
Glycosidesubstrates for nucleophilic hydrolysis



Scheme 1

anomeric ethyl glycoside derivatives **17** and **18** as well as the diastereoisomeric acetal **19** and **20** have been studied kinetically. The time-dependent distribution of the acetolysis products from **17** and **18** shows that their rapid mutual anomerization precedes their acetolysis to **21** and **22**, undoubtedly by way of the *endo*-cyclic cleavage product **23**, the precursor of **19** and **20** [14] (*Fig. 2*).

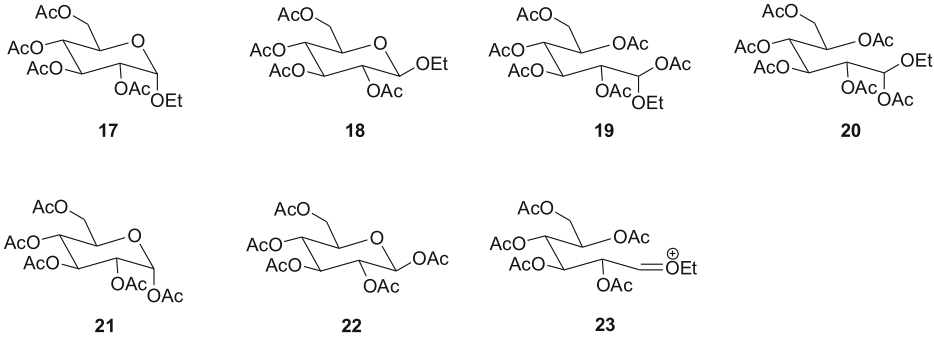


Figure 2
Substrates and intermediates in acetolysis of ethyl glycoside

Sialosides have a distinct mechanism of hydrolysis for its unusual sugar structure of sialic acid. For example, the large β-dideuterium and small primary ^{14}C kinetic isotope effects observed at the anomeric carbon and the large secondary ^{14}C kinetic isotope effect observed at the carboxylate carbon in the acid-catalyzed solvolysis of CMP-*N*-acetyl neuraminate **24** support an oxocarbenium ion-like transition state **25** having the $_5S$ conformation without nucleophilic participation of carboxylate and with the carboxylate anion in a looser environment than in the ground state [15] (*Fig. 3*). Such a zwitterion structure is consistent with the results from calculations using the COSMO-AM1 method for aqueous solutions [16].

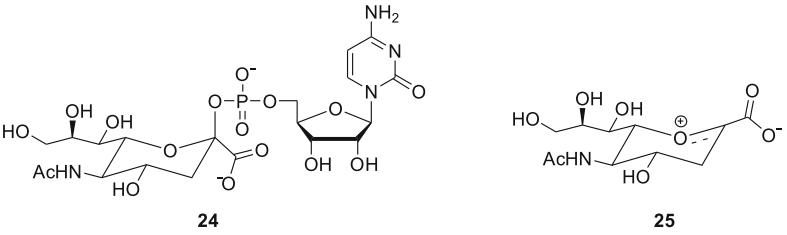
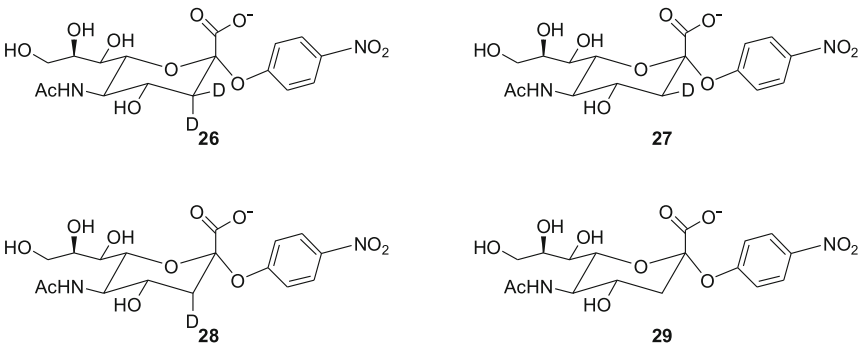


Figure 3
CMP-*N*-acetyl neuraminic acid and oxocarbenium ion-like transition state in sialoside hydrolysis

2.2 Enzymatic Hydrolysis

Glycoside hydrolase is one of the main categories of hydrolases in nature. Many references have suggested a distorted conformation for the substrate, which accelerated the hydrolytic process dramatically [17,18]. The influenza A sialidase hydrolyzes sialyl glycosides with retention of the anomeric configuration [16], whereas the *Salmomella typhimurium* sialidase works with inversion, although their protein folds and presumed active site residues are very similar [19,20]. Comparative studies using deuterium-labeled*p*-nitrophenyl *N*-acetyl-α-neuraminides **26**–**28** have postulated that the reactive substrate adopts a B_{25} conformation with

significant proton donation to the leaving group for the influenza virus enzyme, whereas the *S. typhimurium* enzyme works through a single chemical transition state derived from the ground state $^{2}C_{5}$ conformation with little proton donation to the leaving group [13]. The leaving group ^{18}O isotope effects are higher at pH 6.67 and 60 °C than at pH 2.69 and 50 °C in the nonenzymatic hydrolysis of **29** (◉ *Fig. 4*) [21,22]. This indicates that the C/O bond dissociation is complete at the transition state [21].

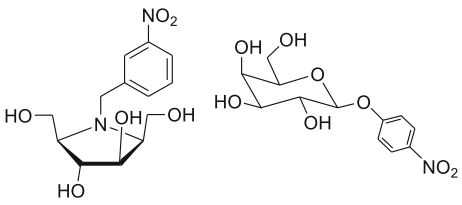


◘ Figure 4
Deuterium-labeled *p*-nitrophenyl *N*-acetyl-α-neuraminides

New analytic tools can be helpful in the research of enzymatic processes. For instance, time-course examination of enzymatic hydrolysis has recently been studied with ^{1}H-NMR spectroscopy. Thus, α-L-rhamnosyl and α-D-galactosyl hydrolysates from *Aspergillus* fungi have recently been found to be inverting hydrolyses [23,24].

With newly gained knowledge of hydrolytic mechanisms a novel artificial enzyme, the antibody enzyme AbZyme, was designed using the known mimics of the transition states [25]. Antibody Ab24, produced by in vitro immunization using the carrier-free hapten **30** and spleen cells in culture, catalyzes the hydrolysis of **8** with a k_{cat} of 0.02 h^{-1} and K_m of 160 µM ($k_{cat}/k_{uncat} = 2.2 \times 10^{4}$). Similarly, antibody Ab21 can catalyze the hydrolysis of galactoside **31** with a k_{cat} of 0.035 h^{-1} and K_m of 310 µM ($k_{cat}/k_{uncat} = 2.5 \times 10^{4}$) (◉ *Fig. 5*) [26].

At the same time, with the progress in development of new separation techniques and biotechnology, more and more enzymes have been found with interesting properties. For instance,



◘ Figure 5
Hapten and substrate for catalytic antibody Ab24

the α-1,4 glucan lyase (EC 4.2.2.-) from *Gracilariopsis lemeneiformis* is a new class of starch/glycogen degrading enzyme that digests the substrate from the nonreducing end while releasing 1,5-anhydro-D-fructose **32** successively, instead of the usual D-glucose **33** (*Fig. 6*) [27,28,29].

32 **33**

Figure 6
1,5-anhydro-D-fructose and D-glucose

Several recent books review the enzymes used in the conversion of renewable feedstocks such as starch and cellulose [30,31,32]. They provide many examples of the use of enzymes in the resource sector, specifically addressing their use in agriculture, forest products, and pulp and paper; they also address the greater use of agriculture and forestry residues and possible enzymatic modification. One recent example is the use of crude α-galactosidase from *Gibberella fujikuroi* to reduce the flatulence-inducing raffinose family sugars in chickpea flour. Crude enzyme treatment of chickpea flour resulted in complete hydrolysis of sugars of the raffinose family [33,34].

3 Degradation of Free Sugars

Although the free sugars are important industrial starting materials, they have not been focused upon until the recent findings of their degradation into useful organic resources [35,36].

3.1 Thermal Degradations

Thermal degradations in aqueous carbohydrate solutions are well documented [37,38,39]. Innovation of technology for the degradation of phytomass has focused upon the production of pyrolysis oil with high H/C and C/O ratios. Hydrothermal degradation appears to be attractive from this point of view [36,40,41,42]. Early in 1964, Qua and Fagerson tentatively identified furfural **34**, dihydroxyacetone **35**, glycolic acid **36**, glycolaldehyde **37**, and 5-(hydroxymethyl)-2-furaldehyde (HMF) **38**, and noted the presence of six additional volatile products from glucose **33** heated at 250 °C for 1 min in air. Recently, the scientists found that HMF **38** can be utilized as a very important intermediate for the petroleum industry [43,44,45].
For example, a problem is the formation of **35** during autoclave sterilization of various solutions for parenteral injection containing **33** as an excipient or a nutritional carbohydrate [46]. Similar degradations occur during food processing, especially in soft-drink production, with compound L-ascorbic acid **39** degrading into **34** and **35** [47,48]. Another example includes the roasting of coffee, during which there are many aphilic acids formed by carbohydrate degradation, which contribute to the smell and taste impact for coffee beans [49,50,51].

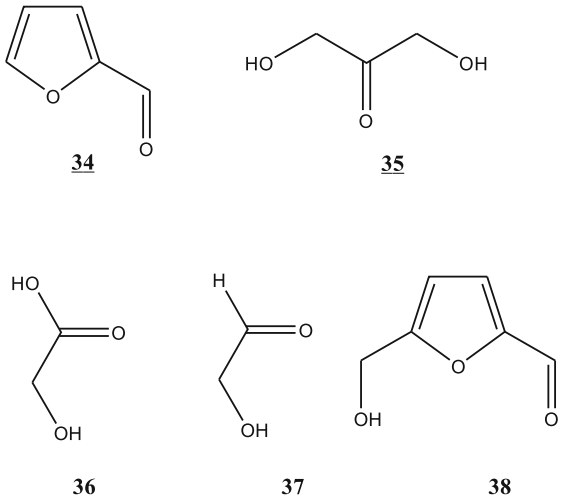
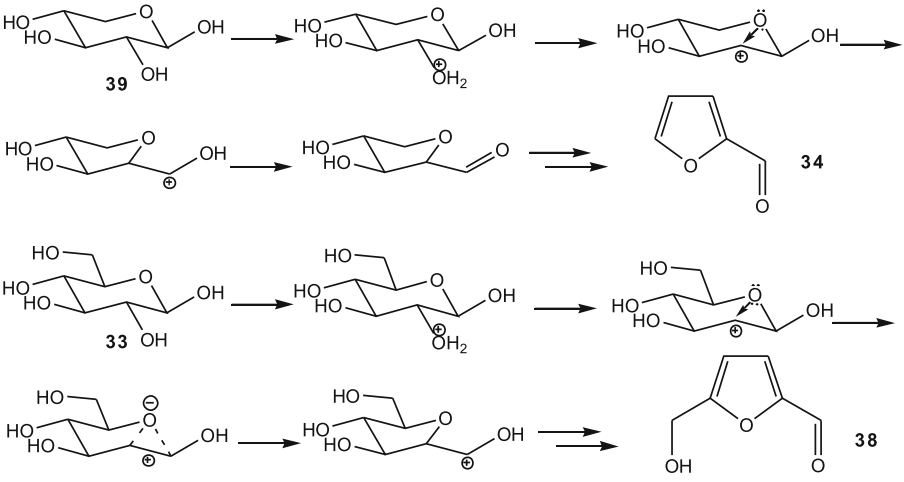


Figure 7
Main thermal degradation products from D-glucose

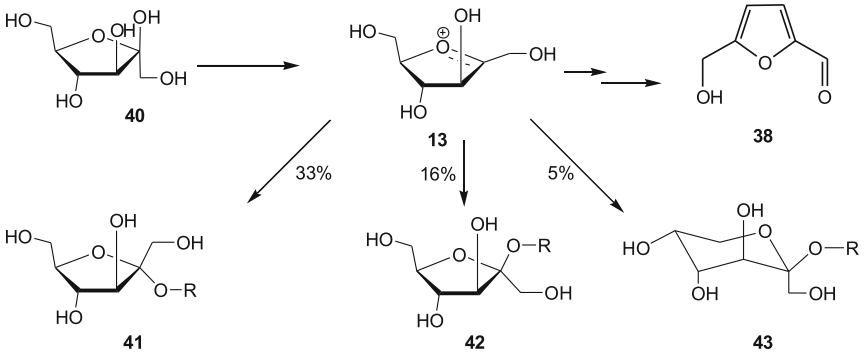
Ab initio molecular dynamics (MD) simulations were also applied in elucidation of xylose and glucose degradation pathways (*Scheme 2*). In the case of D-xylose **39**, a 2,5-anhydride intermediate was observed leading to the formation of furfural **34** through elimination of water. This pathway agrees with one of the mechanisms proposed in the literature in that no open chain intermediates were found. In the case of D-glucose **33**, a series of intermediates were observed before forming the 2,5-anhydride intermediate that eventually leads to HMF **38** (*Fig. 7*). One of these intermediates was a very short-lived open-chain form. Furthermore, two novel side-reaction pathways were identified, which lead to degradation products other than **38** [52].



Scheme 2

3.2 Acidic Degradations

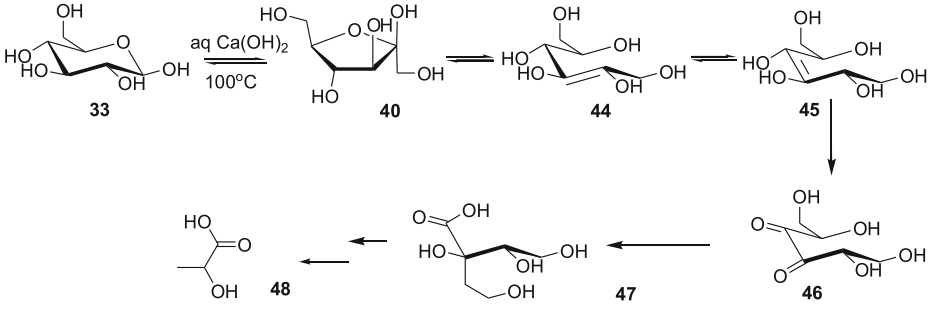
Alkyl glycosides are environmentally benign biosurfactants due to their biodegradability and low toxicity [53]. Usually they are produced through Fisher glycosylation using hydrophobic alcohols in acidic media. A practical problem is the control of the degradation reactions of starting free sugars in the acidic Fischer reaction. The situation is more serious in the case of D-Fructose **40**, which degrades into **38** [54,55,56] (*Scheme 3*). In Fischer reactions of this type, silica-alumina cracking catalysts effectively catalyze reactions to give the glycosides **41**, **42**, and **43**, without formation of **38** [57]. These results convincingly indicate that both the glycosylation giving the furanosides **41** and **42** and the degradation to **38** proceed via the common cyclic intermediates **13** [54].



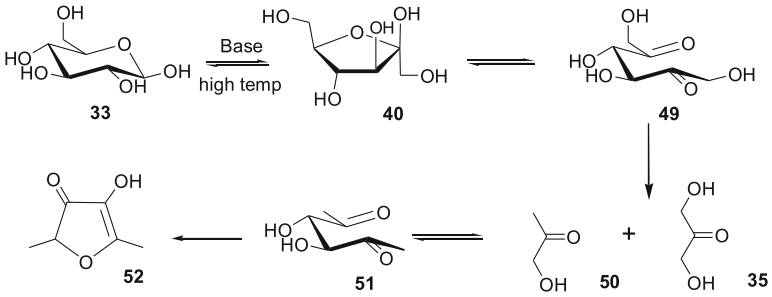
Scheme 3

3.3 Alkaline Degradations

The alkaline degradation of reducing monosaccharides involves a series of consecutive reactions and gives many kinds of products [58]. For example, the alkaline degradation of **33** in aqueous calcium hydroxide at 100 °C results in a complex mixture of more than 50 compounds (*Scheme 4*). Products obtained by the same degradation of **40** are similar to those from the



Scheme 4



Scheme 5

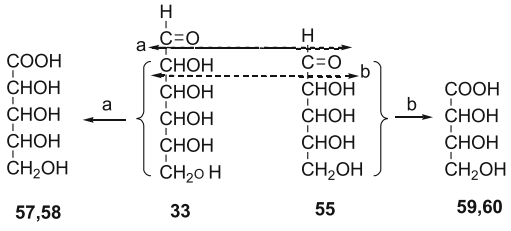
reaction of **33**. Among the degradation products, lactic acid **44** is almost the sole major product in each case [59].

High-temperature alkaline degradation of **33** forms furaneol (**52**), an aroma compound, probably because of fragmentation of **49** into the C_3-fragments **35** and **50** (*Scheme 5*). Fragment **50** dimerizes into the diketone **51**, the precursor of **52** [60].

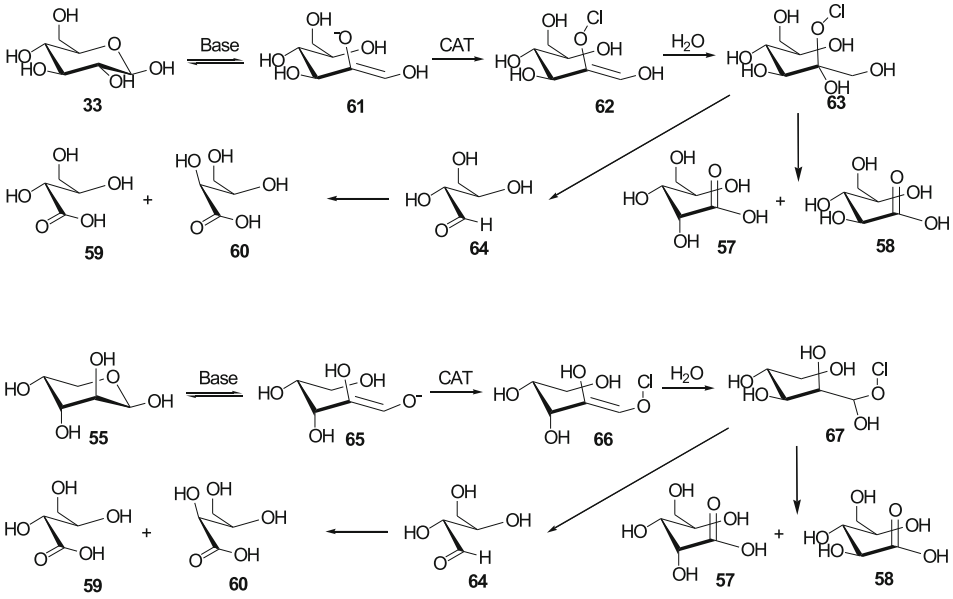
3.4 Oxidative Degradations

Oxidative degradation reactions involving the anomeric center are classic processes and are well documented [61,62]. For example, lactose, maltose, cellobiose, and galactose can be degraded selectively in one step and in high yield into the corresponding next lower aldose and formic acid by H_2O_2 in the presence of borate. The selectivity further improves when a small amount of EDTA is added, in order to suppress the influence of transition metal ions, which catalyze the decomposition of H_2O_2 via radical pathways, leading to nonselective oxidative degradation of aldoses. The function of borate in the selective oxidative degradation of aldoses is two-fold: catalysis of the degradation of the starting aldose and protection of the next lower aldose against oxidation [63].

On alkaline oxidation of aldoses with (*N*-chloro-*p*-toluenesulfonamido) sodium (CAT), the monosaccharides **33**, **40**, D-mannose **54**, D-arabinose **55**, and D-ribose **56**, belonging to the 4,5- or 3,4-*ethythro*-series, afford the C_4-acids **59** and **60** in 35 to 49% yields while the yields of glyceric acid are low [64]. Thus, as illustrated in *Scheme 6*, hexoses are cleaved at the C1/C2 (a) and C2/C3 (b) bonds, whereas pentoses break at the C1/H1 (a) and C1/C2 (b) bonds.



