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A Mine for Functional Molecules and Materials

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Aims and Scope

The series *Topics in Current Chemistry* presents critical reviews of the present and future trends in modern chemical research. The scope includes all areas of chemical science, including the interfaces with related disciplines such as biology, medicine, and materials science.

The objective of each thematic volume is to give the non-specialist reader, whether at the university or in industry, a comprehensive overview of an area where new insights of interest to a larger scientific audience are emerging.

Thus each review within the volume critically surveys one aspect of that topic and places it within the context of the volume as a whole. The most significant developments of the last 5–10 years are presented, using selected examples to illustrate the principles discussed. A description of the laboratory procedures involved is often useful to the reader. The coverage is not exhaustive in data, but rather conceptual, concentrating on the methodological thinking that will allow the non-specialist reader to understand the information presented.

Discussion of possible future research directions in the area is welcome.

Review articles for the individual volumes are invited by the volume editors.

In references *Topics in Current Chemistry* is abbreviated *Top Curr Chem* and is cited as a journal.

Impact Factor 2009: 4.291; Section "Chemistry, Multidisciplinary": Rank 20 of 138

Preface

Chemists are well aware that it is urgent to develop sustainable processes and to design new chemical entities that improve the efficiency and the environmental impact of chemical transformations. Carbohydrates are the most abundant class of natural compounds: they offer unique structures for multiple transformations into a variety of industrial products based on their multifunctionality and stereochemical diversity. Chemistry using carbohydrates, unprotected or functionalized, continues to be a challenging field of investigation. Because of the complexity of sugars, the issues of regio- and stereoselectivity are among the most difficult to monitor. The low solubility of carbohydrates in several solvents is often a handicap, but sometimes an opportunity. In this volume, entitled "Carbohydrates and Sustainable Development, Part 2 – A Mine for Functional Molecules and Materials," several aspects of the chemistry of carbohydrates are discussed. Green processes involving their conversion into industrial products for cosmetics are illustrated by straightforward transformations using clean solvents and nontoxic catalysis. Other contributions focus on multistep sequences toward elaborated products, starting from these inexpensive and readily available materials. A survey on the state of the art of ionic liquids derived from sugars is also presented. Synthetic polymers can now be made based on carbohydrate building blocks. The potential of these biocompatible and biodegradable macromolecular materials to replace the polluting petroleum-based polymers is also discussed. Bioconversions toward rather complex molecules of biological relevance have made a breakthrough. In all chapters, evidence is given that sugars and polysaccharides are indeed "a mine for functional molecules and materials."

This volume, together with the first volume entitled "Carbohydrates and Sustainable Development, Part 1 – Renewable Resources for Chemistry and Biotechnology," demonstrates that a variety of industrial products can be accessed using renewable and low-cost biomass. Both volumes are based on selected papers presented at "Carbohydrates as Organic Raw Materials V – Building a Sustainable Future" (CORM V), held in Lisbon in January 2009. The conference was chaired by Amélia Pilar Rauter (University of Lisboa) and Yves Queneau (University of Lyon, INSA Lyon), in collaboration with Frieder W. Lichtenthaler (Technische

Universität Darmstadt) as Honorary Chairman. The CORM meetings were started by Lichtenthaler in 1990. Both volumes highlight the importance of carbohydrates for sustainable processes as abundant, renewable, and low-cost materials and show how sugars contribute significantly to the indispensable new processes for tomorrow's chemistry. With the chemical and biochemical transformations of readily available carbohydrates, we are on the way toward a more sustainable future.

Lisbon and Lyon, July 2010

Amélia P. Rauter, University of Lisbon
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Contents

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Knoevenagel Reaction of Unprotected Sugars

Marie-Christine Scherrmann

Abstract The Knoevenagel reaction of unprotected sugars was investigated in the 1950s using zinc chloride as promoter. The so-called Garcia Gonzalez reaction had been almost forgotten for 50 years, until the emergence of new water tolerant catalysts having Lewis acid behavior. The reaction was thus reinvestigated and optimal conditions have been found to prepare trihydroxylated furan derivatives from pentose or β-tetrahydrofuranylfuran from hexoses with non-cyclic β-keto ester or β-diketones. Other valuable compounds such as β-linked tetrahydrobenzofuranyl glycosides or hydroxyalkyl-3,3,6,6,-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione can be obtained using cyclic β-dicarbonylic derivatives. Apart from one report in the 1950s, the Knoevenagel reaction of unprotected carbohydrate in basic condition has been studied only in the mid-1980s to prepare *C*-glycosyl barbiturates from barbituric acids and, later on, from non-cyclic β-diketones, β-*C*-glycosidic ketones. The efficient method exploited to prepare such compounds has found an industrial development in cosmetics.

Keywords Acetylacetates, 2-Amino-2-deoxyaldoses, Barbituric acids, C-Glycosides, Dimedone, Furans, García-Gonzalez reaction, Green chemistry, Hexoses, Meldrum's acid, Penta-2,4-dione, Pentoses, Pyrroles, Reactions in water, Tetrahydrofuranylfurans

Contents

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1 Introduction

The Knoevenagel condensation is a simple and easy to perform reaction for carbon–carbon bond formation by reacting carbonyl compounds and activated methylene [1, 2]. Various promoters have been found to be efficient for this reaction, the most conventional being soluble bases [2–6]. Lewis acids have been found to be effective in this reaction, some examples being the use of $TiCl_4$ [7, 8], $Ti(O\textit{i}Pr)_4$ [9, 10], $MgBr_2.OEt_2$ [11], $Mg(ClO_4)_2$ [12], or lanthanide salts [13, 14]. Recent efforts have been focused on the search for solid catalyst to facilitate their recovery by simple filtration. These systems include modified silica [15–20] or other modified oxide matrices [21, 22], hydrotalcites [23–25], zeolites [26–31], ion exchange resin [32], or nitrogen containing carbon nanotubes [33]. Organocatalysis has become a subject of interest in recent years because the use of a substoichiometric amount of an organic compound to accelerate the reactions is more environmentally friendly compared to organometallic catalysis [34]. The mechanism of the organocatalyzed reaction involves the corresponding iminium intermediate as the acceptor as shown by Knoevenagel himself in 1898 using piperidine [35]. The use of other organocatalysts [4, 36–38], including dendrimeric structures [39, 40], has been investigated.

The reaction could also be promoted using alternative activation conditions such as high pressure [41], ultrasound [39–46], or microwaves [6, 47–51]. Although a wide range of solvents has been used, it could also be carried out in neat conditions. These solvent-free experiments have been carried out with various promoters such as perchlorate salts [12], lanthanum chloride [14], zeolites [28, 29], other solid catalysts [19, 21, 50, 52–54], and organocatalysts [4, 37], sometimes under microwave heating [49, 50]. A solvent-, catalyst-, and support-free procedure has also been reported [55]. Despite the fact that the Knoevenagel reaction involves dehydration, it is surprisingly favored in water [5, 18, 26, 40, 49, 51–61], the most abundant liquid on Earth, which is very cheap, nontoxic, and can be used in large amounts without associated hazards. Water is able to promote reaction owing to its polarity and hydrophobic effects [62–65]. Some cases of uncatalyzed Knoevenagel condensations have been reported in this medium [66, 67].

Ionic liquids are also alternative reaction media considered as green, mostly because of their lack of vapor pressure and the possibility of reuse [68, 69]. Base-catalyzed Knoevenagel reactions have been described in these media [70–73]. The development of task specific ionic liquids in which the solvent and promoter are coupled is a real breakthrough in the field and some of them have been used in the Knoevenagel condensation [74–81].

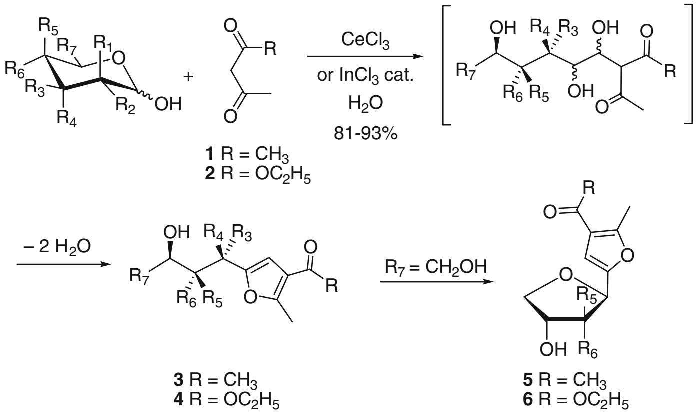
Polyethylene glycols and their monomethyl ethers are inexpensive, thermally stable, recoverable, and nontoxic, and can be used as green solvents for various transformations [82] including Knoevenagel condensations [83–85].

The present review is focused on the Knoevenagel reaction applied to unprotected sugars. It has been divided into two parts (acidic and basic conditions) in which the arguments are treated in chronological order.

2 Condensation Under Acidic Conditions

The condensation of unprotected reducing sugars with 1,3-dicarbonylic compounds under acidic conditions was reported in the 1950s by Garcia Gonzalez. His group has extensively studied the zinc chloride promoted reaction in methanol leading to polyhydroxylated furans [86]. The $ZnCl_2$-catalyzed Knoevenagel reaction in alcoholic solvents has been used recently as the first step of the syntheses of a cytotoxic compound [87], of selective inhibitors of L-fucosidases [88] of E- and P-selectin ligands [89], of glyco- and peptidomimetics [90], and of furan amino acid analogs of D- and L-serine [91]. The so-called Garcia Gonzalez reaction was reinvestigated in order to improve yields using milder conditions. Misra and Agnihotri obtained good results for the reaction of various aldoses and pentane-2,4-dione (**1**) or ethyl acetoacetate (**2**) using cerium(III) chloride in aqueous solution [92] (Scheme 1). The mechanism of this transformation involves an acid-promoted Knoevenagel condensation of the 1,3-dicarbonylic compound followed by an attack of OH-2 of the sugar moiety (i.e., R_2 or R_3) on the ketone and then aromatization to furan affording the trihydroxyalkyl-substituted furans **3** or **4** from pentoses. When the starting sugar is a hexose ($R_7 = CH_2OH$), the intermediate furans **3** or **4** undergo a cyclization to β-tetrahydrofuranylfuran derivatives **5** or **6**.

In this process, only the configurations at C-3 and C-4 were retained, so that the same trihydroxylated furan derivatives **3b** or **4b** were obtained from D-ribose (**9**) and D-arabinose (**8**) (Scheme 1, Table 1). These compounds were diastereoisomers of the products **3a** or **4a** obtained from D-xylose (**7**).[1] When starting from



Scheme 1 Synthesis of trihydroxyalkyl-substituted furans derivatives **3** or **4** from D-pentose and *C*-furyl glycosides **5** or **6** from D-hexoses

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[1] In [92], the Authors might have inverted the compounds obtained from D-ribose or D-arabinose with those obtained from D-xylose. This error has been reproduced by Nagarapu et al. [94]. A debate of a hypothetic epimerization at C-1’ has been engaged [91].

Table 1 Reaction of aldoses with pentane-2,4-dione (**1**) or ethyl acetoacetate (**2**)

D-Aldose	1,3-Dicarbonylic compound	Product	Catalyst	Yield (%)	References
D-Xylose (**7**)	**1**	**3a**	$CeCl_3.7H_2O$	90	[92]
R_2=R_3=R_6=OH			$InCl_3$	85	[93]
R_1=R_4=R_5=R_7=H	**2**	**4a**	$CeCl_3.7H_2O$	85	[92]
			$InCl_3$	81	[93]
D-Arabinose (**8**)	**1**	**3b**	$CeCl_3.7H_2O$	90	[92]
R_1=R_4=R_6=OH			$InCl_3$	87	[93]
R_1=R_3=R_5=R_7=H	**2**	**4b**	$CeCl_3.7H_2O$	76	[92]
			$InCl_3$	82	[93]
D-Ribose (**9**)	**1**	**3b**	$CeCl_3.7H_2O$	84	[92]
R_2=R_4=R_6=OH			$InCl_3$	85	[93]
R_1=R_3=R_5=R_7=H	**2**	**4b**	$CeCl_3.7H_2O$	80	[92]
			$InCl_3$	81	[93]
D-Glucose (**10**)	**1**	**5a**	$CeCl_3.7H_2O$	93	[92]
R_2=R_3=R_6=OH			$InCl_3$	93	[93]
R_1=R_4=R_5=H	**2**	**6a**	$CeCl_3.7H_2O$	87	[92]
R_7=CH_2OH			$InCl_3$	83	[93]
D-Mannose (**11**)	**1**	**5a**	$InCl_3$	93	[93]
R_1=R_3=R_6=OH			$InCl_3$	85	[93]
R_2=R_4=R_5=H	**2**	**6a**			
R_7=CH_2OH					
D-Galactose (**12**)	**1**	**5b**	$CeCl_3.7H_2O$	92	[92]
R_2=R_3=R_5=OH			$InCl_3$	90	[93]
R_1=R_4=R_6=H	**2**	**6b**	$CeCl_3.7H_2O$	82	[92]
R_7=CH_2OH			$InCl_3$	83	[93]

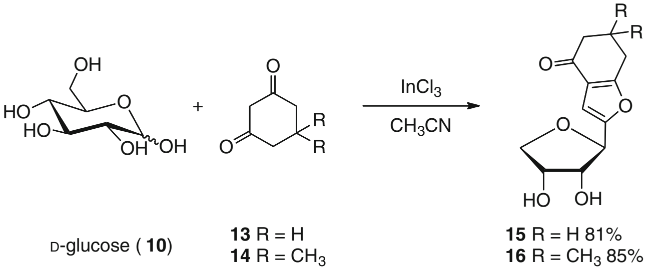
hexoses ($R_7 = CH_2OH$), the cyclization to β-tetrahydrofuranylfuran derivatives **5** or **6** only maintained the configurations at C-4 and C-5 of the starting sugar. As a result, D-glucose (**10**) and D-mannose (**11**) afforded the same compounds **5a** or **6a**, diastereoisomers of the products **5b** or **6b** obtained from D-galactose (**12**).

Later on, Yadav et al. reported the same reaction catalyzed by indium(III) chloride [93], and similar yields were obtained.

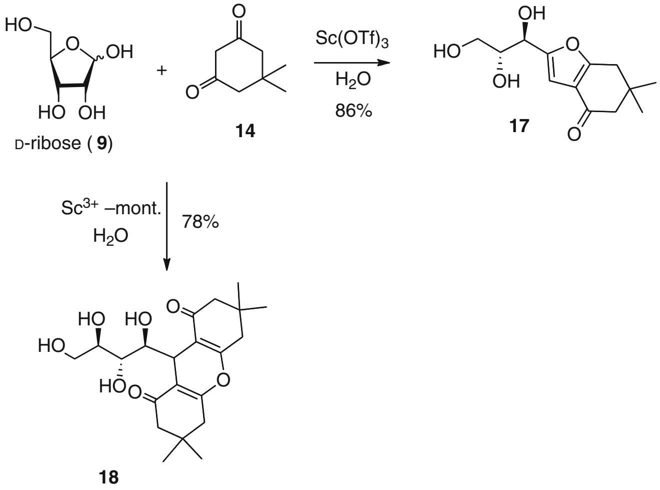
The reaction was applied with success to unprotected reducing disaccharides [92, 93]. The use of iron(III) chloride in ethanol–water gave similar results [94] (see footnote 1).

Bartoli et al. have extensively studied the combination of $CeCl_3.7H_2O$ and NaI in order to increase the activity of the catalytic system [13, 95]. They studied the condensation of D-glucose (**10**) and pentane-2,4-dione (**1**) and showed that **5a** could be obtained in 95% yield by using SiO_2 supported $CeCl_3.7H_2O$-NaI system in solvent-free conditions [96].

Cyclic β-dicarbonyl compounds have also been used in this reaction. Yadav and colleagues reported that when the $InCl_3$ catalyzed reaction between D-glucose and cyclohexane-1,3-dione (**13**) or dimedone (**14**) was carried out in CH_3CN, the β-linked tetrahydrobenzofuranyl glycosides **15** or **16** were obtained [93] (Scheme 2). The stereochemistry of the glycosidic linkage was proved by NMR experiments and was in good agreement with previously reported results. Sato and



Scheme 2 Synthesis of tetrahydrobenzofuranyl glycosides from D-glucose

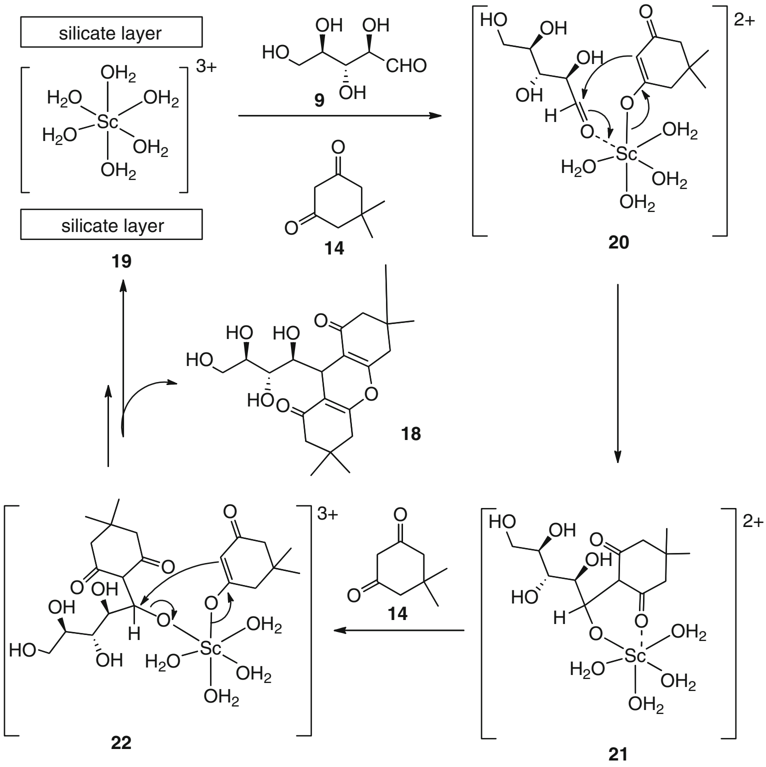


Scheme 3 Reaction of D-ribose with dimedone catalyzed by scandium cation-exchanged montmorillonite or scandium triflate

coworkers explored the use of Sc(OTf)$_3$ as the promoter in water for the same reaction and described a product having an α-linkage [97]. Unfortunately, as Yadav's group characterized their compounds as diacetylated derivatives, the comparison of the spectroscopic and optical data was not possible.

Interestingly, the use of Sc(OTf)$_3$ as the promoter gave hydroxyalkyl-6,7-dihydrobenzofuran-4(5*H*)-one derivatives **17** from D-ribose (**9**), whereas scandium cation-exchanged montmorillonite (Sc^{3+}-mont) afforded hydroxyalkyl-3,3,6,6,-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**18**) in good yield [97] (Scheme 3).

The different selectivity between Sc^{3+}-mont and Sc(OTf)$_3$ has been rationalized by the mechanism of the transformation. While the Sc(OTf)$_3$ catalyzed reaction in water afforded **17** through the classical mechanism, when Sc^{3+}-mont is used the compounds are reacting when coordinated to the Sc center in the silicate layer of Sc^{3+}-mont, giving rise to the addition of two molecules of dimedone



Scheme 4 Possible mechanism involved in the formation of **18** from D-ribose (**9**) and dimedone (**14**)

(Scheme 4). Such a mechanism was proposed for the Sc^{3+}-mont catalyzed Michael reaction [98].

The reaction was applied to D-xylose (**7**), D-arabinose (**8**), and L-arabinose (**23**) affording **24**, **25**, and **26** respectively in 76, 79, and 78% yields whereas D-glucose (**10**) gave **27** in only 43% (Fig. 1). Very interestingly, the author demonstrated that the catalyst could be re-used at least five times without any loss of activity [97].

3 Condensation Under Basic Conditions

The Knovenagel condensation under basic conditions was first investigated with D-glucosamine chlorhydrate (**28**.HCl) as the sugar. The condensation of this reducing amino sugar with pentane-2,4-dione **1** in aqueous acetone in the presence of sodium carbonate afforded the pyrrole derivative **29** in 85% yield [99] (Scheme 5). The reaction was extended to other 2-amino-2-deoxy-aldose and carbon nucleophiles [100–104].