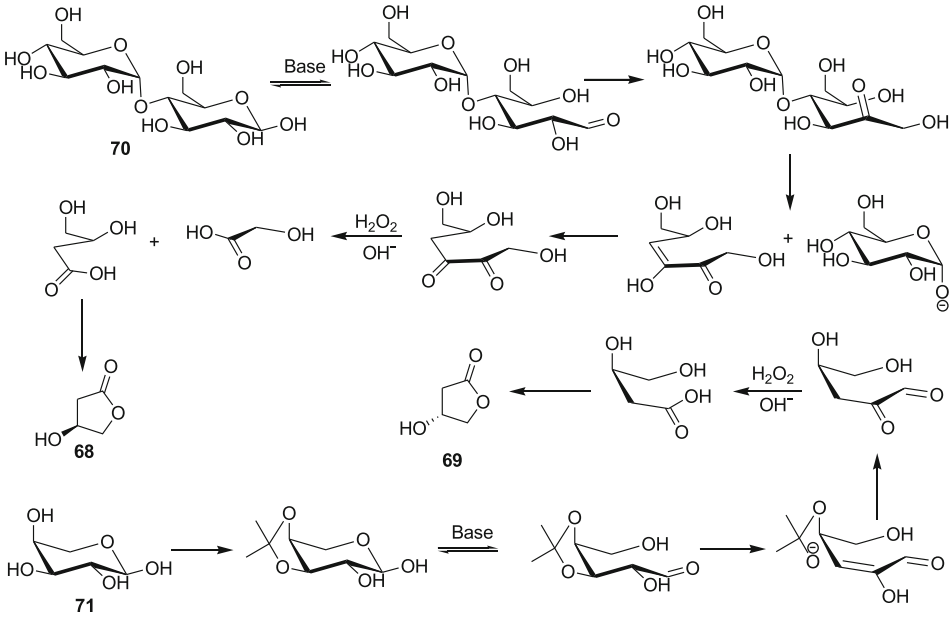
Scheme 6



Scheme 7

These reactions are governed by the alkaline-induced slow equilibrium between hexoses and enediol anions and the irreversible, rate-determining formation of the intermediate **63** (*Scheme 7*). The latter is transformed into **57** and **58** or **64**. In the case of pentose **55**, the intermediate **67** gives out **59** and **60** from the intermediate **64**.

(S)- and (R)-3-hydroxy-γ-butyrolactone (**68** and **69**, respectively) are two extremely flexible chiral synthons. They can be converted to an extremely large number of useful and important intermediates with a wide range of applications. Earlier synthetic routes to these compounds all relied on structural transformations or selective reductions of malic acid. They can now be obtained in high yield from several carbohydrate raw materials. For example, the (S)-lactone **68** can readily be prepared by the oxidation of 4-linked D-hexose sources such as cellobiose, lactose, maltose, maltodextrins, starch, etc., with hydrogen peroxide and an alkaline or alkaline-earth hydroxide. Treatment of a 4-linked hexose **70** with base leads to an isomerization to the 4-linked ketose, which readily undergoes β-elimination to form enone, which then tautomerizes to the diketone. The diketone is readily cleaved with hydrogen peroxide to give the salt of (S)-3,4-dihydroxybutyric acid and glycolic acid. Acidification and concentration yields the lactone **68** [65]. Similarly, the (R)-lactone **69** can be synthesized using a 4-linked L-hexose source since the chiral center in the product is derived from the 5-carbon of the hexose. The (R)-lactone was obtained in high yield from L-arabinose **71** by the simple strategy of functionalizing the 3-position by forming a 3,4-acetal and oxidizing it under similar conditions as those used for the preparation of the other isomer. This oxidation yields the dihydroxy acid and formic acid via the unsaturated aldehyde which tautomerizes to the *R*-dicarbonyl compound. The dihydroxy acid is then converted to the lactone **69** by acidification and concentration (*Scheme 8*) [66].



Scheme 8

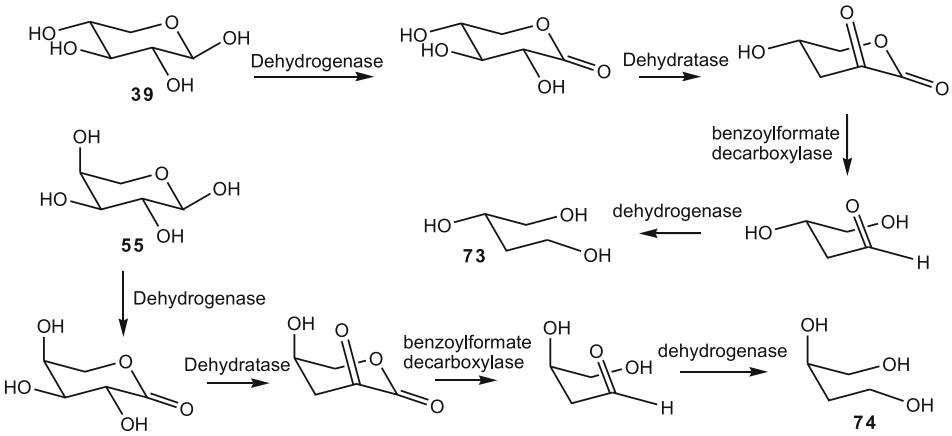
Titanium-containing zeolites, such as Ti-BEA, Ti-FAU, and TS-1 have been tested as catalysts for the Ruff oxidative degradation of calcium D-gluconate **72** to D-arabinose **55** using diluted hydrogen peroxide as the oxidant. Only large-pore zeolites Ti-BEA and Ti-FAU were found to be active. It was shown, in particular, that a very rapid leaching of titanium occurred and that the titanium species present in the solution were responsible for the catalytic activity observed [67,68].

Applying H_2O_2/CuO in alkaline solution, degradation of the carbohydrate-rich biomass residues results with formic, acetic and threonic acids as the main products. Gluconic acid was formed instead of glucaric acid throughout. Reaction of a 10% H_2O_2 solution with sugar beet molasses generated mainly formic and lactic acids. Important advantages of the microwave application were lower reaction times and reduced reagent demands [69].

3.5 Enzymatic Degradations

1,2,4-Butanetriol is an important intermediate in organic synthesis, for instance in the production of D,L-1,2,4-butanetriol trinitrate. Commercial synthesis of D,L-1,2,4-butanetriol employs $NaBH_4$ reduction of esterified D,L-malic acid. For every ton of 1,2,4-butanetriol synthesized, multiple tons of byproduct borates are generated. D,L-malic acid can also be hydrogenated over various catalysts (Cu–Cr, Cu–Al, Ru–Re) at 2900–5000 psi of H_2 and 60–160 °C reaction temperatures. Yields of 1,2,4-butanetriol range from 60 to 80%. A variety of byproducts are also formed during high-pressure hydrogenation. These byproducts are not generated when esterified malic acid is reduced using $NaBH_4$. D,L-malic acid is synthesized from the *n*-butane

component of liquefiable petroleum gas via the intermediacy of maleic anhydride. The new synthesis of 1,2,4-butanetriol has been established with microbes. Enzymes from three different microbes are recruited to create biosynthetic pathways by which D-1,2,4-butanetriol **73** and L-1,2,4-butanetriol **74** are derived from D-xylose **39** and L-arabinose **55**, respectively [70] (*Scheme 9*).



Scheme 9

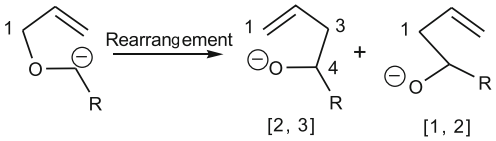
The use of ethanol as an alternative automobile fuel has been steadily increasing around the world for a number of reasons [71]. Domestic production and use of ethanol for fuel can decrease dependence on foreign oil, reduce trade deficits, create jobs in rural areas, reduce air pollution, and reduce global climate change carbon dioxide buildup. Ethanol, unlike gasoline, is an oxygenated fuel that contains 35% oxygen, which reduces particulate and NOx emissions from combustion. Ethanol can be made synthetically from petroleum or by microbial conversion of biomass materials through fermentation. In 1995, about 93% of the ethanol in the world was produced by the fermentation method and about 7% by the synthetic method. The fermentation method generally uses three steps: (1) the formation of a solution of fermentable sugars, (2) the fermentation of these sugars to ethanol, and (3) the separation and purification of the ethanol, usually by distillation. Ethanol-from-cellulose (EFC) holds great potential due to the widespread availability, abundance, and relatively low cost of cellulosic materials. However, although several EFC processes are technically feasible, only recently have cost-effective EFC technologies begun to emerge, which are quite important for rapidly developing countries such as China and Canada [72].

4 Rearrangement with Double Bond Shifts

4.1 [2,3]-Sigmatropic Rearrangements

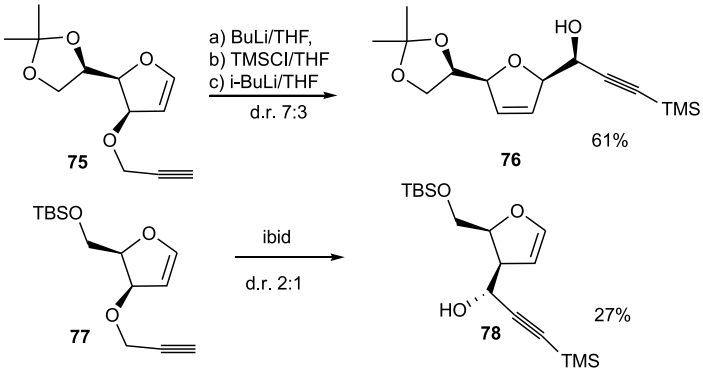
Double bond rearrangements in carbohydrate systems lead to various kinds of sugar transformations. The [2,3]-Wittig rearrangements [73] initiated by deprotonation and followed by

migration of an anionic substituent are illustrated in Scheme 10. The stereochemistry at C1 is well transformed to C3 and/or C4 [74,75]. The [1,2]-Wittig rearrangement without a double bond shift occurs in dependence on the conditions.



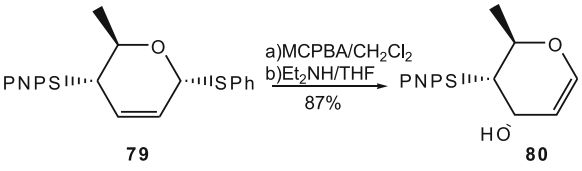
Scheme 10

The [2,3]-Witting rearrangement has been employed in synthetic work on the tetrahydrofuran acetogenins from *Annonaceous* species starting from furanoid glycals [76]. The rearrangement of **75** is induced by a base to generate an anionic species, which rearranges into **76** and its epimer. In this case, erythro-2 predominates. Under the same conditions, **77** with a silyl-protecting group mainly gives the [1,2]-Witting rearrangement product **78** (Scheme 11).



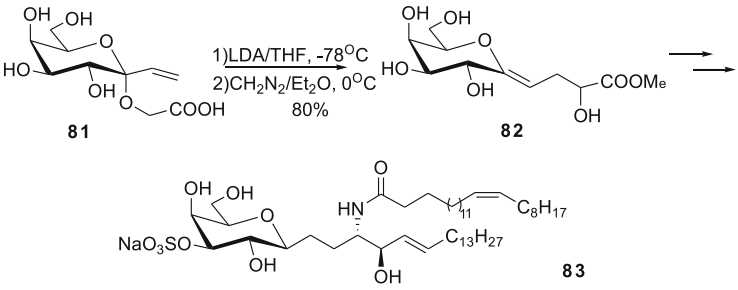
Scheme 11

A [2,3]-sigmatropic rearrangement of a sulfoxide has been employed in the total synthesis of calicheamicin g [77]. The thioglycoside **79** is oxidized to give the sulfoxide intermediate, which spontaneously undergoes a suprafacial sigmatropic shift to the β-position to move the double bond towards the anomeric center. The resulting sulfinate is treated with a secondary amine to afford the desired rearranged glycal derivative **80** (Scheme 12).



Scheme 12

Recently, the *C*-analogue of sulfatide **83** was synthesized through a [2,3]-Wittig sigmatropic rearrangement (*Scheme 13*) [78].

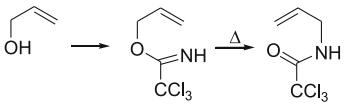


Scheme 13

4.2 [3,3]-Sigmatropic Rearrangements

4.2.1 Overman Rearrangement and Related Reactions

An allylic system that is easy to rearrange is a useful tool in a variety of synthetic methods. Allylic alcohol is readily converted into the corresponding trichloroacetimidate by brief treatment with trichloroacetonitrile in the presence of an appropriate base and usually results in high yields. Simple heating of the imidate of the allylic alcohol system induces the rearrangement reaction [79,80] (*Scheme 14*).

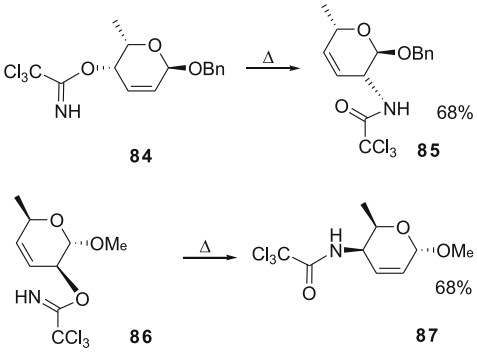


Scheme 14

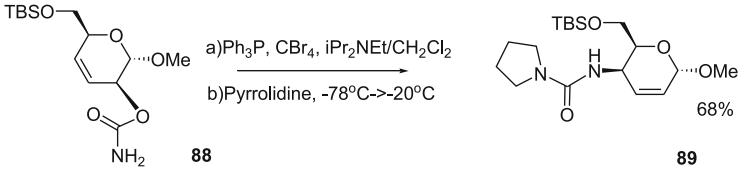
For example, on heating at 160 °C in 1,2-dichlorobenzene, the allylic trichloroacetimidate **84** smoothly rearranges into the corresponding 2-amino-2-deoxy sugar **85** [81]. The suprafacial rearrangement from C2 to C4 is similarly performed to obtain the 4-amino-4-deoxy sugar derivative **87** [82] (*Scheme 15*).

Under dehydrating conditions, the allylic carbamate **88** generates the allyl cyanate which, in turn, rearranges into the reactive allyl isocyanate and then reacts with nucleophiles [83] (*Scheme 16*). The allylic carbamate is prepared by treatment of the allylic alcohol with trichloroacetyl isocyanate in dichloromethane at 0 °C and chemoselective removal of the alkali-labile trichloroacetyl group by mild reaction with cold methanolic potassium carbonate without affecting the carbamate linkage at all. The obtained carbamate **88** is dehydrated by the triphenyl phosphine/tetrabromomethane system under very mild conditions. This leads to the reactive isocyanate via spontaneous rearrangement. The isocyanate thus generated is trapped with a nucleophile such as pyrrolidine to furnish the aminosugar derivative **89**.

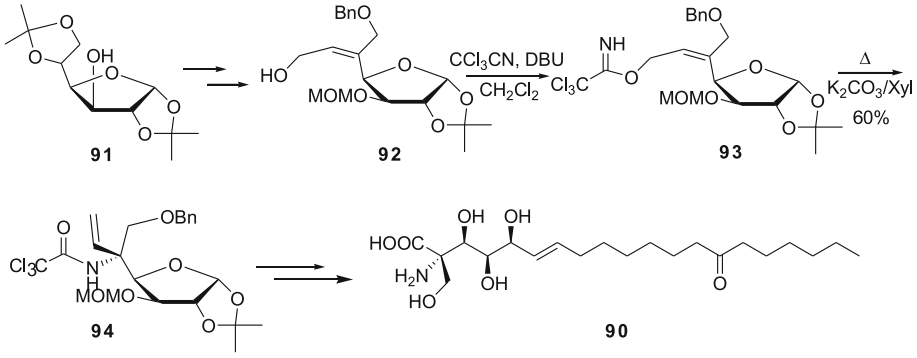
In the recent total synthesis of sphingofungin E (**90**), Overman rearrangement of an allylic trichloroacetimidate derived from diacetone-D-glucose **91** generated tetra-substituted carbon



Scheme 15



Scheme 16



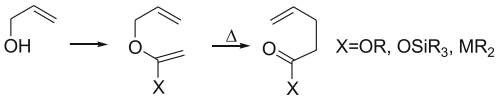
Scheme 17

with nitrogen (**94**), and subsequent Wittig olefination afforded the highly functionalized part in sphingofungin E stereoselectively [84] (*Scheme 17*).

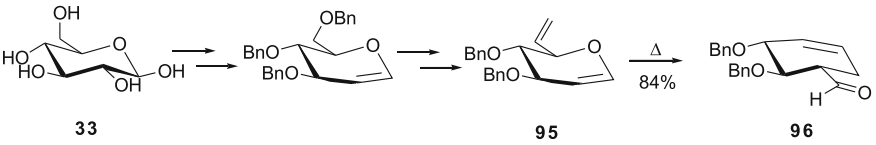
4.2.2 Modified Claisen Rearrangements

Modifications of the Claisen rearrangement have been widely used in a variety of synthetic chemistry reactions [85] (*Scheme 18*).

The simple Claisen rearrangement itself has been employed in the transformation of the vinylglycal **95** into carbocyclic compounds [86] (*Scheme 19*). On heating at 240 °C in o-dichlorobenzene in a sealed tube for 1 h, the desired rearrangement of **95** proceeds in the



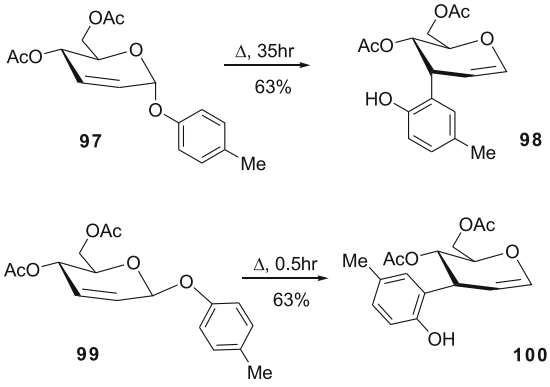
Scheme 18



Scheme 19

expected direction to give the unsaturated carbocyclic system bearing an aldehyde function in 84% yield. This is a useful synthetic intermediate for a variety of pseudosugars.

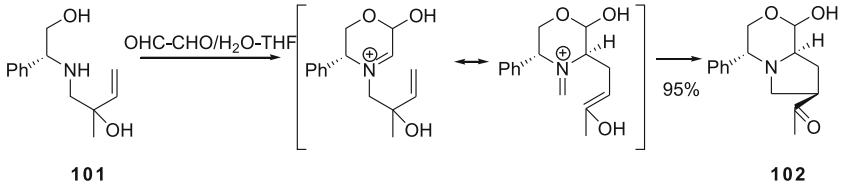
Aromatic Claisen rearrangements in 2,3-unsaturated sugar systems are useful for the stereocontrolled synthesis of aryl-branched sugars [87] (*Scheme 20*). The α-anomer **97** is much less reactive in comparison to the β-anomer **99**. This thermal rearrangement is carried out by refluxing in *N*,*N*-diethylaniline. The efficiency of the reaction is almost independent of the nature of the p-substituent in the phenyl group.



Scheme 20

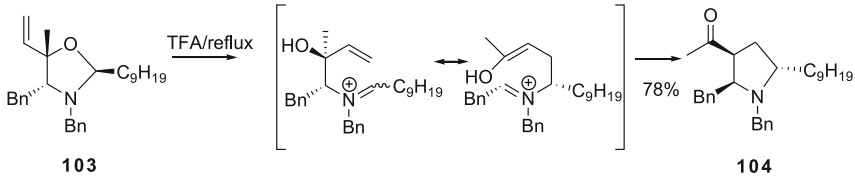
4.2.3 Hetero-Cope Rearrangements

Cationic aza-Cope/Mannich tandem reactions [88,89,90,91] have been applied to the asymmetric synthesis of homochiral proline derivatives (azafuranosides) [92]. The β-amino alcohol **101** reacts with glyoxal at room temperature to generate a cyclic aminoacetal, which undergoes spontaneous dehydration to give rise to the ene-iminium intermediate (*Scheme 21*). Through an aza-Cope reaction, this cationic species transforms into the bond-rearranged exomethylene intermediate. Then a Mannich-type cyclization takes place to give the homochiral proline derivative **102** quantitatively.