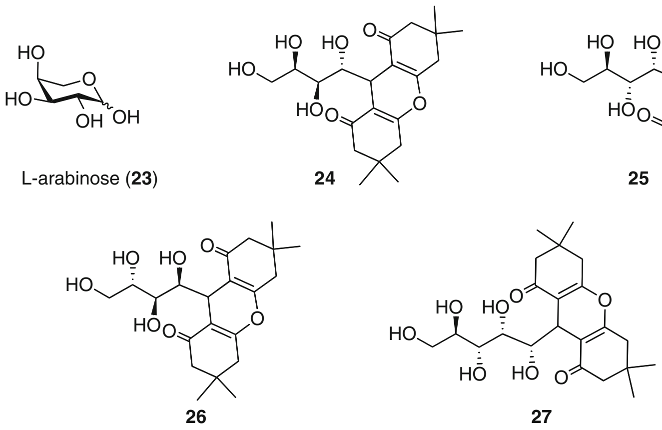
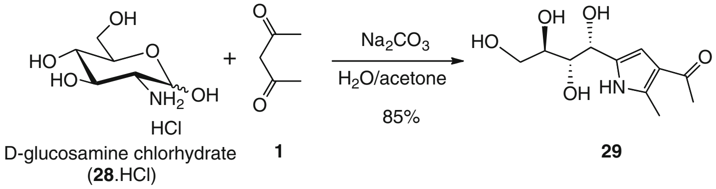


Fig. 1 Structure of L-arabinose and compounds obtained from various carbohydrates and dimedone (**14**) in the Sc^{3+}-mont catalyzed reaction



Scheme 5 Reaction of D-glucosamine chlorhydrate (**28**.HCl) with pentane-2,4-dione (**1**) in basic aqueous medium

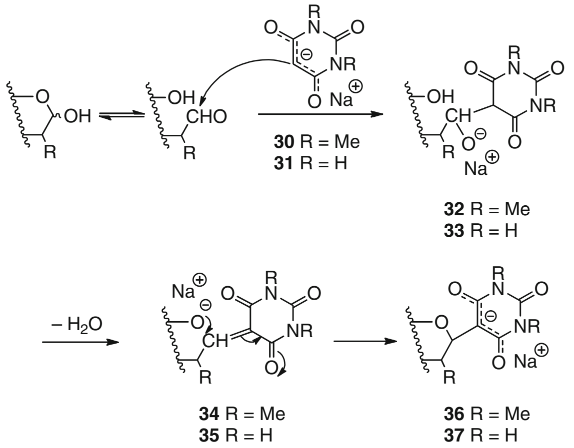
When barbituric acids **30** or **31** were used as 1,3 dicarbonylic compounds, unprotected sugars gave *C*-glycosyl barbiturates **36** or **37** in good yields [105, 106] (Scheme 6). The reaction starts with the Knoevenagel condensation of the carbanion of the barbituric acid with the hemiacetalic sugar affording **32** or **33**. Then the β-elimination of water followed by cyclization through a Michael-type addition afforded the β-D-*C*-pyranoside (equatorial) **36** or **37** probably through a thermodynamic control.

D-Glucose (**10**), D-galactose (**12**), D-mannose (**11**), 2-amino-2-deoxy-D-glucose (**28**), as well as D-glucuronic acid (**38**) were allowed to react with barbituric acids **30** or **31** to give β-D-glycopyranosyl barbiturates **36a–e** or **37a–e** in good yields (Fig. 2).

Using the same experimental conditions, the pentoses D-xylose (**7**), D-ribose (**9**), and D-arabinose (**8**) afforded the pyranoses derivatives **36f–h** or **37f–h**, respectively (Fig. 3).

Although the acidity of Meldrum's acid is quite similar to that of barbituric acids, the same reaction conducted with this dicarbonylic compound in aqueous medium gave a complex mixture instead of the expected adduct [107]. The reaction

Scheme 6 Mechanism of the reaction of carbohydrates with barbituric acids **30** or **31**



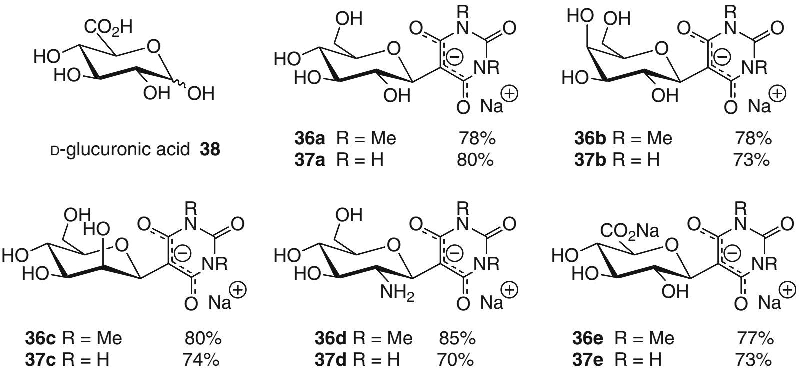


Fig. 2 Structure of D-glucuronic acid (**38**) and β-D-glycopyranosyl barbiturates obtained from hexoses or D-glucuronic acid

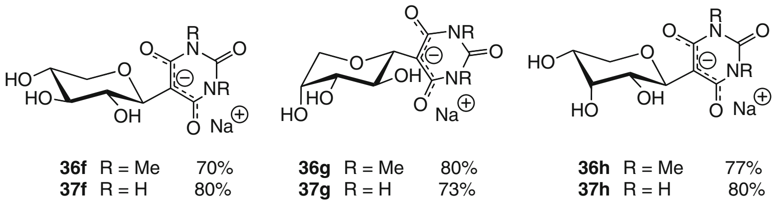
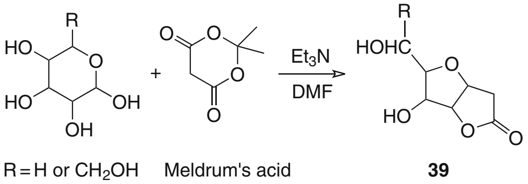


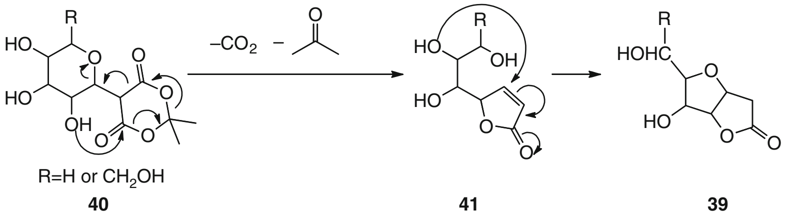
Fig. 3 Structure of β-D-glycopyranosyl barbiturates obtained from pentoses

was thus studied in DMF as the solvent and 3,6-anhydro-1,4-lactones **39** were obtained as main products [107–109] (Scheme 7).

The formation of **39** has been interpreted by assuming a Knoevenagel-Doebner reaction. The *C*-glycoside **40**, obtained via the Knoevenagel condensation of the



Scheme 7 Reaction of pentoses or hexoses with Meldrum's acid in DMF as the solvent



Scheme 8 Mechanism of the formation of **39** through the intermediate **40**

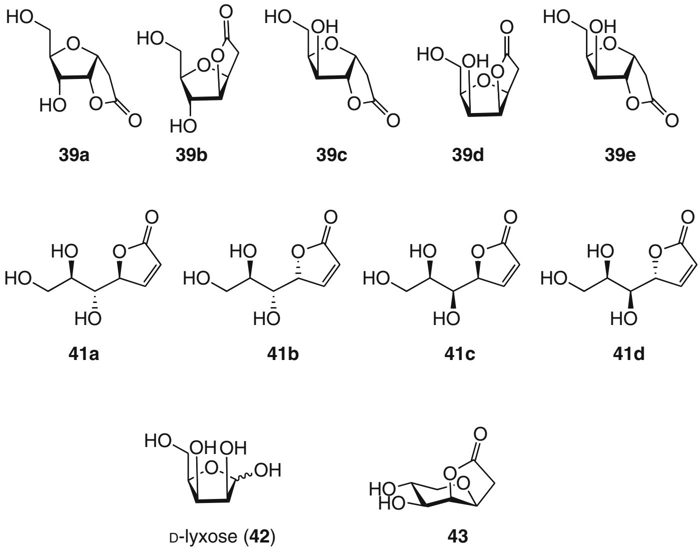
carbanion of the Meldrum's acid followed by β-elimination of water and cyclization through a Michael-type addition, underwent loss of carbon dioxide and acetone to give the unsaturated lactone **41**. A Michael reaction afforded in most cases the furanoid lactone **39** [109] (Scheme 8).

As this reaction is quite slow, epimerization at C-2 occurred so that the same products **39a**, **b** were obtained from D-ribose (**9**) and D-arabinose (**8**) together with the corresponding unsaturated lactones **41a** or **41b**. In the case of D-xylose (**7**), no epimerization was observed and the furanoid lactone **39c** was obtained with the unsaturated lactone **41c**. Compound **39c** was also isolated from the reaction involving D-lyxose (**42**), as well as the non-epimerized lactone **39d**, the unsaturated compound **41d**, and the pyranoid lactone **43** (Fig. 4, Table 2).

Köll et al. also carefully explored the conversion of hexoses and obtained similar results: products were mainly the furanoid lactones **39** (Scheme 7), partial epimerization occurred in most reactions, and D-mannose (**11**) also gave a pyranoid lactone as D-lyxose (**7**) [109].

The condensation of pentane-2,4-dione (**1**) with unprotected sugars in alkaline aqueous media was explored by the group of Lubineau [110]. Pentane-2,4-dione reacted with aldoses in the presence of sodium hydrogen carbonate, to give quantitatively the β-*C*-glycosidic ketones **45**. Also in this process, the reaction started with the Knoevenagel condensation of the β-diketone with the hemiacetalic sugar. Then, the β-elimination of water was followed by cyclization to the intermediate *C*-glycoside **44**, which underwent a retro-Claisen aldolization with sodium acetate elimination to give **45** (Scheme 9).

The selectivity for the formation of the β-D-pyranoside (equatorial) stereoisomer in the reaction originated from a thermodynamic control. Indeed, starting from D-glucose, after 24 h at room temperature, a mixture of the four possible α,β-furanosides **46** and **47,** and α,β-pyranosides stereoisomers **48** and **45a**, in which



39a **39b** **39c** **39d** **39e**

41a **41b** **41c** **41d**

D-lyxose (**42**) **43**

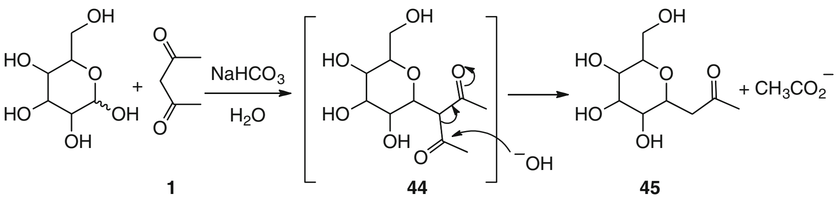
Fig. 4 Structure of D-lyxose and compounds obtained from the condensation of pentoses with Meldrum's acid

Table 2 Products of the condensation of pentoses with Meldrum's acid

Pentose	Unsaturated lactone (yields)	Furanoid lactone (yields)	C-2 epimerized furanoid lactone (yields)	Pyranoid lactone
D-Ribose (**9**)	**41a** (5%)[a] (5%)[b]	**39a** (41%)[a] (20%)[b]	**39b** (21%)[a] (61%)[b]	–
D-Arabinose (**8**)	**41b** (6%)[a] (6%)[b]	**39b** (51%)[a] (61%)[b]	**39a** (20%)[a] (15%)[b]	–
D-Xylose (**7**)	**41c** (5%)[a] (6%)[b]	**39c** (67%)[a] (63%)[b]	–	–
D-Lyxose (**42**)	**41d** (5%)[a] (6%)[b]	**39d** (5%)[a] (3%)[b]	**39c** (41%)[a] (51%)[b]	**43** (10%)[a] (22%)[b]

[a] Pentose, Meldrum's acid, *t*BuNH$_2$ (1:2:1), 5 days, 40°C [109]

[b] Pentose, Meldrum's acid, Et$_3$N (1:1:1), 10 days 48–49°C [107, 108]



Scheme 9 Reaction of aldoses with pentane-2,4-dione (**1**) in alkaline aqueous media

the α-furanosides **47** predominated, was obtained (Fig. 5). Under further equilibration in basic medium, an almost exclusive formation of the β-glucopyranoside isomer **45a** was observed.

D-Mannose (**11**), D-galactose (**12**), D-maltose (**49**), and D-cellobiose (**50**) (Fig. 6) gave compounds **45b**, **c**, **d**, and **e** respectively [110–112] (Fig. 7, Table 3).

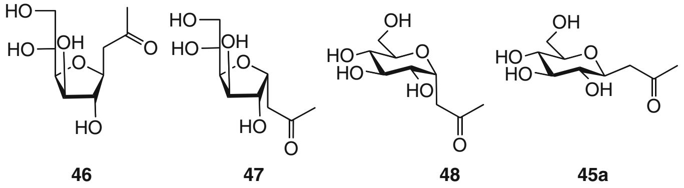


Fig. 5 The four possible α,β-furanosides **46** and **47,** and α,β-pyranosides stereoisomers **48** and **45a** obtained during the reaction of D-glucose with pentane-2,4-dione (**1**)

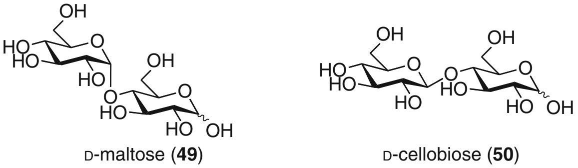


Fig. 6 Structure of D-maltose and D-cellobiose

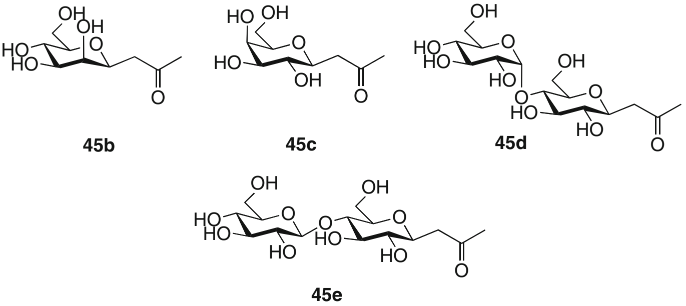


Fig. 7 Compounds obtained from D-mannose (**11**), D-galactose (**12**), D-maltose (**49**), and D-cellobiose (**50**)

Table 3 Reaction conditions and results for the condensation of unprotected carbohydrates with pentane-2,4-dione (**1**) in aqueous medium

Starting sugar	Conditions	Product (yield %)	References
D-Glucose (**10**)	H_2O, pentane-2,4-dione **1** (1.2 equiv.), $NaHCO_3$ (1.5 equiv.), 6 h, 90°C	**45a** (100)	[110]
D-Mannose (**11**)	H_2O, pentane-2,4-dione **1** (1.2 equiv.), $NaHCO_3$ (1.5 equiv.), 12 h, 90°C	**45b** (100)	[110]
D-Galactose (**12**)	H_2O/THF (2/1), pentane-2,4-dione **1** (2 equiv.), $NaHCO_3$ (4 equiv.), 24 h, 90°C	**45c** (90)	[112]
D-Maltose (**49**)	H_2O, pentane-2,4-dione **1** (1.2 equiv.), $NaHCO_3$ (1.5 equiv.), 12 h, 90°C	**45d** (91)	[111]
D-Cellobiose (**50**)	H_2O, pentane-2,4-dione **1** (1.2 equiv.), $NaHCO_3$ (1.5 equiv.), 12 h, 90°C	**45e** (100)	[111]

It is worth pointing out that the ketones derivatives **45a**, **45e** obtained in one step from D-glucose and D-cellobiose were previously prepared in seven and eight steps, respectively, and low overall yields from commercial 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose [113].

Riemann et al. [114] reported that, in certain cases, working a lower temperature, small amounts of the α-linked compounds as well as furan derivatives **3** were obtained.

Researchers of L'Oréal confirmed the results obtained by Lubineau's group and applied the reaction to other sugars such as D-xylose (**7**), D-lactose (**51**), D-fucose (**52**), D-arabinose (**8**), and 3-deoxy-D-arabinose (**53**) [115] (Fig. 8).

Using the experimental conditions described by Lubineau's group (Table 3), they obtained the corresponding β-D-linked ketones **54**–**59** in excellent to moderate yields (Fig. 9).

The effect of the base used for the condensation of xylose (**7**) with pentane-2,4-dione (**1**) was carefully examined. The best results were obtained using NaOH since **54** was obtained in 45 min at 50°C in 97% yield. Reduction of **54** gave **60**, an activator of glycosaminoglycans biosynthesis, launched on the market in cosmetic skincare products as Pro-Xylane™ by L'Oréal in 2006 [116, 117] (Fig. 10).

In the aim to prepare isosteric analogs of nucleotide-activated sugars, this straightforward method was applied to the preparation of *C*-glycosides related

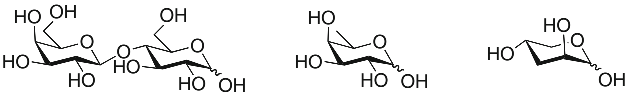
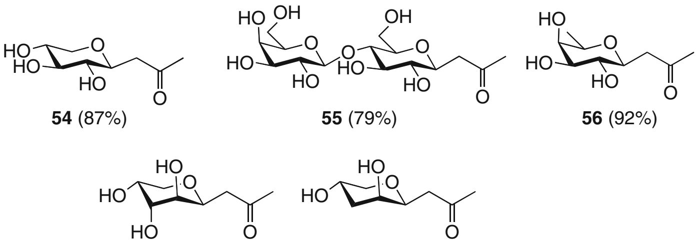

D-lactose (**51**) D-fucose (**52**) 3-deoxy-D-arabinose (**53**)

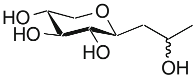
Fig. 8 Structure of D-lactose, D-fucose, and 3-deoxy-D-arabinose

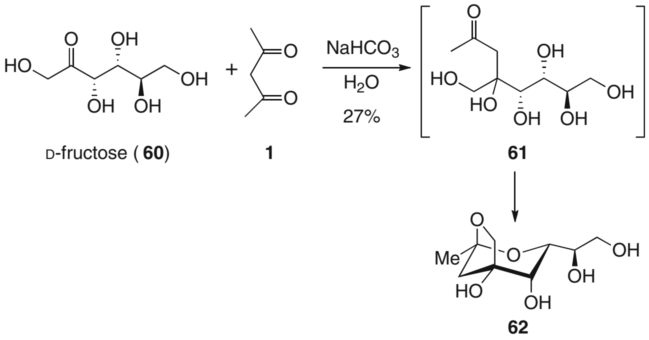

54 (87%) **55** (79%) **56** (92%)

58 (40%) **59** (59%)

Fig. 9 Compounds obtained from D-xylose (**7**), D-lactose (**51**), D-fucose (**52**), D-arabinose (**8**), and 3-deoxy-D-arabinose (**53**)

Fig. 10 Structure of Pro-Xylane™, an activator of glycosaminoglycans biosynthesis (L'Oréal)


Pro-Xylane™ (**60**)



Scheme 10 Reaction of D-fructose with pentane-2,4-dione (**1**) in alkaline aqueous media

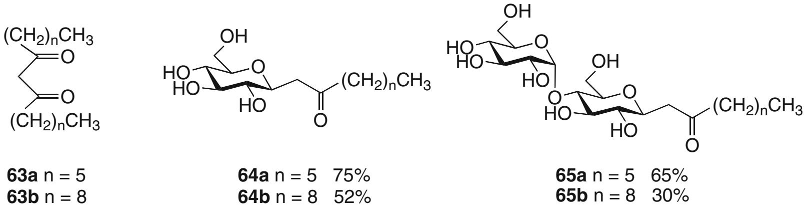


Fig. 11 Symmetrical fatty β-diketones **63** used to prepare the *C*-glycolipids **64** and **65**

to D- and L-*glycero*-β-D-*manno*-heptoses by the group of Kosma [118, 119]. Lichtenthaler and colleagues studied the application of this reaction to D-fructose (**60**) [120]. Surprisingly enough, a bicyclic product **62** was obtained in 27% yield by a double cycloketalization of the intermediate **61** (Scheme 10).

The use of other 1,3-dicarbonyl compounds as nucleophilic species was also investigated in this reaction. In particular, unsymmetrical diketones were tested in the condensation, giving rise to mixtures of *C*-glycosides [111, 114].