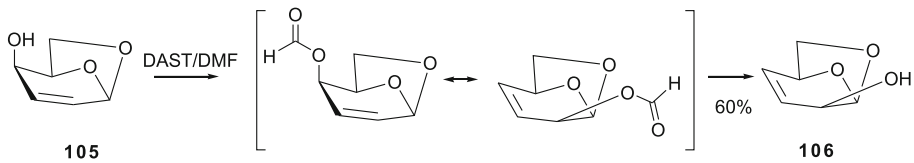
Scheme 21

This protocol was later employed for the synthesis of (−)-α-allokainic acid [93]. Tandem aza-Cope/Mannich reactions of this type have also been employed to construct the framework of (−)-preussin [90]. On refluxing in trifluoroacetic acid, the protonated and functionalized oxazolidine **103** changes into the ene-iminium intermediate, which equilibrates with the bond-rearranged enol compound through an aza-Cope process (*Scheme 22*). This is followed by cyclization through the Mannich reaction to give the functionalized pyrrole **104** in 78% yield with 86% ee. To proceed to (−)-preussin, a retro-Mannich fragmentation-Mannich cyclization of **104** is needed to establish the desired configuration of the pendants on the pyrrolidine ring.



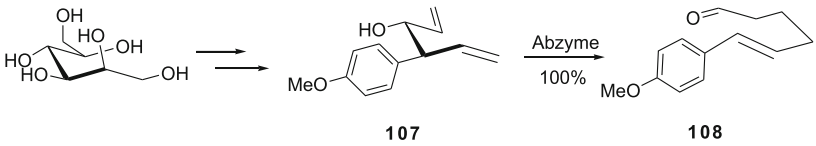
Scheme 22

A neutral, metal-free rearrangement, formally a suprafacial [1,3]-sigmatropic migration, of the hydroxy group has been reported [94] (*Scheme 23*). The direct migration of the hydroxy group is thermally forbidden. This rearrangement reaction probably proceeds by way of an intermediate formate, which undergoes an oxy-Cope rearrangement. Diethylaminosulfur trifluoride (DAST) is considered to react with the solvent DMF to generate the reactive quaternary amine salt, which rapidly converts **105** into the corresponding formate. The hypothetical 4-*O*-formate would then undergo acyloxy group migration accompanied by a double bond shift through an oxy-Cope rearrangement to give the 2-*O*-formate. Thus, the net results are suprafacial 1,3-shifts of the hydroxy group from the C4 to the C2 position. No substitution reaction of the hydroxy group with the fluoride ion seems to occur during this reaction.



Scheme 23

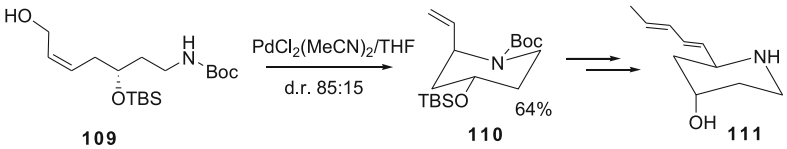
As an artificial enzyme, AbZyme was applied in a similar [3,3]-sigmatropic rearrangement [95,96]. The substrate **107** is prepared from a diacetone-D-mannitol through conventional synthetic transformations. On exposure to the artificial polychronal antibody in the presence of 2-(*N*-morpholino)ethanesulfonic acid and sodium chloride at 37 °C, with a molar ratio of 100:1 of the hexadiene **107** to the antibody, **107** is completely converted into the product **108** in 20 h (*Scheme 24*).



Scheme 24

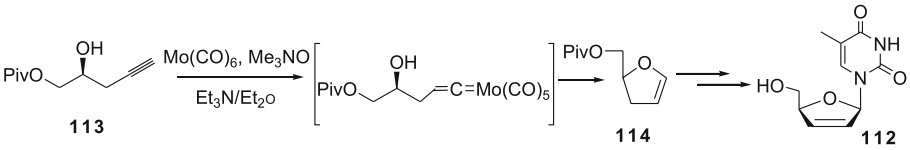
4.3 Double Bond Inducing Ring-Closing Rearrangements

There are a variety of examples of ring-closing rearrangements with exhausting double and/or triple bonds and some recent examples are shown here. Pd(0)-complexes catalyze reactions of the unsaturated amine **109** to give the azasugar **110**, an intermediate in the synthesis of SS20846A **111** [97,98,99,100] (*Scheme 25*).



Scheme 25

Besides the conventional methods, the metallo-carbene route to access cyclic compounds has become a versatile tool in sugar chemistry. Synthesis of stavudine **112**, an antiviral nucleoside, from an allyl alcohol [101] is realized by a $Mo(CO)_5$-mediated cyclization reaction (*Scheme 26*). Molybdenum hexacarbonyl smoothly reacts with the triple bond of **113** to generate the intermediate Mo-carbene, which undergoes a clean cyclorearrangement to yield the furanoid glycal **114**. Alkynol isomerization is effected by group-6 transition metal carbonyl complexes [102].



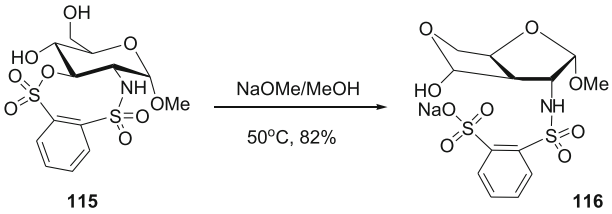
Scheme 26

5 Ring Isomerizations

Ring transformations are useful reactions in synthetic carbohydrate chemistry [103].

5.1 Ring Contractions

Nucleophilic displacement reactions of the sulfonyloxy group or its equivalents in the sugar ring are known to induce unexpected ring-contraction reactions [104]. However, the first target-oriented ring-contraction reaction of the sulfonate **115** (Scheme 27) in the stereoselective total synthesis of (−)-rosmarinecine from D-glucosamine impressively demonstrated the novel utility of this kind of reaction [105]. Ring-contraction reactions of carbohydrates have now become a useful tool for syntheses of various types of compounds [103].

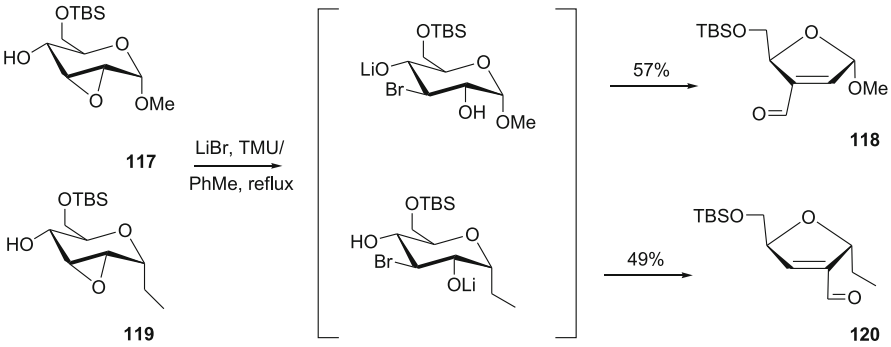


115 **116**

Scheme 27

Epoxy sugars are good starting materials for the preparation of ring-contracted products. Various 2,3-epoxypyranosides such as **117** can be converted into furanosides directly by simple heating under reflux in toluene containing lithium bromide and *N*,*N*-tetramethylurea (TMU) [106] (Scheme 28). Usually, the more stable 3-*C*-formyl derivatives are formed. In the case of the *C*-glycoside **119**, however, the mode of reaction changes to yield mainly the 2-*C*-formyl compound **120**.

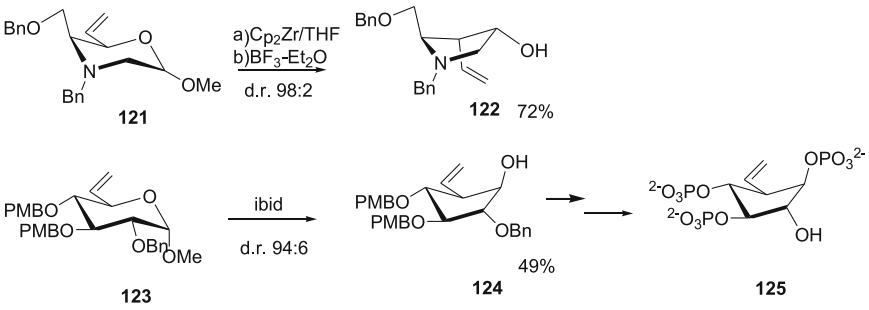
Zr-mediated ring-contraction reactions using vinyl sugars are useful to synthesize carbocycles [107,108]. This method was later employed successfully for aza-sugar synthesis. The



117 **119** **118** **120**

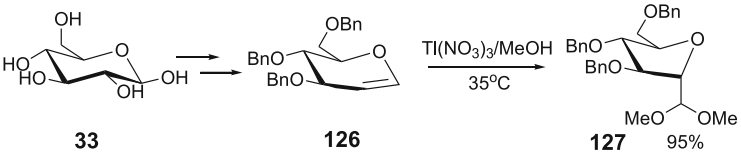
Scheme 28

functionalized morpholine **121** is transformed into the pyrrolidine **122** with excellent stereoselectivity. The stereochemistry at the junction of the main product is *cis*. This protocol has been applied to the synthesis of inositol phosphate analogs using the 5-*C*-vinyl glycoside derivative **123** [109] (● *Scheme 29*).



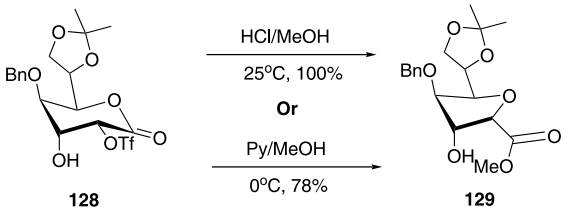
Scheme 29

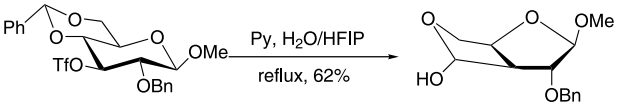
The *O*-benzyl derivative of the glycal **126** undergoes stereoselective ring contractions on treatment with thallium(III) nitrate [110] (● *Scheme 30*).

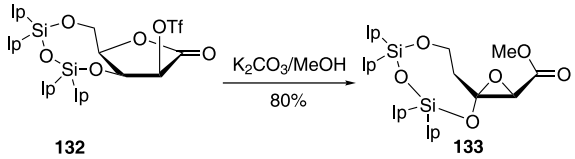


Scheme 30

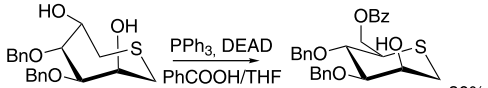
Triflates of aldonolactones are a productive source of ring-contraction reactions. Compound **128** contracts its ring under acidic and basic conditions to give *C*-furanosides [111,112] (● *Scheme 31*). Triflates of glycosides occasionally yield ring-contracted products [113]. Another paper has provided an additional example of a ring-contraction reaction of a sugar triflate on reaction with tetrabutylammonium nitrite in moist toluene; the triflate yields a ring-contracted byproduct [114]. It has been found that the ring-contraction reactions of the triflate in the presence of pyridine depend on the acidity of the solvent; in the acidic solvent 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), ring-contraction of **130** proceeds smoothly. Oxygenophilic silyl protection of the 2-*O*-triflate of aldonolactone **131** prohibits ring contraction so that the reaction results in the formation of the silyl-migrated epoxide **132** [115].
Mitsunobu conditions smoothly effect clean ring-contraction reactions of thiosugars [116] (● *Scheme 32*). From the thioheptanoid **134**, the thiopyranoid **135** is obtained. Mild sulfonation induces a spontaneous ring-contraction of the azaheptanoid **136** to afford the azapyranoside **137** [117].
Some rare, four-membered sugar rings have been synthesized by ring-contraction reactions [103]. Similar to 2-*O*-triflates, which easily undergo ring-contraction reactions [118]. DAST-treatment of the thiopentofuranose derivative **138** affords the ring-contracted product **139** having a thietane framework (● *Scheme 33*). DAST-assisted ring-contraction has

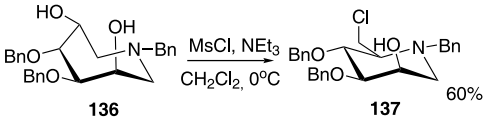






Scheme 31



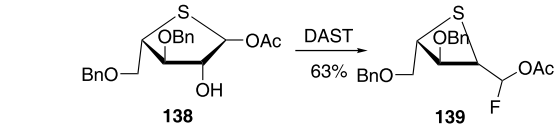


Scheme 32

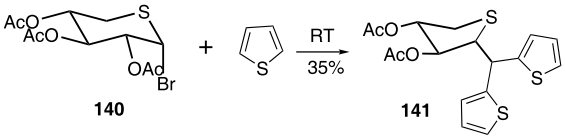
been found in the fluorination reaction of the thiosugar furanose **138** [119]. It is known that the sulfur(IV) fluoride/hydrogen fluoride system also promotes such ring-contraction reactions [120]. On Friedel–Craft reaction of the thiopentosyl bromide **140**, a ring-contraction process occurs [121]. The per-*O*-alkylated glycoside **142** is converted into the δ-lactone **143** with concomitant ring-contraction to furnish product **144** [122].

The Chan rearrangement was effectively used to build up the furanoid structure on the way to taxol [123,124] (*Scheme 34*).

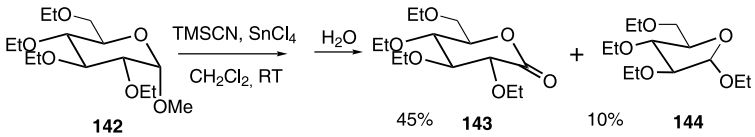
In the syntheses of staurosporin congeners, ring-contraction reactions have been used effectively [125,126]. Novel stereoselective Beckmann-type rearrangement of TAN-1030A **147** produces the K-252 analog **148** via a hypothetical hemiacetal intermediate [127]. Oxidation of the model compound **149**, the staurosporin analog, results in ring contractive benzilic acid rearrangement to give a furanoid **150** possessing the framework of K252a [128] (*Scheme 35*).



138 139

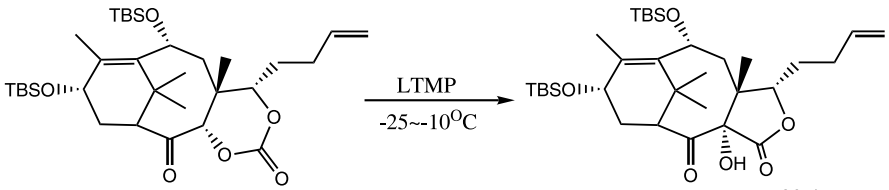


140 141



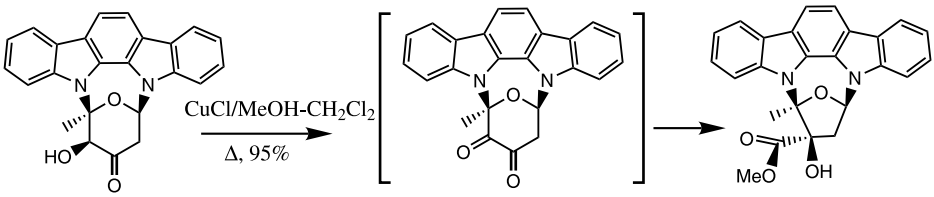
142 45% 143 10% 144

Scheme 33



145 146

Scheme 34



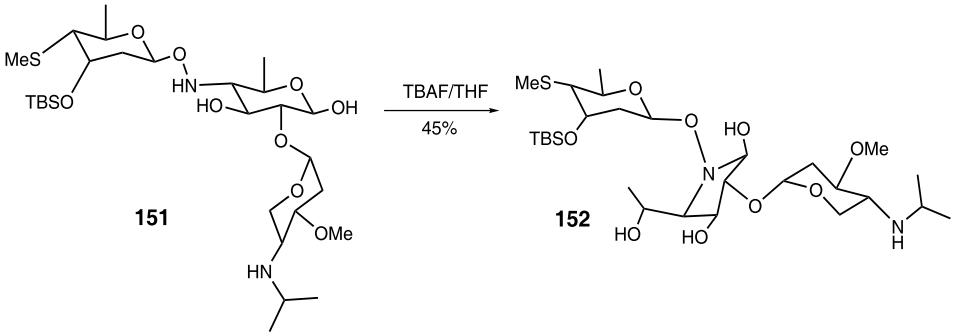
149 150

Scheme 35

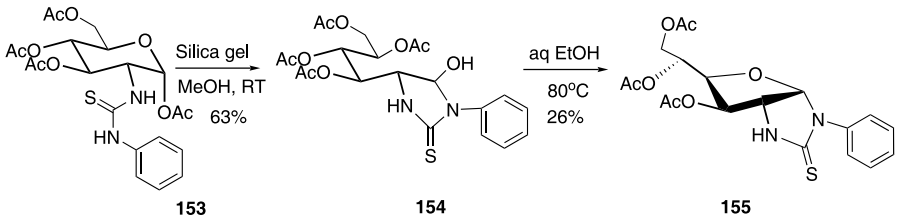
The protected oxyaminoglucoside **151** rearranges to the azafuranose form under deprotecting conditions [77] (*Scheme 36*).

The mild reaction of the thioureido derivative **153** with methanol produces the compound **154** with migration of the acetyl group. On heating, this compound isomerizes into the *cis*-fused cyclic **155** [129] (*Scheme 37*).

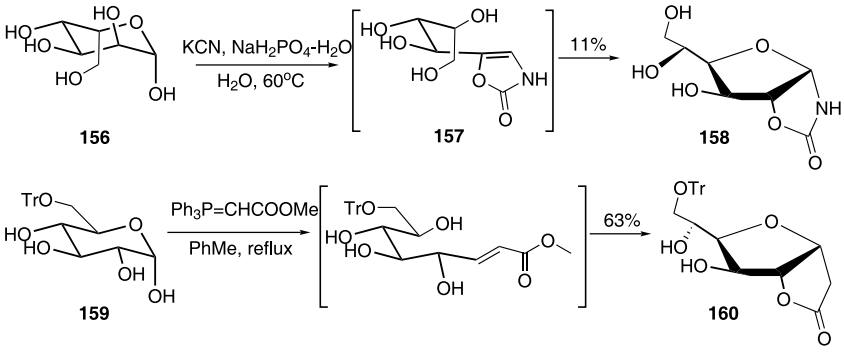
Epimerization at C2 of L-gulose **156** on reaction with KCN in buffered aqueous solution is thought to proceed by way of the open-chain intermediate. Free sugars produce cyclic products directly on reaction with the Wittig reagent. Thus, **159** is converted into **160** on prolonged heating with the reagent (*Scheme 38*).



Scheme 36



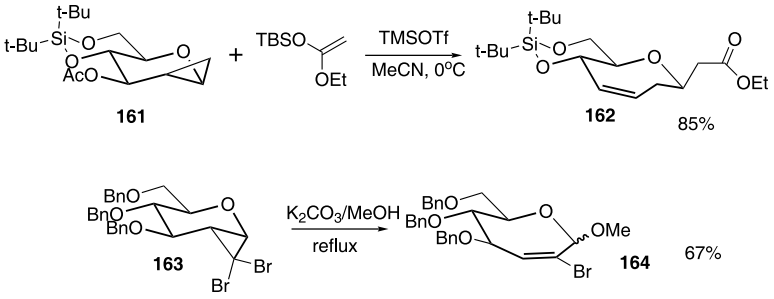
Scheme 37



Scheme 38

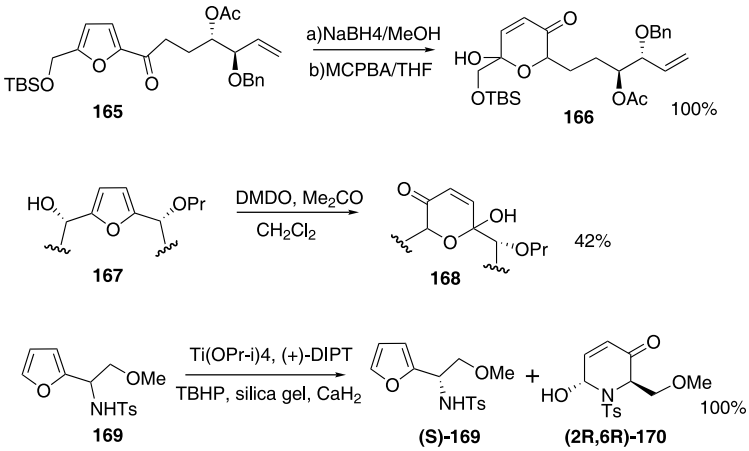
5.2 Ring Expansions

The cyclopropane system is a tool for inserting a methylene unit into a ring system to form a larger ring structure. Even densely functionalized pyranoids such as **161** [130,131] and cyclohexanes [132] expand into heptanoids and cycloheptanes, respectively. 1,2-*C*-dibromomethylene sugar **163** expands its pyranose ring to give oxepine **164** [133] (*Scheme 39*).



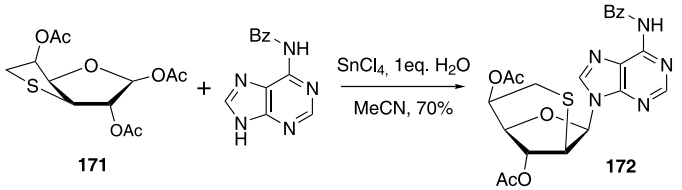
Scheme 39

α-Hydroxyfurans expand to pyranoids via sequential epoxyalcohol rearrangements. Epoxidation of the α-hydroxyfuran **165** with *meta*-chloroperoxybenzoic acid (m-CPBA) induces a cationic rearrangement, followed by dehydration, to form a pyranoid on the way to (+)-resineferatonin [134] (*Scheme 40*). Dimethyldioxirane (DMDO), apparently more sensitive to the steric circumstances than m-CPBA, has been used for the selective epoxidation of the furan **167** [135]. The monoepoxide rearranges followed by hemiacetalization to afford the pyranoid intermediate **165** of the total synthesis of the eleuthesides. α-Aminofurans similarly expand into azapyranoids [136]. Racemic **169** is kinetically resolved to give (S)-**169** and the rearranged (2R, 6R)-**170** with modified Sharpless epoxidation. Compound (S)-**169** is transformed into (2S, 6S)-**170** on treatment with m-CPBA.

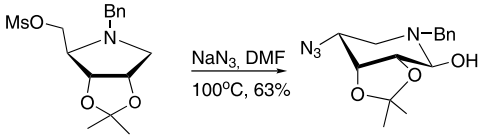


Scheme 40

The reaction of the bicyclic thiosugar **171** with N6-benzoyladenine in the presence of moist tin(IV) chloride furnishes the ring-rearranged nucleoside product **172** instead of the normal glycosylation product [137]. On heating mesylate **173** under reflux in the presence of a nucleophile, the thermal ring-expanding reaction occurs [138] (*Scheme 41*).

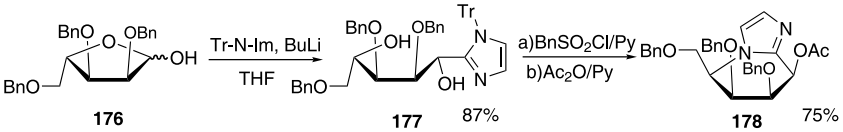


171 172



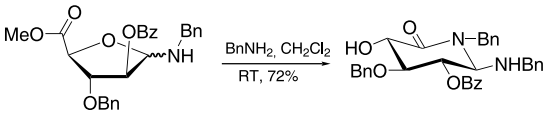
173 174

Scheme 41

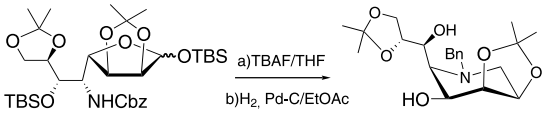


176 177 87% 178 75%

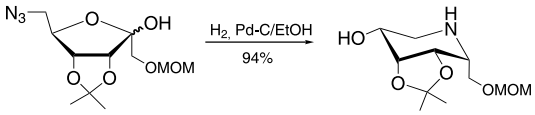
Scheme 42



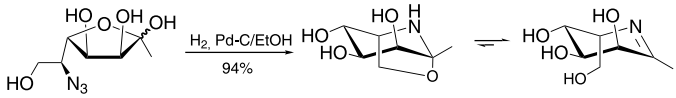
179 180



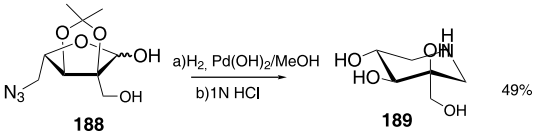
181 182



183 184



185 186 187



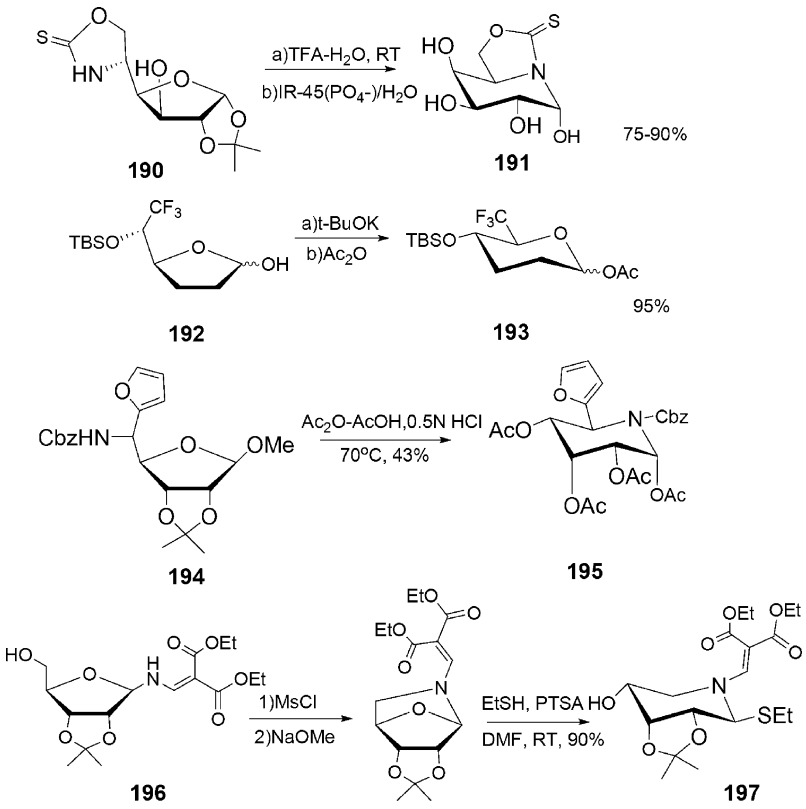
188 189

Scheme 43

The key compound on the way to the debranched nagstatin **175** has been synthesized from the L-ribose derivative **176** by employing ring-chain interconversion involving addition of trityl imidazole, selective sulfonylation, and warm acetylation which causes detritylation with cyclization [139] (*Scheme 42*).

The glycosylamine **179** transforms to the piperidinone **180** on reductive amination [140]. Sequential deprotection to regenerate hemiacetal OH and amino groups from **181** induces ring interconversion and reduction to give the azasugar **182** [141]. Similarly, the azidodeoxyketose derivative **183** can be converted to the piperidine derivative **184** by reductive aminocyclization [142]. Reduction of **185** affords the bicyclic azasugar **186** on intramolecular reductive cyclization, which is not a stable system and forms an equilibrium mixture with the monocyclic imine **187** [143]. Reactions of this type are also of use for the synthesis of the branched-chain 1-*N*-iminosugars such as **189**, which have been the subject of continuous attention as glycosidase inhibitors [144,145,146,147,148,149,150,151,152] (*Scheme 43*).

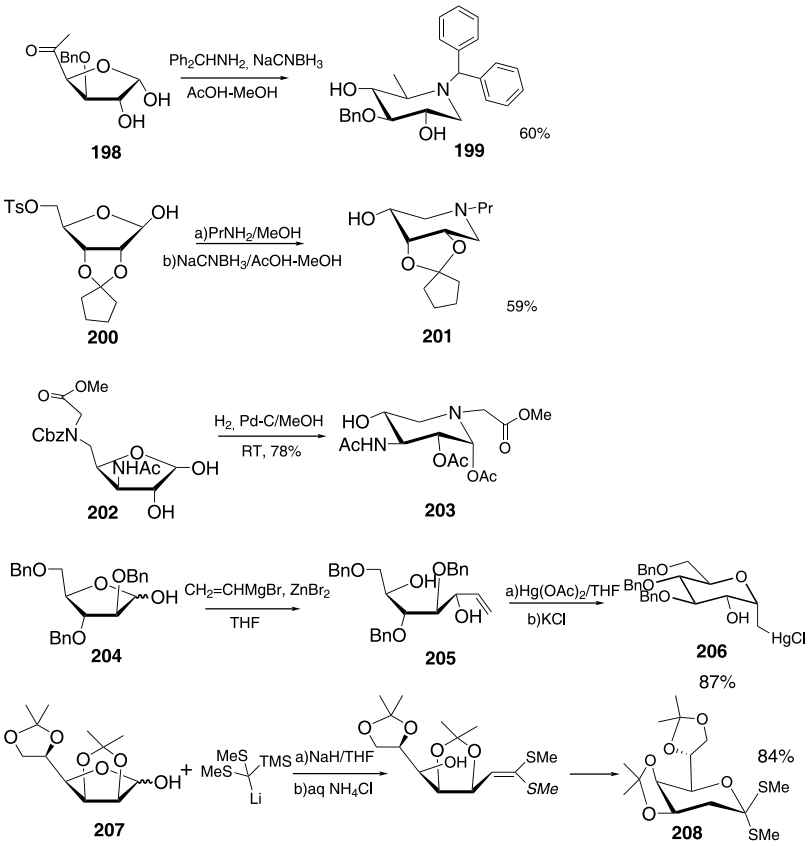
On deprotection, followed by neutralization, the acetal **190** rearranges spontaneously to the azasugar **191** [153], an analog of the indolizine alkaloids for which synthetic approaches starting from carbohydrates [154] have recently been described [155] employing the olefin



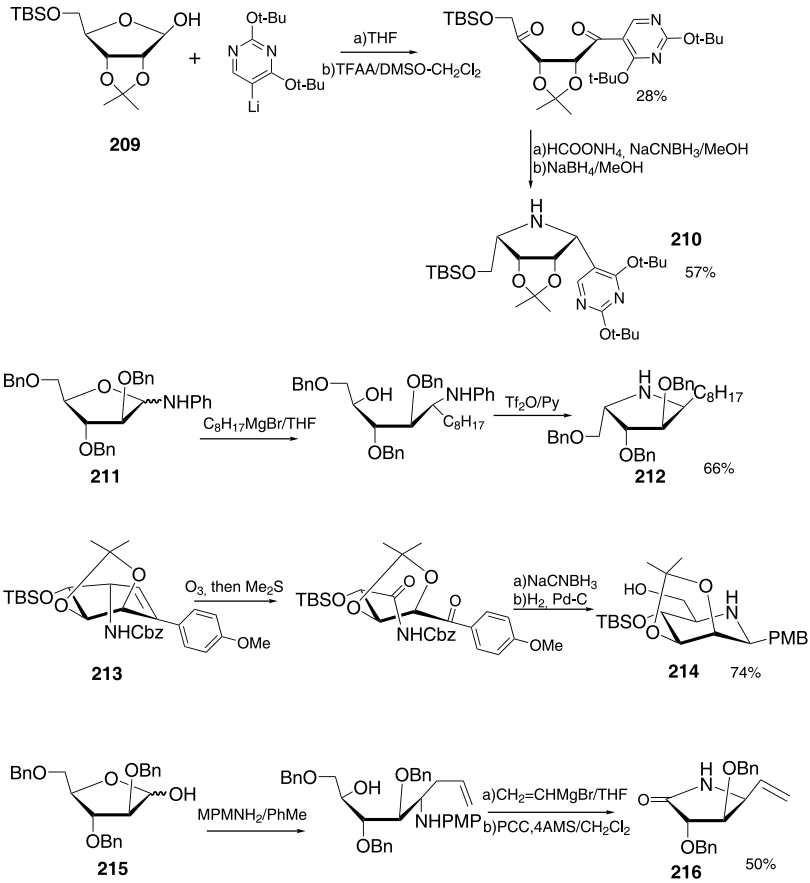
Scheme 44

metathesis protocol [156,157,158,159]. Under basic conditions, silyl-group shifts occur in a 6-deoxy-6,6,6-trifluorosugar **192** and form a pyranoside derivative [160]. Acetolysis of the methyl glycoside **194** mainly affords the piperidine **195** [161]. Azasugar ethyl thioglycoside **197**, a new type of azasugar derivative, can be stereoselectively prepared from suitable glycosylenamine **196**, through anhydroazasugar derivatives. The thioethoxy group is introduced through a highly stereoselective substitution. The attack of EtSH was 100% stereoselective [162,163] (*Scheme 44*).

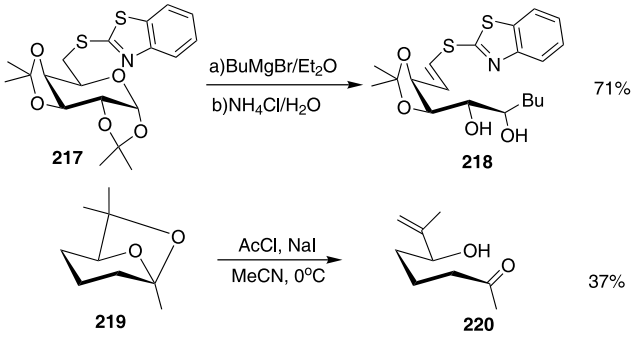
The protected 5-ulose derivative **198** can be converted into the piperidine **199** by reductive amination [164]. The 5-*O*-sulfonyllactol **200** is reductively transformed into the azasugar **201** by way of oxime formation [165]. Reductive deprotection of the aminodeoxylactol derivative **202** affords the *N*-substituted piperidine **203** [166]. The unsaturated alcohol, readily obtained from the lactol **204** and Grignard reagent, cyclizes into the *C*-glycoside **206** [167]. The lactol **207** is converted into the unsaturated dithioacetal, which cyclizes slowly to give **208** on storage [168] (*Scheme 45*).



Scheme 45



Scheme 46



Scheme 47

5.3 Ring Transformation

Additive ring-opening of **209**, followed by Swern oxidation and aminocyclization, affords the aza-*C*-nucleoside **210** [169], belonging to an attractive class of *C*-glycosides [170,171,172,173,174,175]. The glycosylamine **211** is converted to the azasugar **212** via an alkylative ring-opening reaction [176,177]. The aminoaldehyde derivative generated from the unsaturated aminocyclitol **213** cyclizes to give **214** [178] (● *Scheme 46*). Descending oxidative aminocyclization of **215** affords the lactam **216** [179].

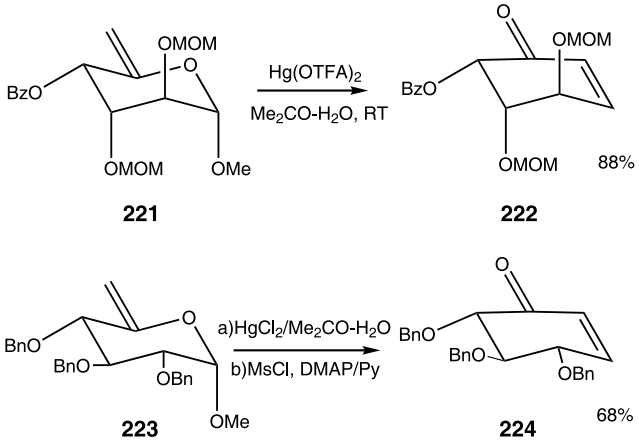
5.4 Ring-Opening Rearrangements

A fragmentation ring-opening rearrangement reaction of **217** using a Grignard reagent has been reported [180]. The combined reagent acetyl chloride/sodium iodide induces a ring-opening rearrangement of the bicyclic ketal **219** [181]. The iodide ion serves to promote the reaction [182] (● *Scheme 47*).

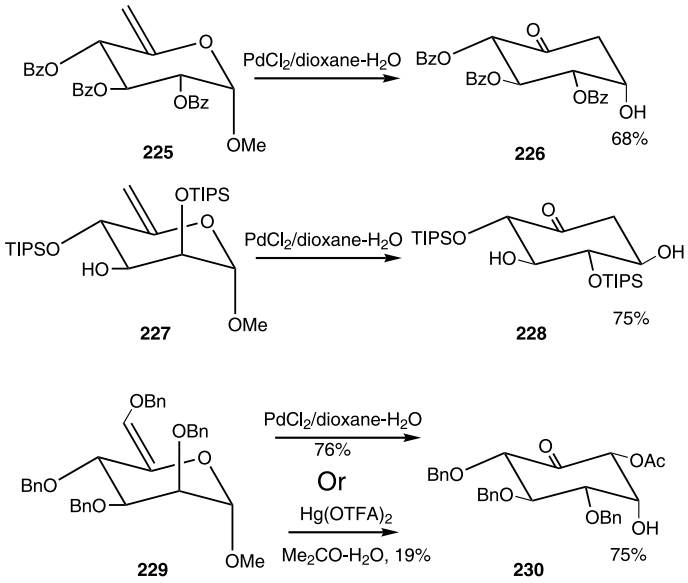
6 Miscellaneous Reactions

6.1 Ferrier Carbocyclization and Related Reactions

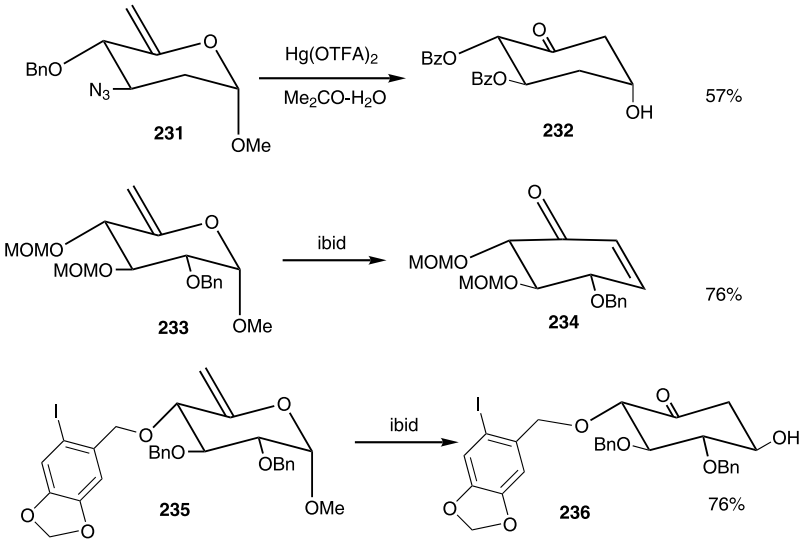
The Ferrier II reaction, a carbocyclization reaction, is of widespread use as a tool for the conversion of glycosides into cyclitols [183,184,185]. Newer examples for the utilization of the reaction conducted under catalytic conditions [186,187] have appeared in the recent literature. Compound **221** is converted into cyclohexanone **222** on the way to (−)-mesembranol [188] (● *Scheme 48*). Compound **223** is transformed to the enone **224**, the precursor of several new cyclitol derivatives [189,190,191].



Scheme 48



Scheme 49

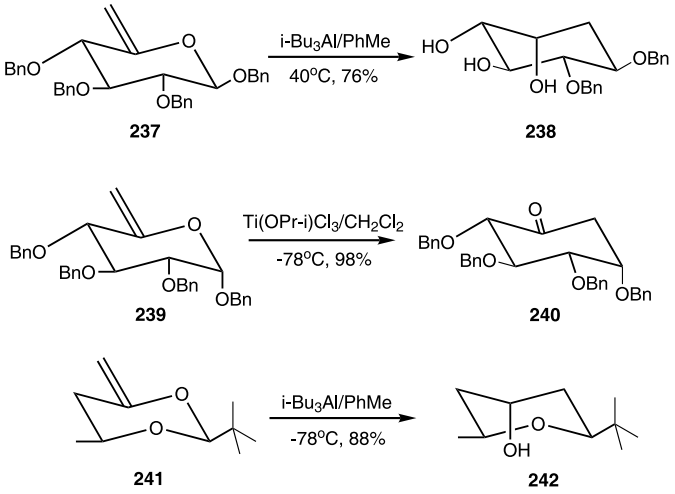


Scheme 50

The Pd-catalyzed carbocyclization affects good control on the orientation of the newly formed OH group [192] (*Scheme 49*). Thus, **225** and **227** afford the corresponding cyclitols with almost complete selectivity. In the rearrangement of **227**, the stereoselectivity is controlled by the bulky silyl ether-protecting group, which effects the conformational change.