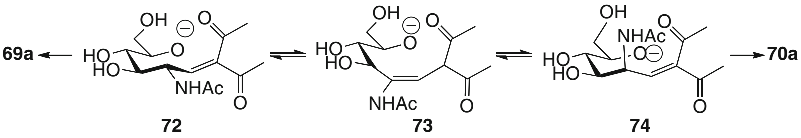
In order to prepare carbohydrate-based amphiphiles by this efficient methodology, symmetrical β-diketones **63a**, **b** were used [111]. The reactions of these diketones with D-glucose (**10**) in EtOH/H_2O as the solvent and $NaHCO_3$ as the base were complete and the *C*-glycolipids were isolated in 75% (**64a**) and 52% yield (**64b)** using the less soluble diketone **63b**. The condensation was also applied to D-maltose (**49**) to obtain **65a** or **65b** (Fig. 11) [111, 121].

The condensation of pentane-2,4-dione with unprotected *N*-acetyl-D-gluco-, manno-, and galactosamine (**66**, **67**, and **68**) in alkaline aqueous media was first investigated by Riemann et al. [114]. This group reported that the condensation of pentane-2,4-dione with *N*-acetyl-D-glucosamine (**66**) gave a 1:1 mixture of α- and β-*C*-glycosidic ketones in poor yield (36%). This reaction was reinvestigated and it was demonstrated that actually, *gluco* and *manno* *C*-glycosidic ketones **69a** and **70a** were obtained [112] (Fig. 11).

The formation of the *N*-acetyl-D-mannosamine ketone **70a** could be rationalized considering the alkaline epimerization of *N*-acetyl-D-glucosamine (**66**) giving

N-acetyl-D-mannosamine (**67**), but the intermediate **72** can undergo an epimerization to **74** (Scheme 11) through the formation of **73** before the Michael addition took place, as observed by Wen and Hulting in the preparation of *C*-linked glycophosphonates [122].

Using optimized conditions (pentanedione 2 equiv., $NaHCO_3$ 4 equiv., H_2O-THF 2:1, 90°C, 24 h), *N*-acetyl-D-glucosamine (**66**) gave the *gluco*- and *manno* ketones **69a** and **70a** in a 4:6 ratio and 83% yield, whereas *N*-acetyl-D-mannosamine (**67**) led to the same products in a 3:1 ratio and 40% yield. This poor yield has been explained by the instability of **70a** in the reaction mixture. These compounds were easily separated by crystallization of their acetylated derivatives **69b** and **70b.** Applied to *N*-acetyl-D-galactosamine (**68**), the same reaction conditions gave the *C*-glycosidic ketone **71a**, isolated as the acetylated compound **71b** (Fig. 12, Table 4).



Scheme 11 Possible intermediates involved in the reaction of *N*-acetyl-D-glucosamine (**66**) and *N*-acetyl-D-mannosamine (**67**)

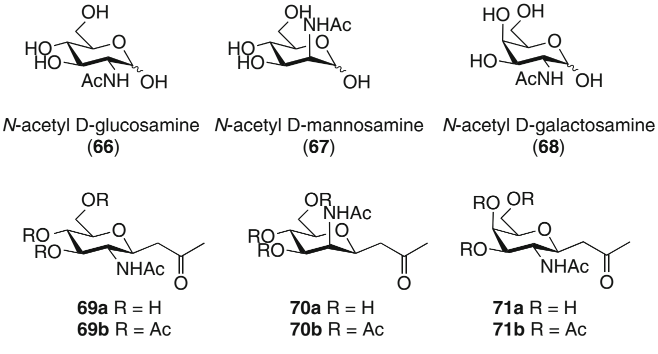


Fig. 12 Structure of *N*-acetyl-D-gluco-, manno-, and galactosamine and the *C*-glycosyl ketones derivatives

Table 4 Results for the aqueous condensation of *N*-acetylated amino sugars with 2,4-pentanedione (**1**) in the presence of $NaHCO_3$ at 90°C

Starting sugar	Products (ratio)	Yield (%)
N-Acetyl-D-glucosamine (**66**)	**69a 70a** (4:6)	83
N-Acetyl-D-mannosamine (**67**)	**69a 70a** (1:3)	40
N-Acetyl-D-galactosamine (**68**)	**71a**	50

4 Conclusion

An important task of today's chemistry is to design new products prepared from renewable starting materials and produced using green processes. This chapter has described many reactions that follow these concepts. The development of reactions allowing the transformation of carbohydrates without the use of the tedious protecting and deprotecting steps is of great interest because it allows time, money, and atom economies. The Knoevenagel reaction is one of these reactions; it can afford different types of compounds, depending on the acidic or basic catalysis employed, and its compatibility with the use of water as solvent make it particularly attractive in the context of green chemistry.

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Carbohydrate-Based Lactones: Synthesis and Applications

Nuno M. Xavier, Amélia P. Rauter, and Yves Queneau

Abstract The synthesis and uses of different kinds of carbohydrate-based lactones are described. This group of compounds includes aldonolactones, other related monocyclic lactones and bicyclic systems. The latter can arise from uronic acids, carboxymethyl ethers or glycosides, or from *C*-branched sugars.

Keywords Aldonolactones, Bicyclic lactones, Gluconolactone, Sugar lactones, Synthons, Uronic acids

Contents

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Abbreviations

AAPDH	2,2’-Azobis(2-amidinopropan) dihydrochloride
AD	Asymmetric dihydroxylation
AIBN	2,2’-Azobisisobutyronitrile
CMC	Critical micellar concentration
CMG	Carboxymethyl glycoside
CMGL	Carboxymethyl glycoside 2-*O*-lactones
CSA	Camphorsulfonic acid
DCC	Dicyclohexylcarbodiimide
DEAD	Diethyl azodicarboxylate
DIBAL-H	Diisobutylaluminum hydride
DMAP	4-(Dimethylamino)pyridine
DMJ	1-Deoxymannojirimycin
DNJ	Deoxynojirimycin
GABA	γ-Aminobutyric acid
mCPBA	*m*-Chloroperoxybenzoic acid
Ms	Mesyl (methanesulfonyl)
MW	Microwave irradiation
NBS	*N*-Bromosuccinimide
NeuAc	*N*-Acetyl neuraminic acid
NIS	*N*-Iodosuccinimide
NMO	*N*-Methylmorpholine *N*-oxide
Oct	Octoate (2-ethylhexanoate)
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Piv	Pivaloyl
PMPOH	*p*-Methoxyphenol

PPL	Porcine pancreatic lipase
Py	Pyridine
ROP	Ring-opening polymerization
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
Tf	Trifluoromethanesulfonyl (triflyl)
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TMEDA	*N*,*N*,*N*’,*N*’-Tetramethyl-1,2-ethylenediamine
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate
Ts	Tosyl, 4-toluenesulfonyl

1 Introduction

Carbohydrate lactones have found broad applications as building blocks for the synthesis of important bioactive compounds and natural products, and constitute a valuable family of synthons for diverse types of transformations. Previous survey articles were published by De Lederkremer [1], Lundt [2–4], and Fleet [5]. In this revision, emphasis will be given to sustainable approaches involving a limited number of steps, to environmentally friendly synthetic methodologies for conversion of these molecules into functional compounds, and to multi-step sequences for the preparation of more complex targets. Starting with simple and available aldonolactones, the chemistry of more elaborated carbohydrate-based lactones, such as α,β-unsaturated δ-lactones as well as other types of bicyclic systems will then be presented and discussed. Allying the chirality inherent to the sugar to the reactivity of the lactone functionality turns these classes of compounds into useful chemical intermediates towards a variety of purposes.

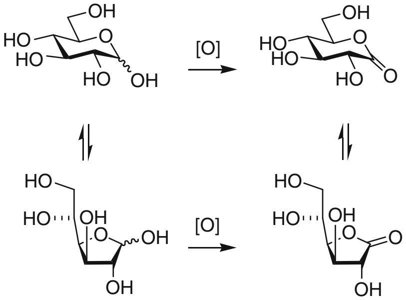
2 Aldonolactone Synthesis

2.1 General Aspects

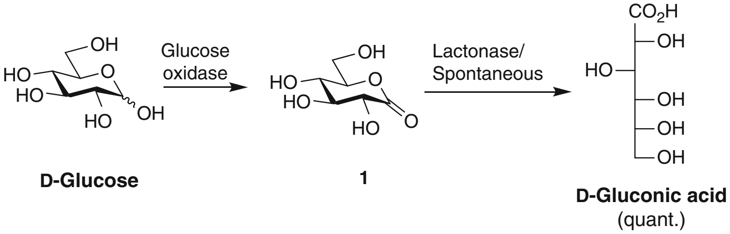
Aldonolactones are commercially available at low cost, when compared to most of the common monosaccharides. They are typically synthesized by selective anomeric oxidation of unprotected aldoses with bromine [6]. Usually the thermodynamically more stable five-membered lactone (γ-lactone) predominates over the six-membered form, with the exception of D-gluconolactone, which crystallizes as the 1,5-pyranolactone (δ-lactone) [7] (Scheme 1). Another method for the preparation of sugar lactones is the dehydrogenation of unprotected or partially protected alditols and aldoses catalyzed by a transition metal complex in the presence of a hydrogen acceptor [8–10]. Protected aldoses with a free anomeric hydroxyl group can be converted into the corresponding aldonolactones by common oxidation protocols, such as those employing chromium(VI) reagents [11] or DMSO-based oxidizing systems [12, 13]. Methods for aerobic oxidation of unprotected aldoses over heterogeneous catalysts, including Pd/C, Au/C, or a combination of Bi-Pd/C, have also been developed [14–17]. However enzymatic processes for the synthesis of aldonolactones/aldonic acids are preferred on the industrial scale.

2.2 Glucono-1,5-Lactone

Glucono-1,5-lactone (δ-D-gluconolactone, **1**) is the cyclic ester of D-gluconic acid, which is produced on the industrial scale by enzymatic oxidation of glucose (for a review of the production, properties, and applications of gluconic acid and its derivatives see [18]). This process is mediated by enzymes from selected micro-organisms, including bacteria such as *Pseudomonas* or *Gluconobacter oxydans* and fungi such as *Aspergillus niger*. The method involving *A. niger* is widely used and is based on glucose oxidase. The oxidation pathway consists in the oxidation of glucose to δ-D-gluconolactone, which is mediated by the latter enzyme, followed by hydrolysis to gluconic acid, which may occur spontaneously or be promoted by the lactonase enzyme (Scheme 2). After the fermentation process, the lactone can simply



Scheme 1 Formation of 1,4 and 1,5-lactone from D-glucose



Scheme 2 Oxidation of D-glucose by *Aspergillus niger*

be recovered from the broth by crystallization. Under appropriate conditions, glucose can be quantitatively converted into gluconic acid. About 100,000 tons of D-gluconic acid, mainly used in the food industry, are produced annually worldwide [19]. Glucono-1,5-lactone (**1**) has widespread application as a food additive, particularly in dairy products, confectionery, and meat.