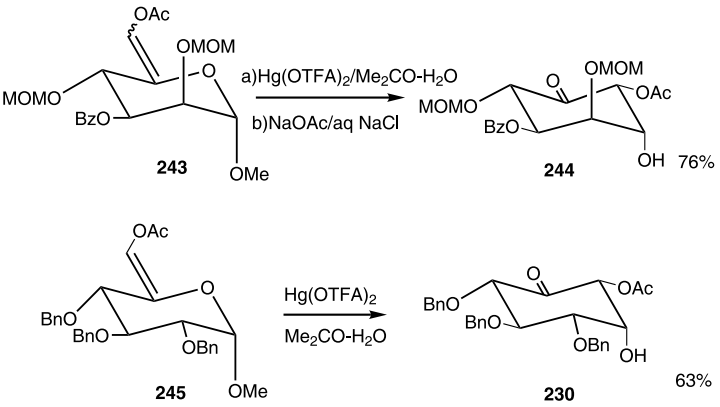
This protocol can be applied to the 6-*O*-acetyl-5-enopyranoside **229** with good efficiency and the utility is well demonstrated by the synthesis of the D-myo-inositol phosphate, IP3 [193,194].

Compound **231** is converted to the Ferrier product **232**, the precursor of novel aminoglucosides [183] (*Scheme 50*). Carbocyclization of the glycoside **233** gives the cyclohexane **234**, from which tetrazoline analogs can be synthesized [195]. The Ferrier cyclization found new utility in the synthetic chemistry of *Amaryllidaceae* alkaloids [196]. Thus, the glycoside **235** is transformed to the Ferrier-II product **236**, the logical intermediate to 7-deoxypancratistatin. A novel reductive carbocyclization of hex-5-enopyranosides retains the substituent at the anomeric center and the ring oxygen remains as the new hydroxy group [197]. The stereo-



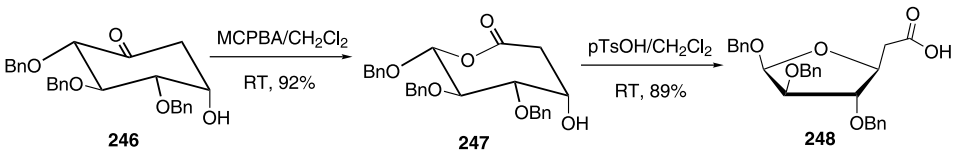
237 **238** **239** **240** **241** **242**

Scheme 51

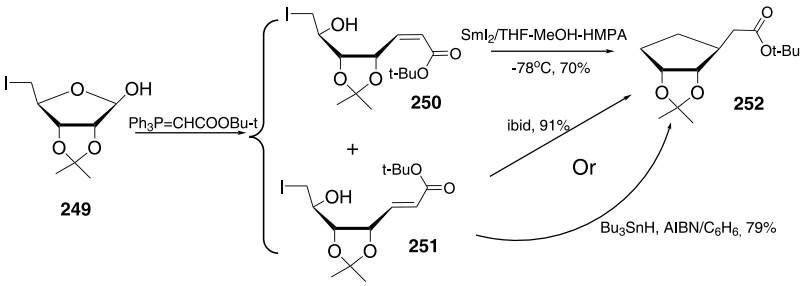


243 **244** **245** **230**

Scheme 52



Scheme 53



Scheme 54

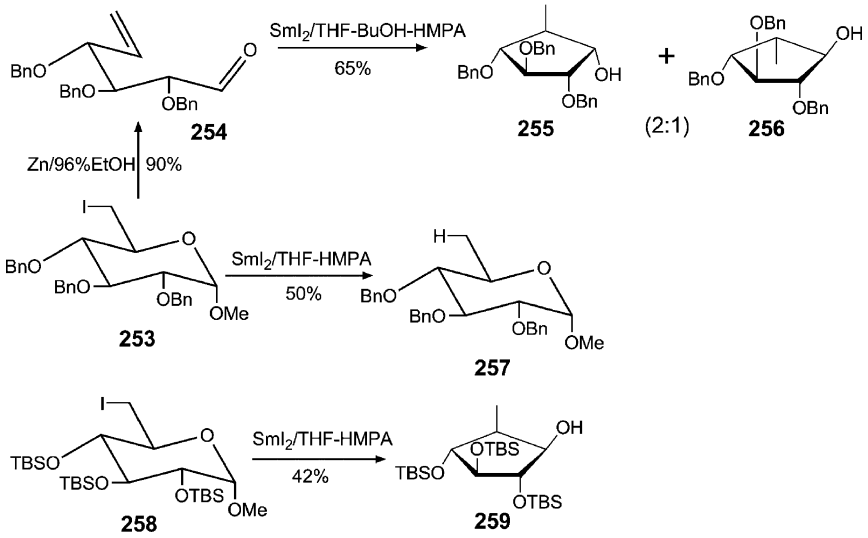
chemistry at the anomeric centers is retained as exemplified by the conversion of **237** to **238** (*Scheme 51*). A more efficient cyclization also retains the aglycone; the glycoside **239** affords the cyclohexanone **240**. The cyclic acetal **241** is converted to the pyran **242** reductively [198,199,200].

The enol acetate **243** affords the Ferrier product **244**, a key compound to L-chiro-inositol polyphosphates [201]. The Ferrier cyclization of **245** is useful for the preparation of the key intermediate to glycosylphophetidylinositols [202] (*Scheme 52*).

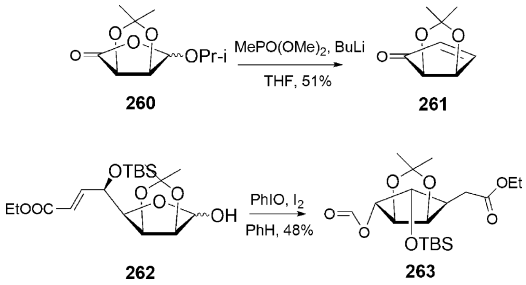
Combination of the Ferrier-II and the Baeyer–Villiger reactions leads to the stereoselective synthesis of rare 5-deoxyfuranosiduronic acids [203]. As exemplified, the oxidation of the Ferrier II product **246**, followed by hydrolysis, gives the acid **248** [204] (*Scheme 53*).

The evolution of SmI_2 as a reagent in synthesis has been one of the exciting recent developments in organic chemistry. The construction of highly functionalized carbocycles from carbohydrates promoted by SmI_2 is currently receiving significant interest and a series of carbocyclization strategies have been described in the literature. Treatment of the lactol **249** with the Wittig reagent readily gives the olefins, which undergo radical-induced cyclization [205]. Cyclization of the (Z)-isomer **250** under the action of SmI_2 is more stereoselective than that of the (E)-isomer **251** [206]. In the case of **252**, the diastereomeric excess of the products significantly depends on the choice of the reducing agents (*Scheme 54*).

Stepwise conversion of the iodoglycoside **253** via Grob–Vasella fragmentation and cyclorearrangement induced by SmI_2 furnishes the carbocycles **255** and **256** with a trans-junction [207,208]. This reaction can be carried out in a one-pot manner whereby SmI_2 induces the fragmentation of the iodoglycoside [209]. While the iodoglycoside **258** mainly affords the carbocycle **259** with a *cis*-junction, the reaction of **253** only gives the quinovoside **257** (*Scheme 55*).



Scheme 55

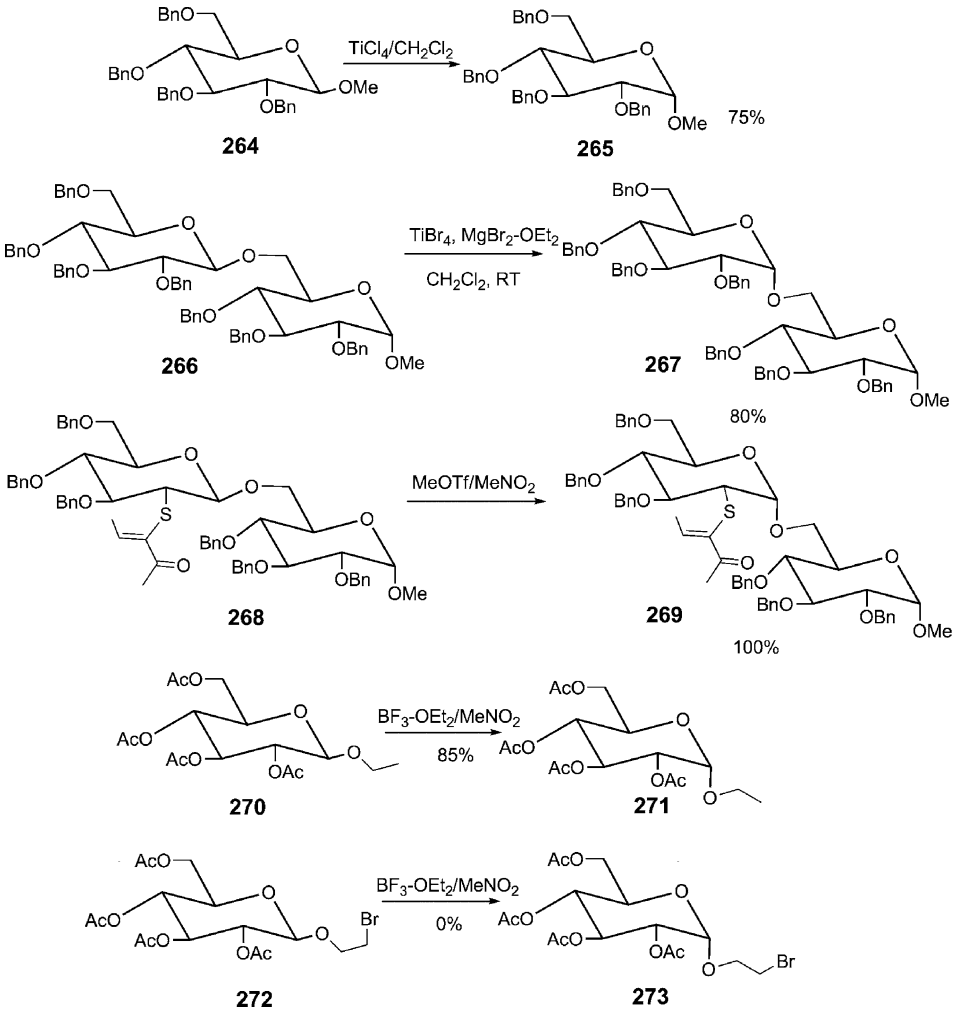


Scheme 56

The glycoside **260** is converted into the cyclopentenone **261** on reaction with dimethyl methanephosphonate and base [210] (*Scheme 56*). The tandem β-fragmentation-cycloisomerization of the unsaturated lactol **262** gives the carbocycle **263** [211].

6.2 Anomerization and Related Rearrangements

Anomerization is a characteristic reaction of sugar [212,213]. The well-known reagent, Pascu's $TiCl_4$ for the anomerization of acetylated glycoside, rapidly anomerizes the benzyl-protected glucoside **264** [214,215] (*Scheme 57*). The results from inhibition experiments indicate that $TiCl_4$ might coordinate with O5 and O6 to form a ring-opened intermediate. The use of catalytic amounts of $TiBr_4$ combined with $MgBr_2 \cdot OEt_2$ allows us to carry out longer reactions: the disaccharide **266** anomerizes to **267** completely. It has been reported that β-glycosides such as **268** anomerizes quantitatively [216]. Although the acetylated glycoside **270** is anomer-

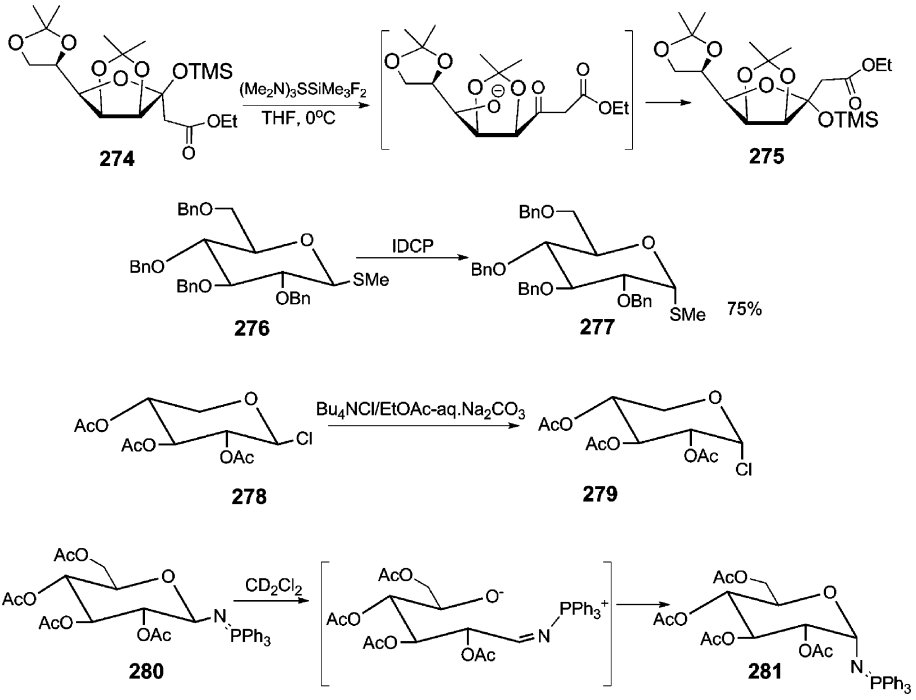


Scheme 57

ized in polar nitromethane containing $BF_3{\cdot}OEt_2$, the bromide **272** is practically inert [217] (*Scheme 57*).

The silylated ketose **274** slowly anomerizes in the presence of TASF by way of the keto-form [218]. The thioglycoside **276** anomerizes in the presence of a catalytic amount of IDCP [219]. Under PTC conditions, the β-chloride **278** also anomerizes [220]. Anomerization of **280** to the α-form **281** via an open-chain zwitterionic intermediate has been suggested [221] (*Scheme 58*).

An investigation of the time course of the anomerization of β-iodide **282** has been carried out using ^{1}H-NMR spectroscopy [222]. The NMR titration method to measure the shift of



Scheme 58

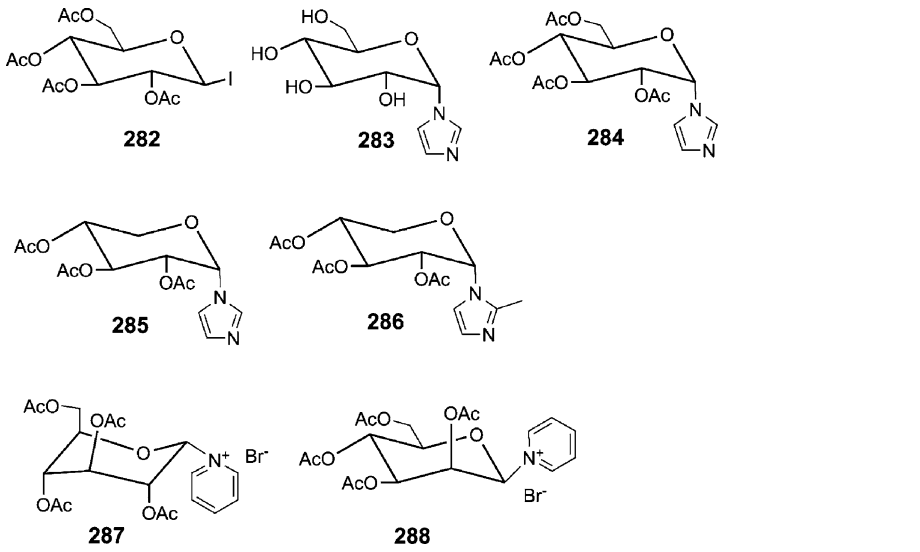
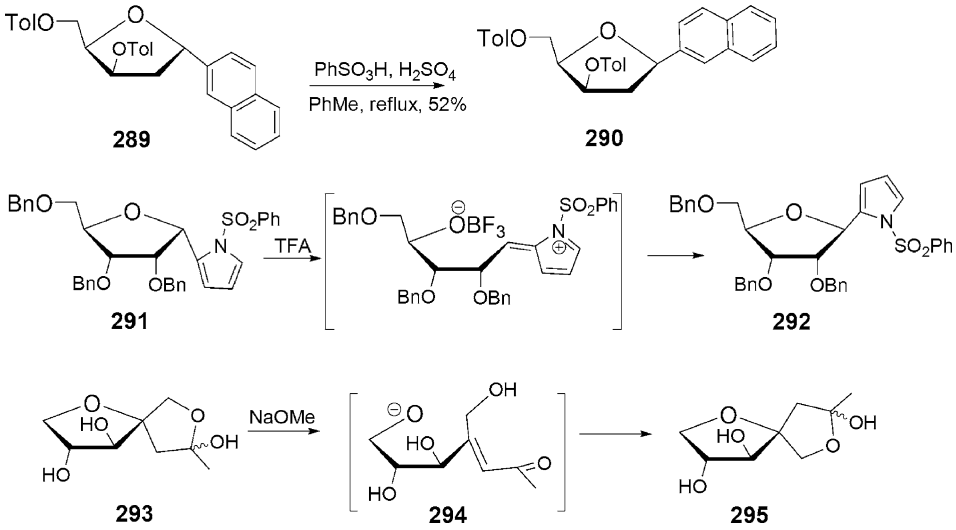


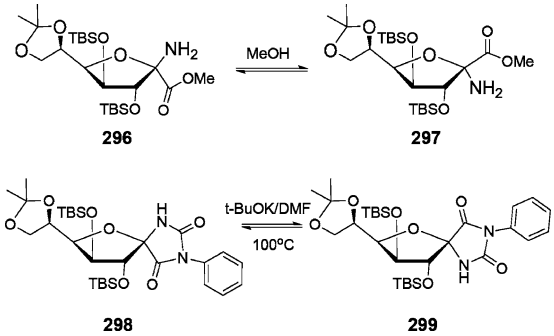
Figure 8
Anomeric equilibrium of glycosides and reverse anomeric effect

the anomeric equilibrium on protonation of **283** and **284** reveals that the protonated imidazoyl group has a small but distinct preference for the axial disposition than does the unprotonated group; which is the opposite of what the reverse anomeric effect predicts [223,224,225]. Compounds **285** and **286** increase the proportion of their $^1C_4$ conformers on *N*-protonation but not when the polarity of the solvent is increased as predicted by the reverse anomeric effect [226]. In solution, the α-glycosylpyridinium salt **287** adopts the $^1C_4$ conformation and the β-mannosyl compound **288** has the $^4C_1$ form; both of them have positively charged groups in an equatorial position at the anomeric center, indicating the manifestation of the reverse anomeric effect [227] (● *Fig. 8*).

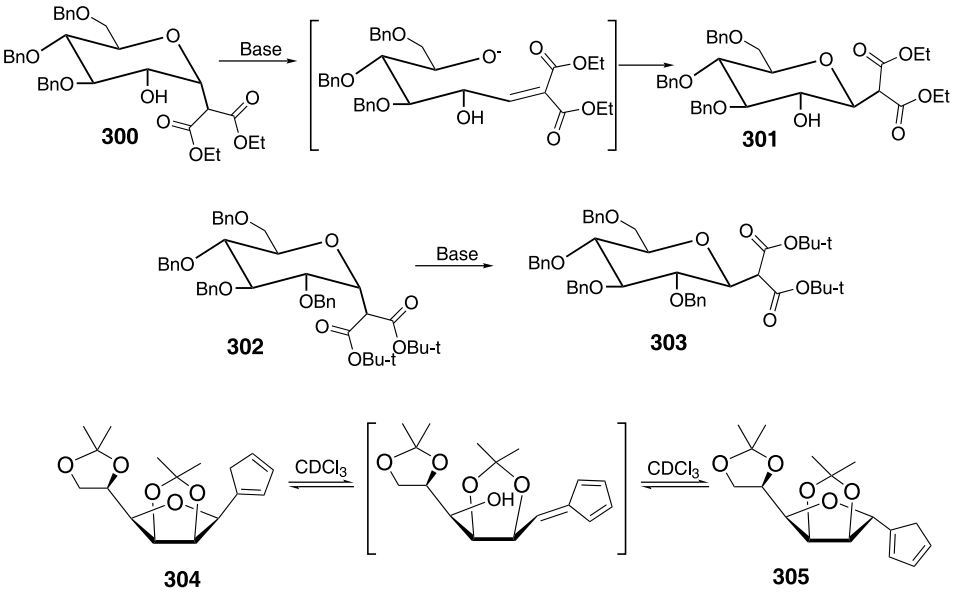
Aryl *C*-glycosides such as **289** and **291** undergo α- to β-anomerization in the presence of an acid by way of open-chain intermediates [228,229]. Under basic conditions, **293** isomerizes into **295** through **294** [230] (● *Scheme 59*).



Scheme 59



Scheme 60

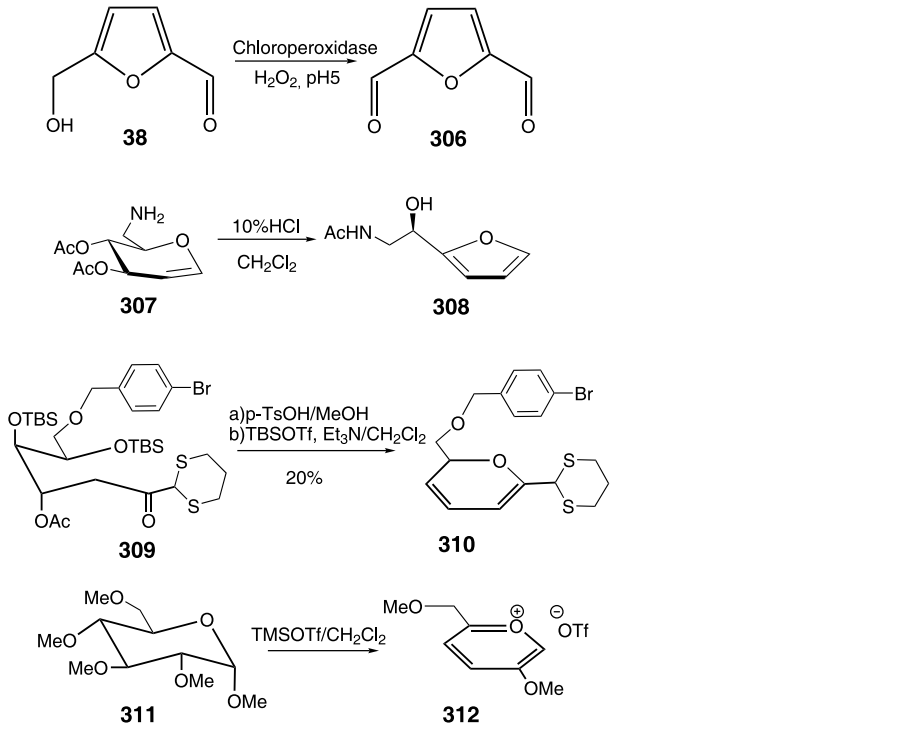


Scheme 61

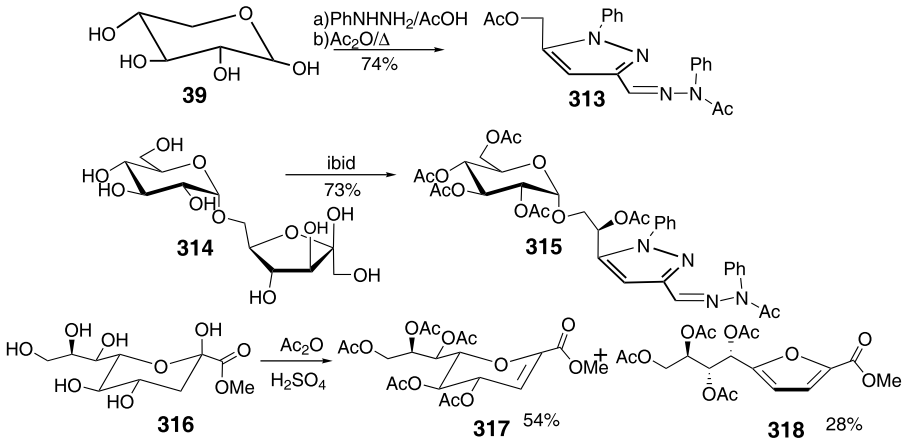
The glycosylamine **296** anomerizes in methanolic solution. The spirohydantoins **298** and **299** form an equilibrium mixture under basic conditions [231] (*Scheme 60*.
A possibility for the α- to β-anomerization of *C*-glycosides **300** and **302** by way of open-chain intermediates generated under basic conditions has been discussed [232,233]. Isomerization of pure **303** to **304** and vice versa probably occurs by way of open-chain isomerization through the linear intermediate [234] (*Scheme 61*).

6.3 Aromatization of Sugars

Sequential elimination reactions, most of them being dehydration, involving the reaction at the anomeric center often produce various aromatic compounds [235] especially furans which have diverse use [236,237]. Explorations have been continued to open a new route to aromatics based on renewable biomass in place of fossilized material.
Oxidation of 5-hydroxymethylfuraldehyde **38** with hydrogen peroxide catalyzed by chloroperoxidase, a hemeperoxidase from *Caldariomyces fumago*, proceeds with good selectivity to furnish **306** [238] (*Scheme 62*). The 6-aminodeoxyglycal derivative **307** is similarly converted into the furan **308** [239]. The dithiane **309** gives the oxacyclohexadiene **310**, on acid treatment [240]. Treatment of **311** with TMSOTf produces the pyrylium salt **312** [241].
The phenylosazone from D-xylose **39** can be converted into the pyrazoles **313** [242] . Isomaltulose **314** affords the glycosylated aromatic compound **315** [243]. On acidic acetylation the ulosonic acid ester **316** forms concomitantly the glycal derivative **317** and the furanoic acid derivative **318** [244] (*Scheme 63*).

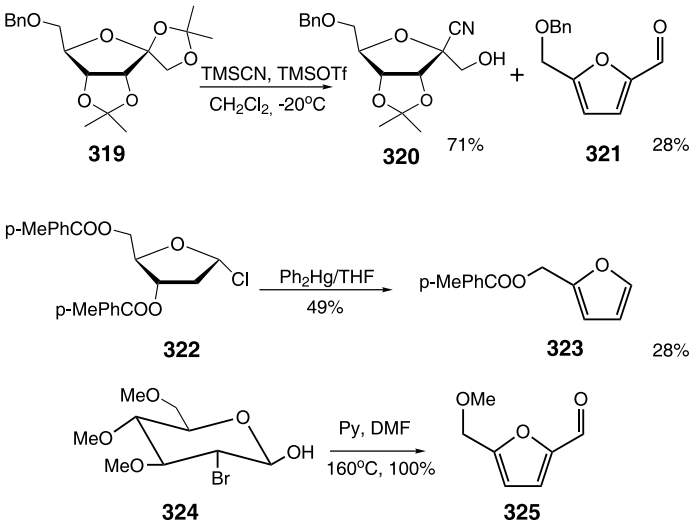


Scheme 62



Scheme 63

Even on mild *C*-glycosylation using the TMSCN/TMSOTf system, a notable amount of the D-psicofuranose derivative **319** degrades to the furan **321** [245]. On reaction with Ph_2Hg, the chloride **322** gives the furan **323** exclusively [246]. The bromohydrin **324** degrades into furan **325** on heating with a base [247] (*Scheme 64*).



Scheme 64

7 The Maillard Reaction

The Maillard reaction is a complex group of degradation/rearrangement reactions initiated by reactions of free sugars and amines [248,249,250,251]. The reaction is of major interest for food processing [252,253,254,255,256,257] and life sciences [258,259,260,261,262,263,264, 265]. Degeneration of amine drugs in the presence of reducing sugars as excipients and deterioration of sugar artifacts are also related to the reaction [266,267].

The nonenzymatic reaction between reducing sugars and long-lived proteins *in vivo* results in the formation of glycation and advanced glycation end products, which alter the properties of proteins including charge, helicity, and their tendency to aggregate. Such protein modifications are linked with various pathologies associated with the general aging process such as Alzheimer disease and the long-term complications of diabetes. Although it has been suggested that glycation and advanced glycation end products altered protein structure and conformation, little structural data and information currently exist on whether or not glycation does indeed influence or change local protein secondary structure [268]. For example, in the blood, D-glucose can react with an NH_2 group of hemoglobin to form an imine that subsequently undergoes an irreversible rearrangement to a more stable a-aminoketone known as hemoglobin-AIc \index{hemoglobin-AIc}% [269].

Diabetes results when the body does not produce sufficient insulin or when the insulin it produces does not properly stimulate its target cells. Because insulin is the hormone that maintains the proper level of glucose in the blood, diabetics have increased blood glucose levels. The amount of hemoglobin-AIc formed is proportional to the concentration of glucose in the blood, so diabetics have a higher concentration of hemoglobin-AIc than nondiabetics. Thus, measuring the hemoglobin-AIc level is a way to determine whether the blood glucose level of a diabetic is being controlled [270,271].

Cataracts, a common complication in diabetics, are caused by the reaction of glucose with the group of proteins in the lens of the eye. It is thought that the arterial rigidity common in old age may be attributable to a similar reaction of glucose with the NH_2 group of proteins [250,272].

7.1 Mechanism of the Maillard Reaction

As illustrated in *Scheme 65*, **33** reacts with an amine to give an imine **326** that isomerizes into an aminoketose **327** (Amadori product), existing as an equilibrium mixture of cyclic hemiacetals, whereas **40** affords, by way of **328**, the hexosamine derivatives **329** and **330** (Heyns products), also in cyclic form. The Amadori–Heyns compounds \index{Amadori–Heyns compounds}% are at the head of the complex sequences of the Maillard reaction. The crystal structure of the Amadori product **331** between **33** and glycine has been determined more than three decades after the first proposal of its structure. Alternative preparations and X-ray analyses of Heyns products **332** and **333** have been reported [273,274].

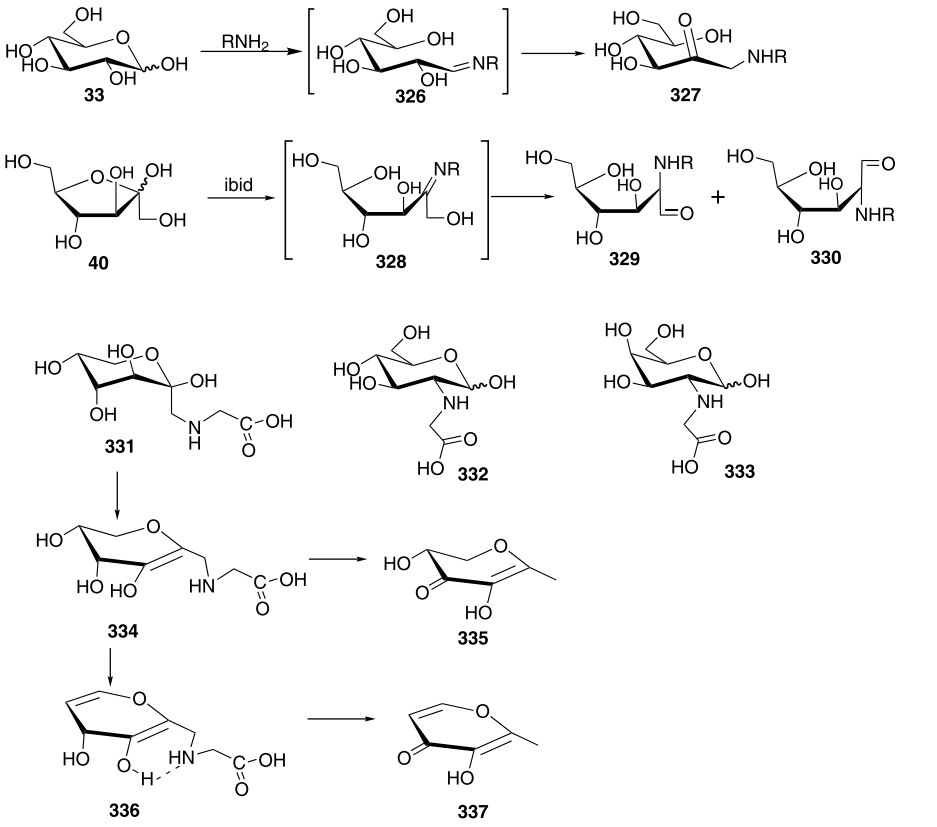
The Amadori product from D-glucose **33** and L-proline decomposes at 130 °C in DMF to afford **33** and D-Mannose **54**, indicating the reversibility of the Amadori reaction. A kinetic study using **33** and phenylalanine indicates that the Schiff's base formation is the rate-determining step of the Maillard reaction [275,276].

Maltol **337** is one of the degradation products in monosaccharide solutions with amino acids forming Amadori compounds but not in the solution of monosaccharides alone. Heated solutions of monosaccharides yield **335**, the logical precursor of **337**, but not **337** itself. On the basis of the molecular mechanics calculation indicating that **335** adopts the conformation unfavorable for dehydration into **337**, a possible route via the dehydrated product **336**, an *ortho*-elimination product, has been postulated as a more favorable alternate reaction pathway [277].

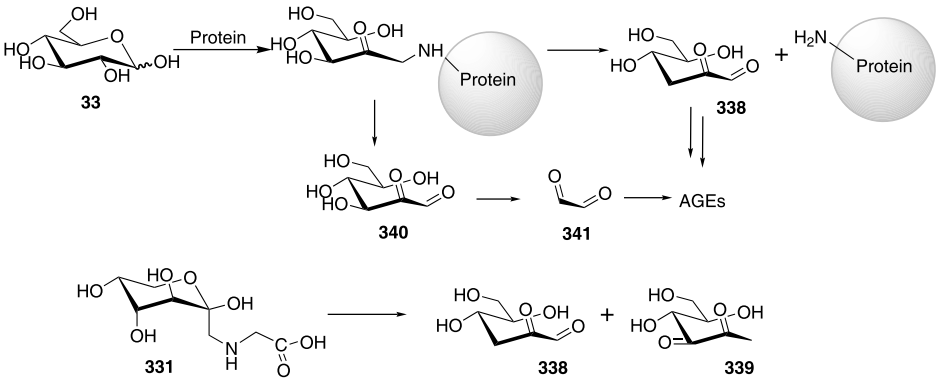
7.2 Chemistry of Biologically Significant Maillard Products

In biological systems, Amadori products formed from aldoses and the amino group in peptides, decompose to release reactive sugar derivatives that are irreversibly consumed in the production of the advanced glycation end products (AGEs). In this sense, **338** is one of the key substances in the Maillard reaction [278]. A new specific assay of **338** has been developed using diaminonaphelene [279]. The dicarbonyl compounds **338** and **339**, the suggested intermediates in the degradation of the Amadori compound **331**, had been trapped with aminoguanidine [280,281]. The role of **338** generated in the Maillard cascade as a cross-linker of proteins has been emphasized [282]. Oxygen and metal cations accelerate the degradation of Amadori products to D-glucosone (**340**), a precursor of glyoxal **341** [283,284] (*Scheme 66*).

It is known that some Maillard products have strand-breaking activities to DNA. Many compounds found in foodstuffs are α,β-unsaturated ketones [285,286]. Compounds **53**, **342**, **343**, and **335** (*Fig. 9*) cleave DNA single strands by generating hydroxyl radicals and other active oxygen radicals in the presence of Fe^{3+} and oxygen [287,288,289,290,291,292]. For example, the key hydrolyzate **344** generates hydroxyl radicals and the oxidation products **345** and **346**. An organic hydroperoxide **347**, presumably formed via direct oxidation of **339** or stepwise from **348**, the precursor of **335**, has been isolated [293,294,295,296,297] (*Scheme 67*).



Scheme 65



Scheme 66

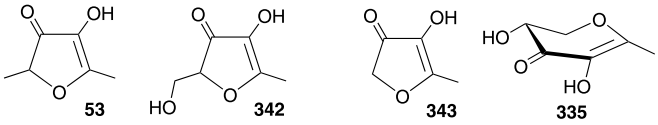
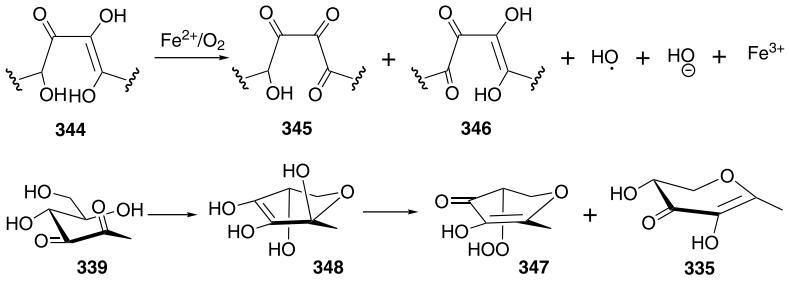


Figure 9
Maillard products having strand-breaking activities to DNA

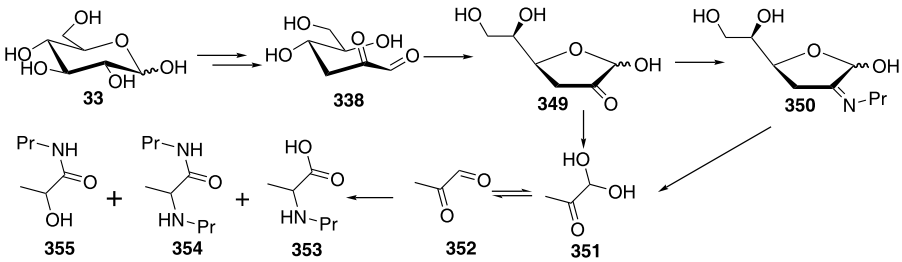


Scheme 67

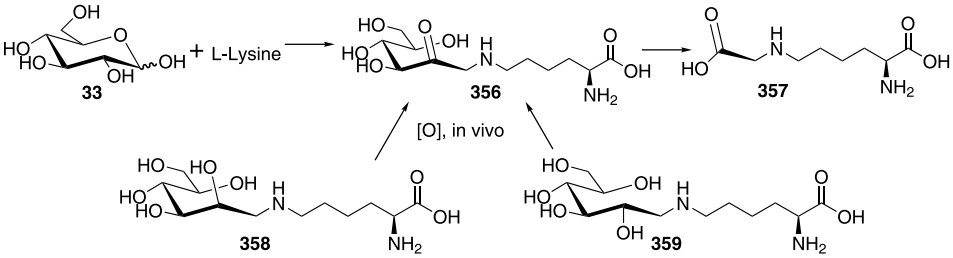
The major intermediate of the Maillard reaction **38**, having an allylic system, seems to furnish a cytotoxic ester on metabolic sulfonation [298]. In contrast to the above findings, some Amadori products, such as pyrazines have antimutagenicity [299,300,301]. Enkastines, the Amadori products of **33** and dipeptides, beneficially prolong the action of enkephaline by inhibiting enkephalinase [302].

Reactive small sugars and related acids appear to play a role in forming AGEs including cross-linked proteins in the aged body as well as inactivation of human Cu,Zn-superoxide dismutase [282,303,304]. Reaction of **33** with *n*-propylamine in phosphate-buffered, neutral solution generates several derivatives of small sugars [305,306], namely, C_2 and C_3 sugar derivatives. The 3-deoxyulose **349**, a hemiacetal form of **338**, yields **351**, the hydrate of methylglyoxal (**352**), as well as the Schiff's base **350** which is thought to be the precursor of the C_3-products [307,308,309] (*Scheme 68*).