2.3 Other Aldono-1,5-Lactones

Glycosyl azides have been shown to be useful precursors for the synthesis of aldonolactones. A viable one-pot procedure for the conversion of per-*O*-alkylated glycopyranosides into the corresponding aldono-1,5-lactones is based on the formation of glycosyl azide intermediates by treatment of the substrates with trimethylsilyl (TMS) azide in the presence of tin(IV) chloride, followed by hydrolysis [20]. In other work, aldono-1,4-lactones and aldono-1,5-lactones could be prepared from glycosyl azides via a two-step methodology consisting in the *N*-bromosuccinimide (NBS) mediated bromination and subsequent hydrolysis of corresponding *N*-bromoiminolactone intermediates [21].

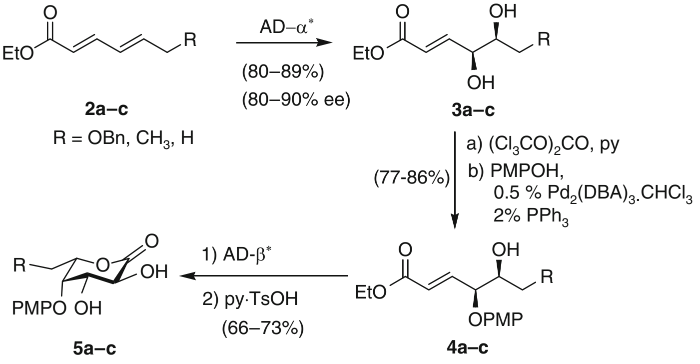
Bierenstiel and Schlaf [22] were able to prepare and isolate for the first time the less stable δ-D-galactonolactone by oxidation of galactose with the Schvo's catalytic system, which is based on the dimeric ruthenium complex $[(C_4Ph_4CO)(CO)_2Ru]_2$. The transformation led to the δ-galactonolactone in 93% yield, against 7% of the isolated γ-lactone isomer. This procedure also allowed the preparation of δ-D-mannonolactone in a much better yield (94%) than that reported in an early procedure [23] based on crystallization from a solution of calcium mannonate in aqueous oxalic acid.

O'Doherty and co-workers have explored the use of 2,4-dienoates as precursors for δ-galactonolactones [24, 25]. The synthetic approach involved sequential dihydroxylation steps of the dienoates (**2a–c**) double bonds by Sharpless AD-mix reagent systems (Scheme 3). After the first enantioselective dihydroxylation step, the resulting γ,δ-dihydroxyenoate intermediates (**3a–c**) were protected at the γ-hydroxyl group as cyclic carbonates, which were then treated with *p*-methoxyphenol (PMPOH) in the presence of a Pd(0) catalyst. The resulting 4-*O*-protected derivatives (**4a–c**) were submitted to diastereoselective dihydroxylation affording triols possessing *galacto* configuration, which were then lactonized to give the target L-galactono-1,5-lactones (**5a–c**) or their enantiomers, depending on the order in which the Sharpless reagents were applied [24].

2.4 Aldono-1,4-Lactones

An efficient method for preparing aldono-1,4-lactones (γ-aldonolactones) as the single products from oxidation of unprotected or partially protected monosaccharides was reported [9]. It consisted in treatment of the latter by catalytic amounts of $[RuH_2(PPh_3)_4]$, in the presence of an excess of benzalacetone (*trans*-4-phenylbut-3-en-2-one) as the hydrogen acceptor, in DMF. The corresponding γ-lactones were obtained in excellent yields, even in the case of D-glucose, for which no 1,5-lactone was observed. The results suggested that the oxidation step is followed by a ring contraction mechanism, probably promoted by coordination of the catalyst to the endocyclic oxygen and to the carbonyl group, facilitating ring opening and its closure into the more thermodynamically stable five-membered form.

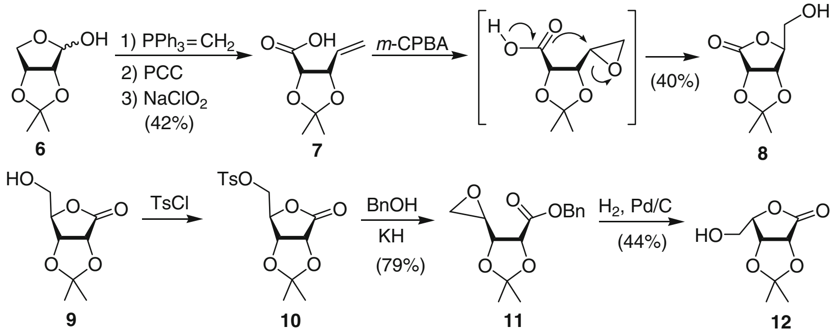
L-Aldonolactones are much less available than their D-enantiomers. Their potential to serve as chiral building blocks for L-sugar derivatives also makes them molecular targets of interest. Stereoselective approaches involving few steps leading to 2,3-*O*-isopropylidene-L-ribono-lactones and L-lyxono-1,4-lactones were reported by Rao and Lahiri [26]. The L-ribono derivative could be synthesized in three steps starting from the easily available isopropylidene-D-erythrose (**6**) (Scheme 4). It was converted into the unsaturated acid **7** by Wittig olefination and further oxidation. Epoxidation of the latter afforded the desired 1,4-lactone



AD–α* = 2% OsO4, 4% $(DHQ)_2PHAL$, 3 eq $K_3Fe(CN)_6$, 3 eq K_2CO_3, 1 eq $MeSO_2NH_2$

AD-β* = 2% OsO4, 4% $(DHQD)_2PHAL$, 3 eq $K_3Fe(CN)_6$, 3 eq K_2CO_3, 1 eq $MeSO_2NH_2$

Scheme 3 Synthesis of L-galactono-1,5-lactones from 2,4-hexadienoates



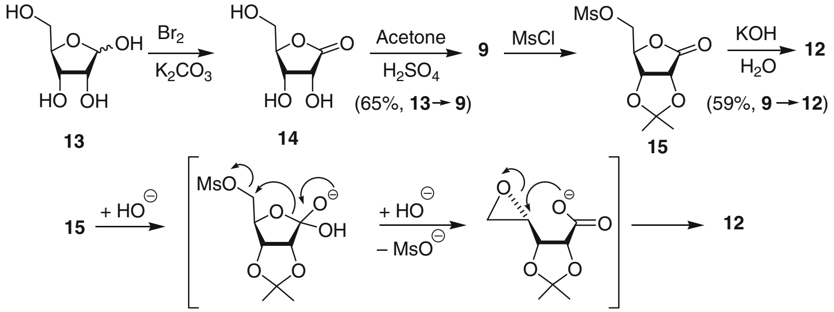
Scheme 4 Synthesis of 2,3-*O*-isopropylidene L-ribono- and L-lyxono-1,4-lactones

(**8**) in 40% yield, due to cyclization of the intermediate epoxide promoted by silica gel when attempting product separation by column chromatography. The synthesis of the L-lyxono-1,4-lactone derivative (**12**) was accomplished starting from D-ribono-1,4-lactone (**9**), of which the 5-*O*-tosyl derivative **10** was treated with the potassium salt of benzyl alcohol to give the epoxy benzyl ester **11,** furnishing directly on catalytic hydrogenation the target compound in 44% yield.

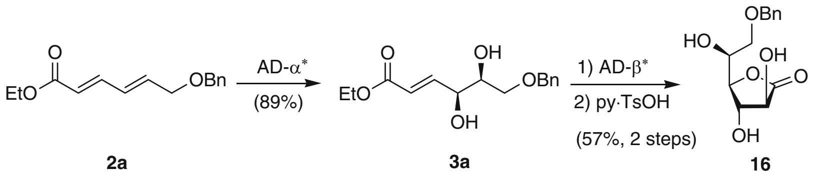
More recently, a simple synthetic route for a large scale production of **12** (2,3-*O*-isopropylidene-L-lyxonolactone) was described [27]. The chosen starting material was D-ribose (**13**), which was oxidized to the corresponding lactone **14** (Scheme 5). The latter was submitted *in situ* to acetonation to provide the 2,3-*O*-isopropylidene derivative **9**, which was then mesylated at OH-5. Treatment of the crude 5-*O*-mesylate **15** with potassium hydroxide led to **12** according to the mechanism proposed in Scheme 5.

L-Galactono-1,4-lactone (**16**) is prepared in three steps (51%, overall yield) from **2a** applying two successive asymmetric dihydroxylations (ADs) [25] (Scheme 6).

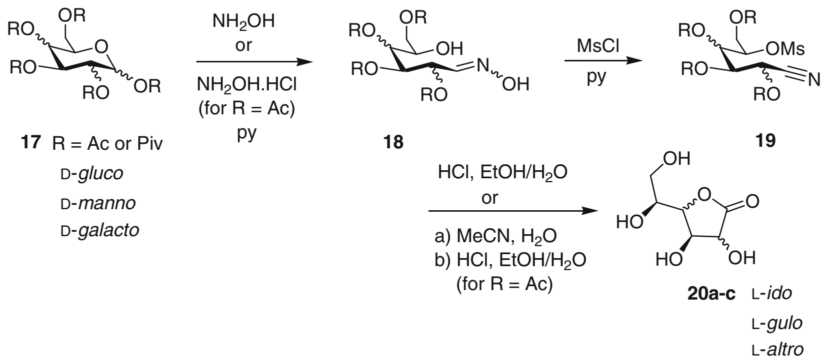
L-Aldono-1,4-lactones can be prepared from D-aldose perpivaloates and peracetates (compounds of type **17**) [28]. The method implies formation of aldoximes (**18**), followed by mesylation (Scheme 7). The resulting 5-*O*-mesyl glyconitrile derivatives (**19**) are then submitted to acid-catalyzed hydrolysis giving the corresponding 1,4-lactones **20a–c**.