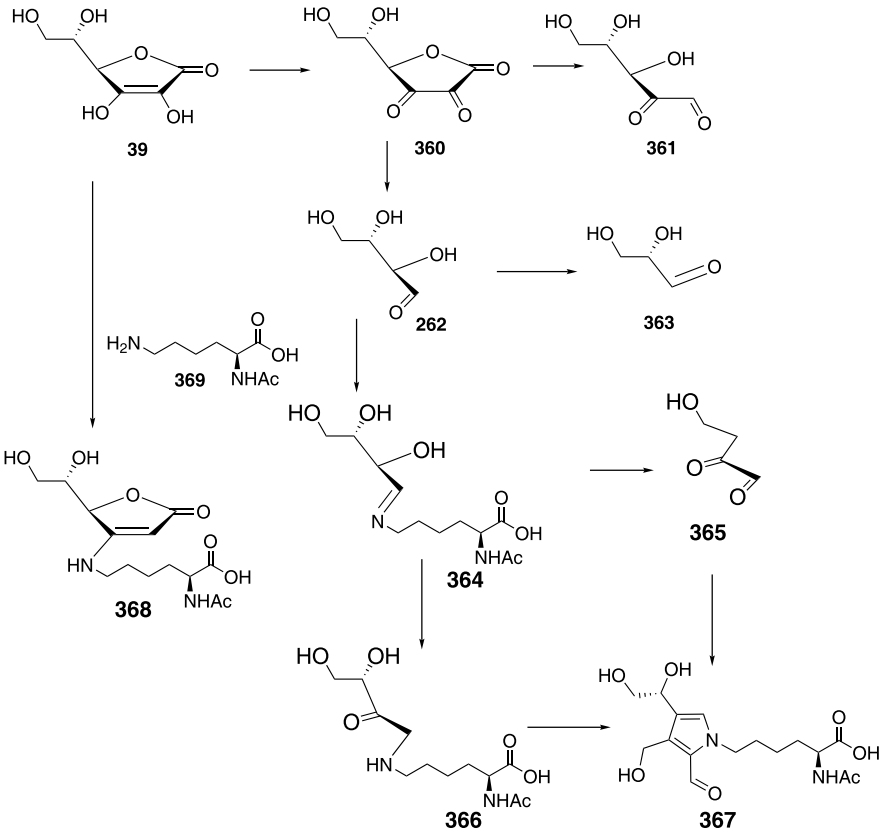
N^{ε}-(carboxymethyl)lysine (**357**), is a main AGE product found in vivo [310,311]. About 50% of **357** seems to be formed via oxidative degradation of the Amadori product **356**. The reduced



Scheme 68



Scheme 69



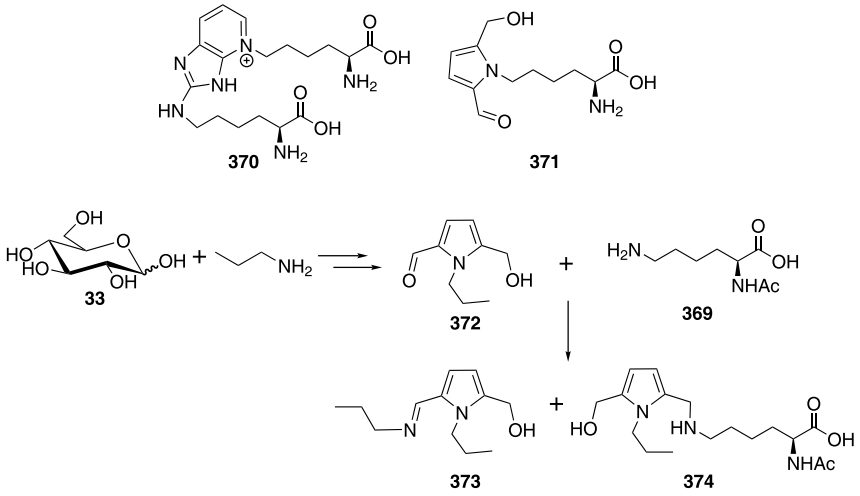
Scheme 70

compounds **358** and **359** also form **356** under aerobic physiological conditions [282]. Reactive **352** combines reversibly with lysine and cysteine residues and irreversibly with arginine residue [312] (*Scheme 69*).

L-threose (**362**), the degradation product of **360** degrades in the presence of N^{α}-acetyl-L-lysine (**369**) at pH 7 into 3-deoxy-tetros-2-ulose (**365**) [313,314]. Only at pH 7 does retro-

aldolization of **362** occur to give glyceraldehyde (**363**). Under physiological conditions, the AGE product **364** is formed from **362** and **369**, apparently via condensation of the Amadori compounds **365** and **366** [315,316,317]. On heating at 100 °C, a hood-processing temperature, in methanol in a sealed vessel, **39** and **369** form an amine **368** [318] (*Scheme 70*).

Some of the heterocyclic compounds among the Maillard products, for example, pentosidine **370** and pyrraline **371**, are AGEs in the skin of diabetic patients as well as in the brain of Alzheimer patients [319,320,321,322,323,324,325,326,327,328,329]. The observation that the aldehyde **372**, the Maillard product of **33** and *n*-propylamine, reacts with the amine and **369** to give **373** and **374**, respectively, led to the assumption that pyrrole aldehydes might also be precursors of the lysine side chain of proteins [320,330,331,332] (*Scheme 71*).



Scheme 71

References

1. Solomons TWG, Fryhle CB (2002) Organic chemistry. Wiley, New York
2. Bruice PY (2004) Organic chemistry. Pearson/Prentice Hall, Upper Saddle River, NJ
3. Stütz AE (2001) Glycoscience: epimerisation, isomerisation and rearrangement reactions of carbohydrates. Springer, Berlin, Heidelberg, New York
4. Lindhorst TK (2003) Essentials of carbohydrate chemistry and biochemistry. Wiley-VCH, Weinheim
5. Levy DE, Fügedi P (2006) The organic chemistry of sugars. Taylor & Francis, Boca Raton, FL
6. Sun Y, Cheng J (2002) Bioresource Technology 83:1
7. Wolfenden R, Lu X, Young G (1998) J Am Chem Soc 120:6814
8. Chenault HK, Chafin LF (1998) J Org Chem 63:833
9. Kirby AJ, Stromberg R (1994) J Chem Soc-Chem Comm: 709
10. Camilleri P, Jones RFD, Kirby AJ, Stromberg R (1994) J Chem Soc-Perkin Trans 2:2085
11. Sidelmann UG, Hansen SH, Gavaghan C, Carless HAJ, Lindon J, Farrant R, Wilson ID, Nicholson JK (1996) Anal Chem 68:2564

12. ManleyHarris M, Richards GN (1996) Carbohydr Res 287:183
13. Sinnott ML (1990) Chem Rev 90:1171
14. Kaczmarek J, Kaczynski Z, Trumpakaj Z, Szafranek J, Bogalecka M, Lonnberg H (2000) Carbohydr Res 325:16
15. Horenstein BA, Bruner M (1996) J Am Chem Soc 118:10371
16. Chong AK, Pegg MS, Taylor NR, von Itzstein M (1992) Eur J Biochem 207:335
17. Davies GJ, Mackenzie L, Varrot A, Dauter M, Brzozowski AM, Schulein M, Withers SG (1998) Biochemistry 37:11707
18. Nagano N, Noguchi T, Akiyama Y (2007) Proteins-Structure Function and Bioinformatics 66:147
19. Crennell SJ, Garman EF, Laver WG, Vimr ER, Taylor GL (1993) Proc Natl Acad Sci USA 90:9852
20. Guo X, Sinnott ML (1993) Biochem J 296 (Pt 2):291
21. Ashwell M, Sinnott ML, Zhang Y (1994) J Org Chem 59:7539
22. Ashwell M, Guo X, Sinnott ML (1992) J Am Chem Soc 114:10158
23. Pitson SM, Mutter M, van den Broek LA, Voragen AG, Beldman G (1998) Biochem Biophys Res Commun 242:552
24. Biely P, Benen J, Heinrichova K, Kester HC, Visser J (1996) FEBS Lett 382:249
25. Schultz PG, Lerner RA (1995) Science 269:1835
26. Yu J, Choi SY, Moon KD, Chung HH, Youn HJ, Jeong S, Park H, Schultz PG (1998) Proc Natl Acad Sci USA 95:2880
27. Yu S, Ahmad T, Kenne L, Pedersen M (1995) Biochim Biophys Acta 1244:1
28. Richard GT, Yu S, Monsan P, Remaud-Simeon M, Morel S (2005) Carbohydr Res 340:395
29. Yu S, Kenne L, Pedersen M (1993) Biochim Biophys Acta 1156:313
30. Saddler JN, Penner MH (1995) Am Chem Soc Meeting. Enzymatic degradation of insoluble carbohydrates. American Chemical Society, Washington, DC
31. Horn SJ, Sikorski P, Cederkvist JB, Vaaje-Kolstad G, Sorlie M, Synstad B, Vriend G, Varum KM, Eijsink VG (2006) Proc Natl Acad Sci USA 103:18089
32. National Research Council (US) Committee on Bioprocess Engineering (1992) Putting biotechnology to work: bioprocess engineering. National Academy of Sciences, Washington, DC
33. Mulimani VH, Ramalingam R (1995) Biochem Mol Biol Int 36:897
34. Kulkarni DS, Kapanoor SS, Girigouda K, Kote NV, Mulimani VH (2006) Biotechnol Appl Biochem 45:51
35. Hollingsworth RI, Wang G (2000) Chem Rev 100:4267
36. Nolasco J, De Massaguer PR (2006) J Food Proc Eng 29:462
37. Hollnagel A, Kroh LW (2000) J Agricult Food Chem 48:6219
38. Miyazawa T, Ohtsu S, Nakagawa Y, Funazukuri T (2006) J Mat Sci 41:1489
39. Srokol Z, Bouche AG, van Estrik A, Strik RCJ, Maschmeyer T, Peters JA (2004) Carbohydr Res 339:1717
40. Griebl A, Lange T, Weber H, Milacher W, Sixta H (2006) Macromolecular Symposia 232:107
41. Kruse A, Gawlik A (2003) Ind Eng Chem Res 42:267
42. Hashaikeh R, Fang Z, Butler IS, Kozinski JA (2005) Proc Combustion Institute 30:2231
43. Chheda JN, Roman-Leshkov Y, Dumesic JA (2007) Green Chem 9:342
44. Sanderson K (2006) Nature 444:673
45. Hayes MH (2006) Nature 443:144
46. Kruse A, Maniam P, Spieler F (2007) Ind Eng Chem Res 46:87
47. Mark J, Pollien P, Lindinger C, Blank I, Mark T (2006) J Agricult Food Chem 54:2786
48. Fan XT (2005) J Agricult Food Chem 53:7826
49. Ginz M, Balzer HH, Bradbury AGW, Maier HG (2000) Eur Food Res Technol 211:404
50. Arya M, Rao LJM (2007) Crit Rev Food Sci Nutrit 47:51
51. Burde RDL, Crayton F, Bavley A (1962) Nature 196:166
52. Qian X, Nimlos MR, Johnson DK, Himmel ME (2005) Appl Biochem Biotechnol 121–124:989
53. Buskas T, Konradsson P (2000) J Carbohydr Chem 19:25
54. Antal MJ, Jr., Mok WS, Richards GN (1990) Carbohydr Res 199:91
55. Halliday GA, Young RJ, Jr., Grushin VV (2003) Org Lett 5:2003
56. Hauck T, Landmann C, Bruhlmann F, Schwab W (2003) J Agric Food Chem 51:1410
57. deGoede ATJW, vanDeurzen MPJ, vanderLeij IG, vanderHeijden AM, Baas JMA, vanRantwijk F, vanBekkum H (1996) J Carbohydr Chem 15:331
58. Cancilla MT, Penn SG, Lebrilla CB (1998) Anal Chem 70:663

59. Yang BY, Montgomery R (2007) Bioresour Technol 98:3084
60. T'i VTU, Pisarnitskii AF (1998) Appl Biochem Microbiol 34:106
61. Manini P, La Pietra P, Panzella L, Napolitano A, d'Ischia M (2006) Carbohydr Res 341:1828
62. Hourdin GL, Germain A, Moreau C, Fajula F (2002) J Catalysis 209:217
63. van den Berg R, Peters JA, van Bekkum H (1995) Carbohydr Res 267:65
64. Rangappa KS, Raghavendra MP, Mahadevappa DS, Gowda DC (1998) Carbohydr Res 306:57
65. Hollingsworth RI (1996) Biotechnol Annu Rev 2:281
66. Hollingsworth RI (1999) J Org Chem 64:7633
67. Stapley JA, BeMiller JN (2007) Carbohyd Res 342:407
68. Hourdin G, Germain A, Moreau C, Fajula F (2000) Catal Lett 69:241
69. Fischer K, Bipp HP (2005) Bioresour Technol 96:831
70. Niu W, Molefe MN, Frost JW (2003) J Am Chem Soc 125:12998
71. Service RF (2007) Science 315:1488
72. Champagne P (2007) Resour Conserv Recy 50:211
73. Kakinuma K, Li HY (1989) Tetrahedron Lett 30:4157
74. Taillefumier C, Chapleur Y (2004) Chem Rev 104:263
75. Sasaki M, Higashi M, Masu H, Yamaguchi K, Takeda K (2005) Org Lett 7:5913
76. Bertrand P, Gesson JP, Renoux B, Tranoy I (1995) Tetrahedron Lett 36:4073
77. Halcomb RL, Boyer SH, Wittman MD, Olson SH, Denhart DJ, Liu KKC, Danishefsky SJ (1995) J Am Chem Soc 117:5720
78. Modica E, Compostella F, Colombo D, Franchini L, Cavallari M, Mori L, De Libero G, Panza L, Ronchetti F (2006) Org Lett 8:3255
79. Jaunzeme I, Jirgensons A (2005) Synlett: 2984
80. Montero A, Mann E, Herradon B (2005) Tetrahedron Lett 46:401
81. Banaszek A, Pakulski Z, Zamojski A (1995) Carbohyd Res 279:173
82. Ichikawa Y, Kobayashi C, Isobe M (1996) J Chem Soc-Perkin Trans 1:377
83. Ichikawa Y, Kobayashi C, Isobe M (1994) Synlett: 919
84. Oishi T, Ando K, Inomiya K, Sato H, Iida M, Chida N (2002) Org Lett 4:151
85. Werschkun B, Thiem J (2001) Glycoscience: Epimerisation, Isomerisation and Rearrangement Reactions of Carbohydrates. Topics in Current Chemistry Vol 215, Springer-Verlag, Berlin, Heidelberg 215:293
86. Sudha AVRL, Nagarajan M (1998) Chem Comm 925
87. Balasubramanian KK, Ramesh NG, Pramanik A, Chandrasekhar J (1994) J Chem Soc-Perkin Trans 2:1399
88. Kuhn C, Legouadec G, Skaltsounis AL, Florent JC (1995) Tetrahedron Lett 36:3137
89. Overman LE, Shim J (1993) J Org Chem 58:4662
90. Deng W, Overman LE (1994) J Am Chem Soc 116:11241
91. Knight SD, Overman LE, Pairaudeau G (1995) J Am Chem Soc 117:5776
92. Agami C, Couty F, Lin J, Mikaeloff A (1993) Synlett: 349
93. Agami C, Couty F, Puchot-Kadouri C (1998) Synlett: 449
94. Oberdorfer F, Haeckel R, Lauer G (1998) Synthesis-Stuttgart: 201
95. Mundorff EC, Hanson MA, Varvak A, Ulrich H, Schultz PG, Stevens RC (2000) Biochemistry 39:627
96. Black KA, Leach AG, Kalani MY, Houk KN (2004) J Am Chem Soc 126:9695
97. Yokoyama H, Otaya K, Yamaguchi S, Hirai Y (1998) Tetrahedron Lett 39:5971
98. Zamojski A (2002) Polish J Chem 76:1053
99. Yokoyama H, Ejiri H, Miyazawa M, Yamaguchi S, Hirai Y (2007) Tetrahedron: Asymmetry 18:852
100. Muzart J (2005) Tetrahedron 61:4179
101. Mcdonald FE, Gleason MM (1995) Angew Chem Int Ed Engl 34:350
102. Castro S, Peczuh MW (2005) J Org Chem 70:3312
103. Redlich H (1994) Angew Chem 106:1407
104. Collins P, Ferrier RJ (1995) Monosaccharides: their chemistry and their roles in natural products. Wiley, New York
105. Tatsuta K, Hosokawa S (2006) Science and Technology of Advanced Materials 7:397
106. Ponten F, Magnusson G (1994) Acta Chemica Scandinavica 48:566
107. Ito H (2003) Yakugaku Zasshi-J Pharmaceut Soc Japan 123:933
108. Ito H, Motoki Y, Taguchi T, Hanzawa Y (1993) J Am Chem Soc 115:8835

109. Jenkins DJ, Riley AM, Potter BVL (1996) J Org Chem 61:7719
110. Bettelli E, D'Andrea P, Mascanzoni S, Passacantilli P, Piancatelli G (1998) Carbohydr Res 306:221
111. Estevez JC, Saunders J, Besra GS, Brennan PJ, Bash RJ, Fleet GWJ (1996) Tetrahedron: Asymmetry 7:383
112. Bichard CJF, Brandstetter TW, Estevez JC, Fleet GWJ, Hughes DJ, Wheatley JR (1996) J Chem Soc, Perkin Trans 1: Organic and Bio-Organic Chemistry: 2151
113. Binkley RW, Ambrose MG (1984) J Carbohydr Chem 3:1
114. Binkley RW (1992) J Org Chem 57:2353
115. Wang YF, Fleet GWJ, Zhao LX (1998) Carbohydr Res 307:159
116. Fuzier M, Le Merrer Y, Depezay J-C (1995) Tetrahedron Lett 36:6443
117. Poitout L, LeMerrer Y, Depezay JC (1996) Tetrahedron Lett 37:1613
118. Charette AB, Cote B (1993) J Org Chem 58:933
119. Jeong LS, Moon HR, Yoo SJ, Lee SN, Chun MW, Lim YH (1998) Tetrahedron Lett 39:5201
120. Welch JT, Svahn B-M, Eswarakrishnan S, Hutchinson JP, Zubieta J (1984) Carbohydrate Research 132:221
121. Baudry M, Barberousse V, Descotes G, Faure R, Pires J, Praly JP (1998) Tetrahedron 54:7431
122. Goebel M, Nothofer HG, Ross G, Ugi I (1997) Tetrahedron 53:3123
123. Holton RA, Somoza C, Kim HB, Liang F, Biediger RJ, Boatman PD, Shindo M, Smith CC, Kim SC, Nadizadeh H, Suzuki Y, Tao CL, Vu P, Tang SH, Zhang PS, Murthi KK, Gentile LN, Liu JH (1994) J Am Chem Soc 116:1597
124. Lee SD, Chan TH, Kwon KS (1984) Tetrahedron Lett 25:3399
125. Csuk R, Fuerstner A, Weidmann H (1986) J Carbohydr Chem 5:271
126. Curran DP, Suh Y-G (1987) Carbohydr Res 171:161
127. Fredenhagen A, Peter HH (1996) Tetrahedron 52:1235
128. Stoltz BM, Wood JL (1996) Tetrahedron Lett 37:3929
129. Avalos M, Babiano R, Cabanillas A, Cintas P, Higes FJ, Jimenez JL, Palacios JC (1996) J Org Chem 61:3738
130. Hoberg JO, Bozell JJ (1995) Tetrahedron Lett 36:6831
131. Hoberg JO (1997) J Org Chem 62:6615
132. Boyer FD, Lallemand JY (1994) Tetrahedron 50: 10443
133. Ramana CV, Murali R, Nagarajan M (1997) J Org Chem 62:7694
134. Wender PA, Jesudason CD, Nakahira H, Tamura N, Tebbe AL, Ueno Y (1997) J Am Chem Soc 119:12976
135. Chen XT, Gutteridge CE, Bhattacharya SK, Zhou BS, Pettus TRR, Hascall T, Danishefsky SJ (1998) Angew Chem Int Ed 37:185
136. Xu YM, Zhou WS (1997) J Chem Soc-Perkin Trans 1:741
137. Marshall JA, Tang Y (1994) J Org Chem 59:1457
138. Kim DK, Kim GH, Kim YW (1996) J Chem Soc-Perkin Trans 1:803
139. Tatsuta K (1998) J Synth Org Chem Japan 56:714
140. Boyer FD, Pancrazi A, Lallemand JY (1995) Synth Comm 25:1099
141. Chen YW, Vogel P (1994) J Org Chem 59:2487
142. Shilvock JP, Fleet GWJ (1998) Synlett: 554
143. Beacham AR, Smelt KH, Biggadike K, Britten CJ, Hackett L, Winchester BG, Nash RJ, Griffiths RC, Fleet GWJ (1998) Tetrahedron Lett 39:151
144. Poitout L, LeMerrer Y, Depezay JC (1996) Tetrahedron Lett 37:1609
145. Ernholt BV, Thomsen IB, Jensen KB, Bols M (1999) Synlett: 701
146. Lohse A, Jensen KB, Bols M (1999) Tetrahedron Lett 40:3033
147. Andreassen V, Svensson B, Bols M (2001) Synthesis-Stuttgart: 339
148. Moriyama H, Tsukida T, Inoue Y, Kondo H, Yoshino K, Nishimura SI (2003) Bioorg Med Chem Lett 13:2737
149. Tschamber T, Gessier F, Neuburger M, Gurcha SS, Besra GS, Streith J (2003) Eur J Org Chem: 2792
150. Fuentes J, Sayago FJ, Illangua JM, Gasch C, Angulo M, Pradera MA (2004) Tetrahedron-Asymmetry 15:603
151. Tsukida T, Moriyama H, Inoue Y, Kondo H, Yoshino K, Nishimura SI (2004) Bioorg Med Chem Lett 14:1569
152. Ichikawa Y, Osada M, Ohtani II, Isobe M (1997) J Chem Soc-Perkin Trans 1:1449
153. Blanco JLJ, Diaz Prez VM, Mellet CO, Fuentes J, Garcia Fernandez JM, Diaz Arribas JC, Canada FJ (1997) Chem Comm (Cambridge): 1969