Scheme 5 Process for a large scale production of 2,3-*O*-isopropylidene-L-lyxono-1,4-lactone



Scheme 6 L-Galactono-1,5-lactones from 2,4-hexadienoates



Scheme 7 L-Aldono-1,4-lactones from D-aldose perpivaloates and peracetates

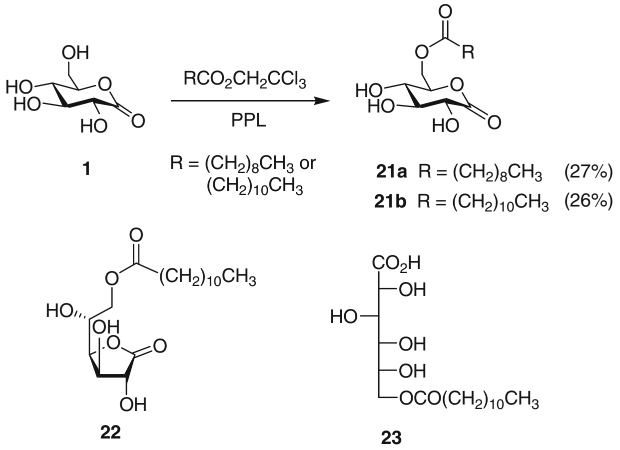
3 Aldonolactones as Useful Chirons

The use of aldonolactones for the preparation of carbasugars and iminosugars has been well explored and documented, particularly by Lundt's group [2–4, 29–31]. Fleet has also given an overview of the utility of sugar lactones as synthons for biologically active compounds [5] and his research group has made major contributions to the synthesis of sugar amino acids from aldonolactones [32–34]. We review here the syntheses of *C*-glycosyl compounds, L-sugars, aza- and thiosugars, natural products and of surfactants and related polymers that make use of aldonolactones as starting materials.

As shown in chapter, "Synthetic polymers from readily available monosaccharides" by J.A. Galbis and M.G. Garcia-Martin, aldonolactones are useful monomeric materials for the synthesis of biodegradable polymers and bio-compatible polymers for medicinal applications.

3.1 Synthesis of Surfactants and Polymers

Among the aldonolactone-based surfactants are aldonolactone-linked fatty esters which have been prepared by selective acylation of unprotected aldono-1,4-lactones or aldono-1,5-lactones. One of the first reported examples of this type of surfactant was applied to the enzymatic synthesis of 6-*O*-alkanoylgluconolactones [35]. Thus, 6-*O*-decanoyl- and 6-*O*-dodecanoyl- derivatives (**21a** and **21b**, respectively, Scheme 8) were obtained in 26–27% yield by esterification of glucono-l,5-1actone (**1**) at C-6 with the corresponding 2,2,2-trichloroethyl carboxylate in the presence of porcine pancreatic lipase (PPL) as catalyst. Compounds **21a**,**b** are soluble in water at 90–96°C but precipitate when cooled to 30–37°C. NMR and GC-MS analysis after dissolution and precipitation indicated the presence in the mixture of compound **21b**, the glucono-l,4-1actone-derived ester **22,** and the



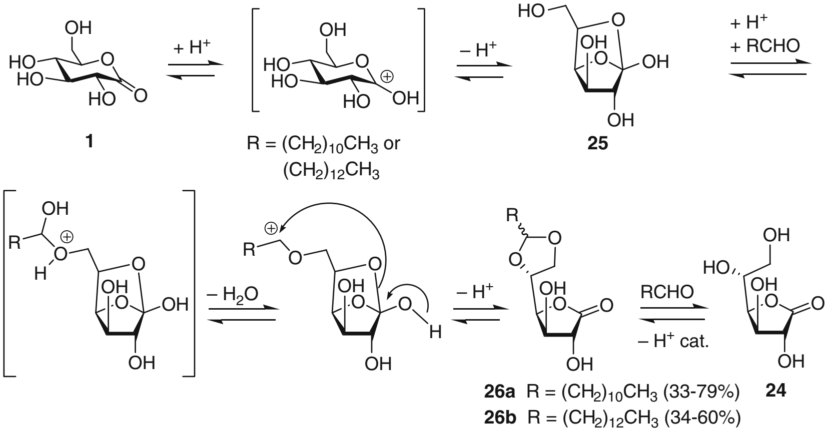
Scheme 8 Enzymatic synthesis of 6-*O*-alkanoylgluconolactones

acyclic dodecanoylgluconic acid **23**, the latter being the major compound. This demonstrates that dissolution of **21b** occurs with hydrolysis of the lactone moiety giving a more soluble mixture of compounds that are more appropriate for detergent applications than the dodecanoylglucono-1,5-lactone itself.

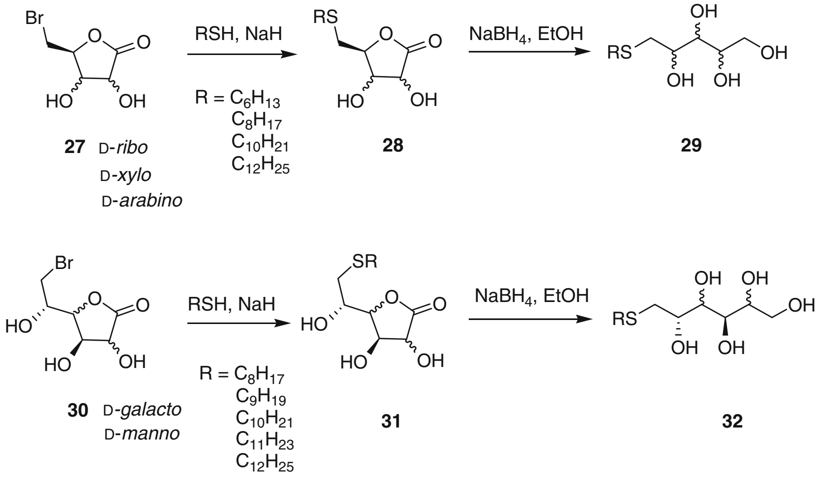
Acylation of D-glucono-1,4-lactone and D-glucono-1,5-lactone with *N*-(11-undecenoyl)-1,3-thiazolidine-2-thione in the presence of triethylamine gave 6-*O*-undecenoyl ester as the single product. In the case of the 1,5-lactone, isomerization to the 1,4-lactone-derived ester was observed, and quantitative conversion was attained when sodium hydride was used as base. In contrast with the expected regioselectivity at OH-6, acylation of L-galactono-1,4-lactone proceeded only at OH-2 although with a rather low yield (ca. 20%). Alternatively, the enzymatic route, employing *Candida antartica* and an ester, proved to be more efficient, affording only 6-*O*-acylated-1,4-lactone derivatives in yields up to 76 and 85%, by acylation of D-glucono-1,5-lactone and L-galactono-1,4-lactone, respectively. The conversion was shown to increase with the electron-withdrawing character of the ester, while acids proved to be virtually unreactive as acylating agents [36].

Another type of amphiphilic-like structure in which an aldonolactone moiety is present was prepared by acetalization of D-glucono-1,4-lactone (**24**) and D-glucono-1,5-lactone (**1**) with dodecanal or tetradecanal in the presence of methanesulfonic acid (Scheme 9) [37]. Both lactone isomers led to 1,4-lactone acetal derivatives **26a**, **b** in optimized yields up to 60–79%. A mechanism for the ring contraction was proposed, involving a hemi-orthoester (**25**) as a key intermediate in the addition to the aldehyde. Then, opening of an intermediate bicyclic-fused system and concomitant cyclization led to the acetal **26**.

In the context of the synthesis of carbohydrate-based amphiphilic (alkylsulfanyl) polyols, Beaupère and co-workers explored the access to 5- and 6-alkylsulfanyl derivatives of pentono- and hexonolactones and their corresponding 1-(alkylsulfanyl) pentitol or 1-(alkylsulfanyl)hexitol [38, 39]. Bromolactones **27** and **30** were treated



Scheme 9 Acetalization of D-glucono-1,4-lactone and D-glucono-1,5-lactone with dodecanal or tetradecanal



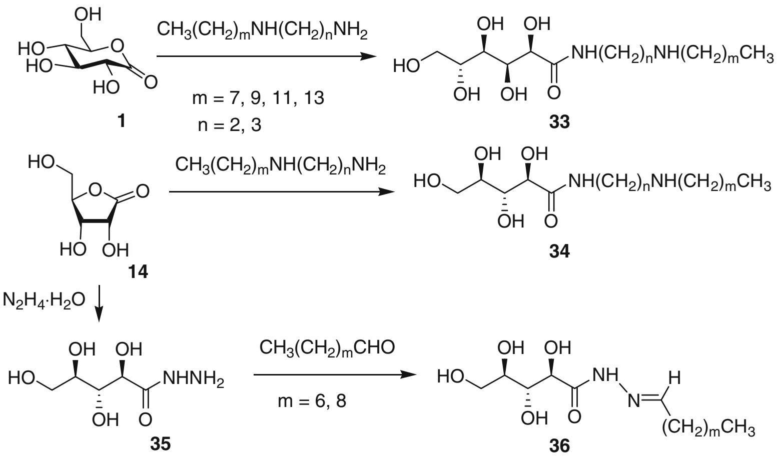
Scheme 10 Amphiphilic (alkylsulfanyl)aldonolactones and corresponding alditols

with alkanethiol in the presence of sodium hydride (Scheme 10) giving compounds **28** and **31**, respectively, in good yields (72–95%). Subsequent lactone reduction with $NaBH_4$ provided the 1-*S*-alkyl-1-thio-alditol derivatives **29** and **32**, respectively. Physico-chemical studies demonstrated surface activity for all compounds **28**, except for the D-ribono derivatives for which no critical micellar concentration (CMC) value was detected [40]. Apart from the lyxitol series, the pentitol derivatives of type **29** were shown to be more efficient in reducing the surface tension than their cyclic counterparts **28**. The mesophasic properties of **28** and **29** were also evaluated [41]. Most of the compounds gave lyotropic and thermotropic liquid crystals, except for the series of D-ribonolactones. This singular behavior for the *ribono* derivatives **28** was ascribed to the position of the vicinal hydroxyl groups which are in the same side of the cycle, favoring intramolecular hydrogen bonding.