154. Goti A, Cacciarini M, Cardona F, Cordero FM, Brandi A (2001) Org Lett 3:1367
155. Overkleeft HS, Bruggeman P, Pandit UK (1998) Tetrahedron Lett 39:3869
156. Haakansson AE, Palmelund A, Holm H, Madsen R (2006) Chemistry-A Eur J 12:3243
157. Kotha S, Mandal K, Tiwari A, Mobin SM (2006) Chemistry 12: 8024
158. Andresen TL, Skytte DM, Madsen R (2004) Org Biomol Chem 2: 2951
159. Ovaa H, Lastdrager B, Codee JDC, van der Marel GA, Overkleeft HS, van Boom JH (2002) J Chem Soc-Perkin Trans 1:2370
160. Yamazaki T, Mizutani K, Kitazume T (1996) ACS Symp Series 639:105
161. Dondoni A, Catozzi N, Marra A (2004) J Org Chem 69:5023
162. Pradera MA, Sayago FJ, Illangua JM, Gasch C, Fuentes J (2003) Tetrahedron Lett 44:6605
163. Fuentes J, Illangua JM, Sayago FJ, Angulo M, Gasch C, Pradera MA (2004) Tetrahedron-Asymmetry 15:3783
164. Dhavale DD, Jachak SM, Karche NP, Trombini C (2004) Tetrahedron 60:3009
165. Sun H, Abboud KA, Horenstein NA (2005) Tetrahedron 61:10462
166. Parr IB, Horenstein BA (1997) J Org Chem 62:7489
167. Castro S, Peczuh Mark W (2005) J Org Chem 70:3312
168. Foulard G, Brigaud T, Portella C (1997) J Org Chem 62:9107
169. Momotake A, Mito J, Yamaguchi K, Togo H, Yokoyama M (1998) J Org Chem 63: 7207
170. Zou W (2005) Curr Topic Med Chem 5:1363
171. Lin C-H, Lin H-C, Yang W-B (2005) Curr Topic Med Chem (Sharjah, United Arab Emirates) 5:1431
172. Lee DYW, He MS (2005) Curr Topic Med Chem 5:1333
173. Bililign T, Griffith BR, Thorson JS (2005) Natural Product Reports 22:742
174. Sharma GVM, Krishna PR (2004) Curr Org Chem 8:1187
175. Gascon-Lopez M, Motevalli M, Paloumbis G, Bladon P, Wyatt PB (2003) Tetrahedron 59:9349
176. Cipolla L, La Ferla B, Nicotra F (1998) Carbohydr Polym 37:291
177. Cipolla L, Peri F, La Ferla B, Redaelli C, Nicotra F (2005) Curr Org Synth 2:153
178. Johnson CR, Johns BA (1997) J Org Chem 62:6046
179. Hashimoto M, Terashima S (1994) Chem Lett: 1001
180. Brochard L, Lorin C, Spiess N, Rollin P (1998) Tetrahedron Lett 39:4267
181. Jun JG, Lee DW, Mundy BP (1998) Synth Comm 28:2499
182. Wei BG, Chen J, Huang PQ (2006) Tetrahedron 62:190
183. Pelyvas IF, Madi-Puskas M, Toth ZG, Varga Z, Hornyak M, Batta G, Sztaricskai F (1995) J Antibiotics 48:683
184. Zhou J, Wang G, Zhang L-H, Ye X-S (2006) Curr Org Chem 10:625
185. Ferrier RJ, Hoberg JO (2003) Advances in Carbohydrate Chemistry and Biochemistry, Vol 58, Academic Press, San Diego, London, 58:55
186. Chida N, Ohtsuka M, Ogura K, Ogawa S (1991) Bull Chem Soc Japan 64:2118
187. Wang A, Auzanneau FI (2007) J Org Chem 72:3585
188. Chida N, Takeoka J, Ando K, Tsutsumi N, Ogawa S (1996) Tennen Yuki Kagobutsu Toronkai Koen Yoshishu 38th: 259
189. Letellier P, Ralainirina R, Beaupere D, Uzan R (1994) Tetrahedron Lett 35:4555
190. Letellier P, Ralainairina R, Beaupere D, Uzan R (1997) Synthesis-Stuttgart: 925
191. Letellier P, ElMeslouti A, Beaupere D, Uzan R (1996) Synthesis-Stuttgart: 1435
192. Iimori T, Takahashi H, Ikegami S (1996) Tetrahedron Lett 37:649
193. Takahashi H (2001) Yuki Gosei Kagaku Kyokaishi 59:484
194. Takahashi H (2002) Yakugaku Zasshi-J Pharmaceut Soc Japan 122:755
195. Miyazaki H, Kobayashi Y, Shiozaki M, Ando O, Nakajima M, Hanzawa H, Haruyama H (1995) J Org Chem 60:6103
196. Friestad GK, Branchaud BP (1997) Tetrahedron Lett 38:5933
197. Das SK, Mallet JM, Sinay P (1997) Angew Chem Int Ed Engl 36:493
198. Sollogoub M, Mallet JM, Sinay P (2000) Angew Chem Int Ed Engl 39:362
199. Sollogoub M, Sinay P (2006) Organic Chemistry of Sugars: 349
200. Petasis NA, Yao X (2001) Abstracts of Papers of the American Chemical Society 222: U99
201. Chung S-K, Yu S-H (1996) Bioorg Med Chem Lett 6:1461
202. Jia C, Pearce AJ, Bleriot Y, Zhang Y, Zhang L-H, Sollogoub M, Sinay P (2004) Tetrahedron: Asymmetry 15:699

203. Strukul G (1998) Angew Chem Int Ed 37:1199
204. Mereyala HB, Guntha S (1995) Tetrahedron 51:1741
205. Zhou H, Wang GN, Zhang LH, Ye XS (2006) Curr Org Chem 10:625
206. Bennett SM, Biboutou RK, Zhou ZH, Pion R (1998) Tetrahedron 54:4761
207. Grove JJC, Holzapfel CW (1997) Tetrahedron Lett 38:7429
208. CronjeGrove JJ, Holzapfel CW, Williams DBG (1996) Tetrahedron Lett 37:1305
209. Chiara JL, Martinez S, Bernabe M (1996) J Org Chem 61:6488
210. Sano H, Sugai S (1995) Tetrahedron-Asymmetry 6:1143
211. deArmas P, GarciaTellado F, MarreroTellado JJ, Robles J (1997) Tetrahedron Lett 38:8081
212. Lewis BE, Choytun N, Schramm VL, Bennet AJ (2006) J Am Chem Soc 128:5049
213. Liu FW, Zhang YB, Liu HM, Song XP (2005) Carbohydr Res 340:489
214. Pacsu E (1930) J Am Chem Soc 52:2563
215. Pacsu J (1928) Berichte der Deutschen Chemischen Gesellschaft [Abteilung] B: Abhandlungen 61B:1508
216. Capozzi G, Mannocci F, Menichetti S, Nativi C, Paoletti S (1997) Chem Comm: 2291
217. Ellervik U, Jansson K, Magnusson G (1998) J Carbohydr Chem 17:777
218. Csuk R, Schaade M (1994) Tetrahedron 50:3333
219. Boons GJ, Stauch T (1996) Synlett: 906
220. Kim JM, Roy R (1997) J Carbohydr Chem 16:1281
221. Maunier V, Boullanger P, Lafont D (1997) J Carbohydr Chem 16:231
222. Gervay J, Nguyen TN, Hadd MJ (1997) Carbohydr Res 300:119
223. Fabian MA, Perrin CL, Sinnott ML (1994) J Am Chem Soc 116:8398
224. Vaino AR, Szarek WA (2001) J Org Chem 66:1097
225. Grundberg H, Eriksson-Bajtner J, Bergquist KE, Sundin A, Ellervik U (2006) J Org Chem 71:5892
226. Vaino AR, Chan SSC, Szarek WA, Thatcher GRJ (1996) J Org Chem 61:4514
227. Skorupowa E, Dmochowska B, Madaj J, Kasprzykowski F, Sokolowski J, Wisniewski A (1998) J Carbohydr Chem 17:49
228. Ren RXF, Chaudhuri NC, Paris PL, Rumney S, Kool ET (1996) J Am Chem Soc 118:7671
229. Yokoyama M, Nomura M, Togo H, Seki H (1996) J Chem Soc-Perkin Trans 1:2145
230. Di Florio R, Rizzacasa MA (1998) J Org Chem 63:8595
231. Brandstetter TW, Kim YH, Son JC, Taylor HM, Lilley PMD, Watkin DJ, Johnson LN, Oikonomakos NG, Fleet GWJ (1995) Tetrahedron Lett 36:2149
232. Leeuwenburgh MA, Timmers CM, vanderMarel GA, vanBoom JH, Mallet JM, Sinay PG (1997) Tetrahedron Lett 38:6251
233. Gervay J, Hadd MJ (1997) J Org Chem 62:6961
234. Vedso P, Chauvin R, Li Z, Bernet B, Vasella A (1994) Helvetica Chimica Acta 77:1631
235. Barker JL, Frost JW (2001) Biotechnol Bioeng 76:376
236. Zhu LZ, Talukdar A, Zhang GS, Kedenburg JP, Wang PG (2005) Synlett: 1547
237. Rowe D (2004) Chem Biodiversity 1:2034
238. vanDeurzen MPJ, vanRantwijk F, Sheldon RA (1997) J Carbohydr Chem 16:299
239. Mathews WB, Zajac WW (1995) J Carbohydr Chem 14:287
240. Devianne G, Escudier JM, Baltas M, Gorrichon L (1995) J Org Chem 60:7343
241. Lee CK, Kim EJ, Lee ISH (1998) Carbohydr Res 309:243
242. Diehl V, Cuny E, Lichtenthaler FW (1998) Heterocycles 48:1193
243. Oikawa N, Muller C, Kunz M, Lichtenthaler FW (1998) Carbohydr Res 309:269
244. Sun XL, Kai T, Takayanagi H, Furuhata K (1997) J Carbohydr Chem 16:541
245. Sano H, Mio S, Kitagawa J, Sugai S (1994) Tetrahedron-Asymmetry 5:2233
246. Chaudhari VD, Kumar KSA, Dhavale DD (2006) Tetrahedron 62:4349
247. Kozlowski JS, Marzabadi CH, Rath NP, Spilling CD (1997) Carbohydr Res 300:301
248. Mauron J (1981) Prog Food Nutr Sci 5:5
249. Ledl F, Beck J, Sengl M, Osiander H, Estendorfer S, Severin T, Huber B (1989) Prog Clin Biol Res 304:23
250. John WG, Lamb EJ (1993) Eye 7 (Pt 2): 230
251. Gerrard J (2005) The Maillard reaction: chemistry, biochemistry and implications by Harry Nursten. Royal Society of Chemistry
252. Erbersdobler HF, Somoza V (2007) Mol Nutr Food Res 51:423
253. Charissou A, Ait-Ameur L, Birlouez-Aragon I (2007) J Agric Food Chem 55:4532

254. van Boekel MA (2006) Biotechnol Adv 24:230
255. Kato A (2002) Food Sci Technol Res 8:193
256. Chen CQ, Robbins E (2000) ACS Symp Series 754:286
257. Gerrard JA (2006) Trends Food Sci Technol 17:324
258. Tuohy KM, Hinton DJ, Davies SJ, Crabbe MJ, Gibson GR, Ames JM (2006) Mol Nutr Food Res 50:847
259. Sun Y, Hayakawa S, Chuamanochan M, Fujimoto M, Innun A, Izumori K (2006) Biosci Biotechnol Biochem 70:598
260. Saraiva MA, Borges CM, Florencio MH (2006) J Mass Spectrom 41:755
261. Robert L, Labat-Robert J (2006) Pathologie Biologie 54:371
262. Reddy VP, Beyaz A (2006) Drug Discovery Today 11:646
263. Peyroux J, Sternberg M (2006) Pathol Biol (Paris) 54:405
264. Somoza V (2005) Mol Nutrit Food Res 49:663
265. Baynes JW (2000) Biogerontology 1:235
266. Colaco CA (1993) J R Soc Med 86:243
267. Wirth DD, Baertschi SW, Johnson RA, Maple SR, Miller MS, Hallenbeck DK, Gregg SM (1998) J Pharm Sci 87:31
268. Howard MJ, Smales CM (2005) J Biol Chem 280:22582
269. Rahbar S (2005) Ann N Y Acad Sci 1043:9
270. Monnier VM, Stevens VJ, Cerami A (1981) Prog Food Nutr Sci 5:315
271. Gottlieb Sheldon H (2002) Diabetes Forecast 55:34
272. Stitt Alan W (2005) Ann N Y Acad Sci 1043:582
273. Mossine VV, Glinsky GV, Barnes CL, Feather MS (1995) Carbohydr Res 266:5
274. Mossine VV, Barnes CL, Mawhinney TP (2007) Carbohydr Res 342:131
275. Yaylayan VA, Huyghues-Despointes A (1996) Carbohydr Res 286:179
276. Ge SJ, Lee TC (1996) J Agric Food Chem 44:1053
277. Yaylayan VA, Huyghues-Despointes A (1994) Crit Rev Food Sci Nutrit 34:321
278. Niwa T, Takeda N, Miyazaki T, Yoshizumi H, Tatematsu A, Maeda K, Ohara M, Tomiyama S, Niimura K (1995) Nephron 69:438
279. Yamada H, Miyata S, Igaki N, Yatabe H, Miyauchi Y, Ohara T, Sakai M, Shoda H, Oimomi M, Kasuga M (1994) J Biol Chem 269:20275
280. Hirsch J, Petrakova E, Feather MS (1992) Carbohydr Res 232:125
281. Hirsch J, Petrakova E, Feather MS, Barnes CL (1995) Carbohydr Res 267:17
282. Zyzak DV, Richardson JM, Thorpe SR, Baynes JW (1995) Arch Biochem Biophys 316:547
283. Hayase F, Shibuya T, Sato J, Yamamoto M (1996) Biosci Biotechnol Biochem 60: 1820
284. Hayase F, Nagaraj RH, Miyata S, Njoroge FG, Monnier VM (1989) J Biol Chem 264:3758
285. Yaylayan VA, Keyhani A (1999) J Agric Food Chem 47:3280
286. Kim SW, Rogers QR, Morris JG (1996) J Nutr 126:195
287. Hiramoto K, Aso-o R, Ni-iyama H, Hikage S, Kato T, Kikugawa K (1996) Mutat Res 359:17
288. Hiramoto K, Ishihara A, Sakui N, Daishima S, Kikugawa K (1998) Biol Pharm Bull 21:102
289. Hiramoto K, Kato T, Kikugawa K (1993) Mutat Res 285:191
290. Hiramoto K, Nasuhara A, Michikoshi K, Kato T, Kikugawa K (1997) Mutat Res 395:47
291. Hiramoto K, Sekiguchi K, Aso OR, Ayuha K, Ni-Iyama H, Kato T, Kikugawa K (1995) Food Chem Toxicol 33:803
292. Hiramoto S, Itoh K, Shizuuchi S, Kawachi Y, Morishita Y, Nagase M, Suzuki Y, Nobuta Y, Sudou Y, Nakamura O, Kagaya I, Goshima H, Kodama Y, Icatro Faustino C, Koizumi W, Saigenji K, Miura S, Sugiyama T, Kimura N (2004) Helicobacter 9:429
293. Lertsiri S, Fujimoto K, Miyazawa T (1995) Biochim Biophys Acta 1245:278
294. Lertsiri S, Maungma R, Assavanig A, Bhumiratana A (2001) J Food Process Preserv 25:149
295. Lertsiri S, Oak JH, Nakagawa K, Miyazawa T (2002) Biochim Biophys Acta 1573:48
296. Lertsiri S, Oak J-H, Nakagawa K, Miyazawa T (2002) Biochimica et Biophysica Acta, General Subjects 1573:48
297. Lertsiri S, Shiraishi M, Miyazawa T (1998) Biosci Biotechnol Biochem 62:893
298. Surh YJ, Liem A, Miller JA, Tannenbaum SR (1994) Carcinogenesis 15:2375
299. Tressi R, Piechotta CT, Rewicki D, Krause E (2002) Int Congr Series 1245:203
300. Jenq SN, Tsai SJ, Lee H (1994) Mutagenesis 9:483
301. Friedman M (1996) J Agric Food Chem 44:631

302. Vertesy L, Fehlhaber HW, Kogler H, Schindler PW (1996) Liebigs Annalen: 121
303. Ukeda H, Hasegawa Y, Ishi T, Sawamura M (1997) Biosci Biotechnol Biochem 61:2039
304. Ukeda H, Shimamura T, Tsubouchi M, Harada Y, Nakai Y, Sawamura M (2002) Anal Sci 18:1151
305. Buttner U, Gerum F, Severin T (1997) Carbohydr Res 300:265
306. Buttner U, Ochs S, Severin T (1996) Carbohydr Res 291:175
307. Ahmed MU, Dunn JA, Walla MD, Thorpe SR, Baynes JW (1988) J Biol Chem 263:8816
308. Ahmed MU, Thorpe SR, Baynes JW (1986) J Biol Chem 261:4889
309. Ahmed N, Babaei-Jadidi R, Howell SK, Thornalley PJ, Beisswenger PJ (2005) Diabetes Care 28:2465
310. Glomb MA, Pfahler C (2001) J Biol Chem 276:41638
311. Glomb MA, Tschirnich R (2001) J Agricult Food Chem 49:5543
312. Lo TW, Westwood ME, McLellan AC, Selwood T, Thornalley PJ (1994) J Biol Chem 269:32299
313. Lopez MG, Mancilla-Margalli NA (2000) Frontiers of Flavour Science. Proceedings of the 9th Weurman Flavour Research Symposium, Freising, Germany, June 22–25
314. Li EY, Feather MS (1994) Carbohydr Res 256:41
315. Nagaraj RH, Monnier VM (1995) Biochim Biophys Acta 1253:75
316. Nagaraj RH, Sady C (1996) FEBS Lett 382:234
317. Nagaraj RH, Sarkar P, Mally A, Biemel KM, Lederer MO, Padayatti PS (2002) Arch Biochem Biophys 402:110
318. Pischetsrieder M, Larisch B, Seidel W (1997) J Agric Food Chem 45:2070
319. Dyer DG, Blackledge JA, Katz BM, Hull CJ, Adkisson HD, Thorpe SR, Lyons TJ, Baynes JW (1991) Z Ernahrungswiss 30:29
320. Dyer DG, Blackledge JA, Thorpe SR, Baynes JW (1991) J Biol Chem 266:11654
321. Smith PR, Somani HH, Thornalley PJ, Benn J, Sonksen PH (1993) Clin Sci (Lond) 84:87
322. Smith PR, Thornalley PJ (1992) Eur J Biochem 210:729
323. Nissimov J, Elchalal U, Bakala H, Brownlee M, Berry E, Phillip M, Milner Y (2007) J Immunolog Method 320:1
324. Meerwaldt R, Lutgers HL, Links TP, Graaff R, Baynes JW, Gans ROB, Smit AJ (2007) Diabetes Care 30:107
325. Yu Y, Thorpe SR, Jenkins AJ, Shaw JN, Sochaski MA, Mcgee D, Aston CE, Orchard TJ, Silvers N, Peng YG, McKnight JA, Baynes JW, Lyons TJ, Grp DER (2006) Diabetologia 49:2488
326. Lutgers HL, Graaff R, Links TP, Ubink-Veltmaat LJ, Bilo HJ, Gans RO, Smit AJ (2006) Diabetes Care 29:2654
327. Stitt AW, Jenkins AJ, Cooper ME (2002) Expert Opin Inv Drug 11:1205
328. Raj DSC, Choudhury D, Welbourne TC, Levi M (2000) Am J Kidney Dis 35:365
329. Chiarelli F, Catino M, Tumini S, Cipollone F, Mezzetti A, Vanelli M, Verrotti A (2000) Pediatr Nephrol 14:841
330. DeGroot J (2004) Curr Opin Pharmacol 4:301
331. Chellan P, Nagaraj RH (2001) J Biol Chem 276:3895
332. Biemel KM, Reihl O, Conrad J, Lederer MO (2001) J Biol Chem 276:23405