It has been known for more than 50 years that carbohydrate lactones undergo ring opening by amines. Using long chain primary amines gives access to amphiphilic structures that are emulsifying agents [42, 43] or liquid crystals [44–47]. The preparation of *N*-arylgluconoamides and *N*-alkylgluconoamides by opening of D-glucono-1,5-lactone, and their subsequent conversion into thiogluconamide derivatives, are reported [48]. Some amphiphilic alkyl aldonamides and diacetylenic aldonamides have the propensity to aggregate into supramolecular assemblies, leading to different structural morphologies [49–52]. Amphiphilic glycodendrimers containing aldonoamide moieties at their molecular surfaces have been prepared by coupling polyamine dendrimers with 1,5-D-glucono-1,4-lactone [53–55]. Such macromolecules are shown to behave as unimolecular micelles in water able to solubilize hydrophobic compounds in the dendritic cavities [55]. Highly enantioselective ketone reduction have been carried out in the presence of these systems.

In recent work [56] aldonoamides (**33**, **34**) have been synthesized in moderate to good yields by addition of long-chain *N*-monoalkylated diamines to D-glucono-1,5-lactone **1** or D-ribono-1,4-lactone **14** (Scheme 11). In addition, hydrazones **36** have been obtained by treatment of the intermediate ribonohydrazide **35** with octanal or decanal. All compounds derived from ribonolactone showed moderate activity against *M. tuberculosis*. Some ribonoamides were also active against *Staphylococcus aureus*. The activities increased somewhat with the elongation of their hydrocarbon chains.

The use of carbohydrates as raw materials for the generation of polymers has attracted particular interest in the last two decades not only because of concerns related with sustainability and biocompatibility, but also due to the unique mechanical and physical properties that the sugar units may provide to the material (for

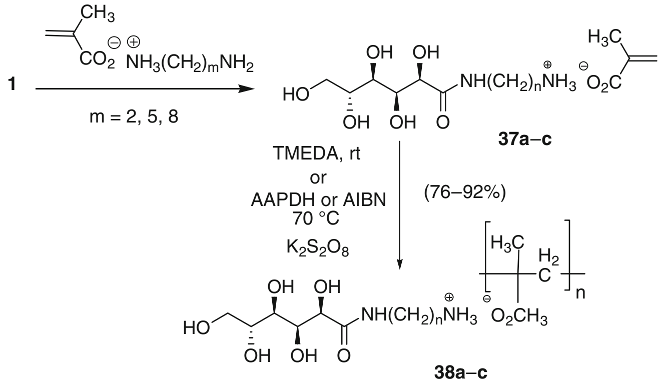


Scheme 11 Amphiphilic compounds by ring-opening of aldonolactones

reviews on carbohydrate-based polymers see [57–59]). The hydrophilic sugar moiety contributes to the specific three-dimensional structure of the polymer and increases its hydrophilicity and water solubility. Due to their particular characteristics, glycopolymers have found interesting applications as flocculating agents, detergents, surface modifiers, and also in the biomedical field as biomaterials for tissue regeneration, as drugs, and for gene delivery systems (See chapter, "From natural polysaccharides to materials for catalysis, adsorption and remediation", by Quignard, Di Renzo and Guibal, and chapter, "Synthetic polymers from readily available monosaccharides", by Galbis and Garcia-Martin).

One of the approaches employed to achieve sugar-based polymers consists in the preparation of monomers comprising the sugar moiety and a polymerizable double bond. Aldonolactones can be useful starting materials for this type of monomers, allowing the introduction of the polymerizable part through selective monofunctionalization of the lactone, without the use of protecting groups. The connection of both parts can be accomplished, for example, through amide linkages. One of the first reported examples applying this approach [60] involved the addition of an aminoalkyl ammonium methacrylate salt, derived from a diamine and methacrylic acid, to D-glucono-1,5-lactone **1** (Scheme 12). The resulting ionic monomers **37** were then subjected to homopolymerization in the presence of a free-radical initiator to give the corresponding polymers **38** in good yields. Studies of the viscosity of their aqueous solution showed a decrease of this parameter when increasing the concentration, proving their polyelectrolyte nature. NMR analysis of polymers **38** revealed their predominant syndiotatic structure. The monomer **37a** ($n = 2$) was also copolymerized with 1-vinylpyrrolidin-2-one and methacrylamide, affording water-soluble copolymers.

Aldonolactones serve as suitable monomers for the generation of homo- and copolymers, especially through ring-opening polymerization (ROP). Among them are the carbohydrate-analogs of ε-caprolactone, i.e., aldono-1,6-lactones. The first example of such derivatives and further ROP was reported by Galbis and co-workers [61], see also chapter, "Synthetic polymers from readily available monosaccharides"



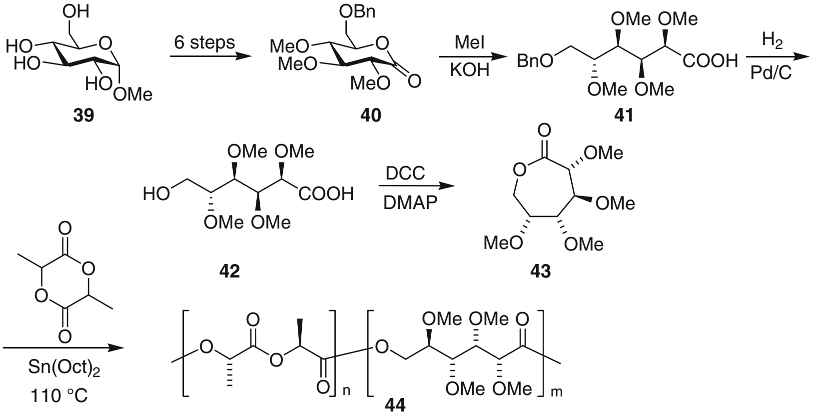
Scheme 12 Gluconolactone-derived vinyl monomers and their polymerization

by J.A. Galbis and M.G. Garcia-Martin. Two alternative routes leading to tetra-*O*-methyl-D-glucono-1,6-lactone **43** were employed, one of them involving the intermediate protected glucono-1,5-lactone **41**, which was prepared from methyl D-glucopyranoside **39**. Opening of the lactone ring of **40**, methylation, and hydrogenation led to the ω-hydroxygluconic acid derivative **42**, which was subsequently converted into **43** by lactonization (Scheme 13). Attempts to homopolymerize **43** failed. However, its copolymerization by bulk ROP with L-lactide Z, using stannous octoate as initiator, provided two copolymers of type **44** containing up to 2.2% of the carbohydrate monomer.

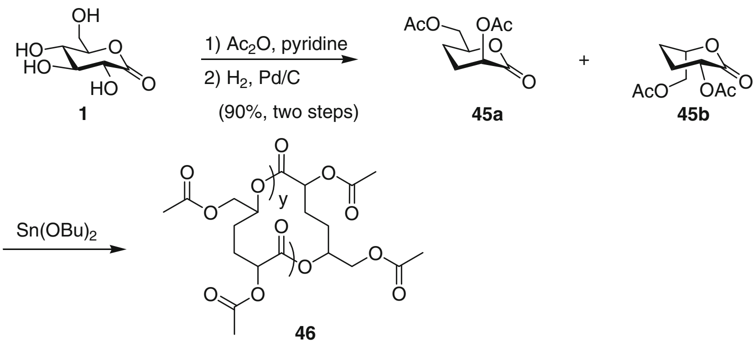
Williams and co-workers [62] have recently explored the ROP of acetylated aldono-1,5-lactones to investigate their propensity to oligomerize/polymerize by a metal alkoxide initiator. Hence, treatment of tetra-*O*-acetyl-D-glucono-1,5-lactone with butane-1,4-diol and stannous octanoate produced only a mixture of mono-, di-, and trialdaric esters. The latter were then subjected to copolymerization with [*R*,*S*]-lactide using an alkyl zinc initiator, which furnished triblock ABA copolyesters. Soon afterwards, the same group reported the ROP of 3,4-dideoxy-aldonolactones **45**, which were prepared in two steps from D-glucono-1,5-lactone (**1**) [63]. The polymerization was performed in the presence of $Sn(OBu)_2$, providing mainly cyclic polyesters **46** (Scheme 14).

An interesting type of polymeric network has been obtained by polymerization of D-gluconolactone (**1**) and citric acid (**47**) (Scheme 15) [64]. Instead of proceeding by an ROP mechanism, this polymerization was shown to occur through the esterification reaction between the hydroxyl groups of gluconolactone or citric acid and the carboxylic acid of citric acid, affording biodegradable cross-linked polyesters (**48**).

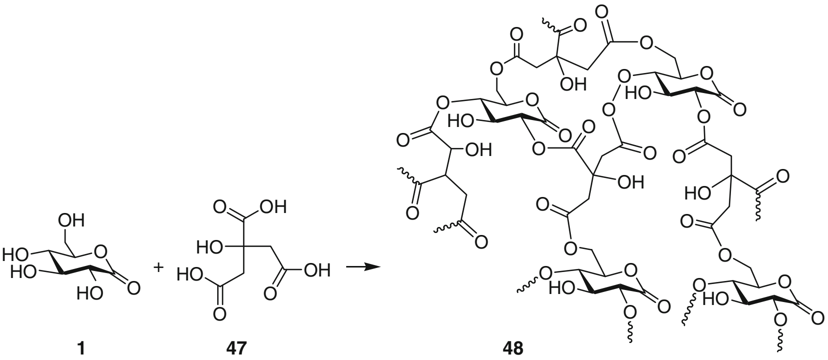
Polyhydroxypolyamides have attracted significant attention since they are more hydrophilic and biodegradable than nylons. Sugar amino acids [65] or aldaric acid



Scheme 13 Synthesis of a ω-hydroxygluconic acid from a protected glucono-1,5-lactone derivative and further copolymerization with L-lactide



Scheme 14 Ring-opening polymerization (ROP) of acetylated aldono-1,5-lactones



Scheme 15 Polymerization of D-gluconolactone and citric acid

derivatives [66, 67] are among the carbohydrate precursors that have been employed for the synthesis of these polyamides.

Simple syntheses of suitable monomers for nylon 5 and nylon 6 analogs, such as 5-amino-5-deoxyaldonic and 6-amino-6-deoxyaldonic acids (**51**, **54**), has been achieved starting from unprotected D-pentono- and hexono-1,4-lactones [68, 69]. Saponification of 5- or 6-azido-D-aldonolactones (*ribo*-, *arabino*-, *xylo*-, *galacto*-, *manno*-, compound types **49** and **52**) provided the corresponding 5- or 6-azido-aldonic acid sodium salts (**50**, **53**). A catalytic hydrogenation after or before treatment with acidic resin afforded compounds **51** and **54** in excellent overall yields (Scheme 16).

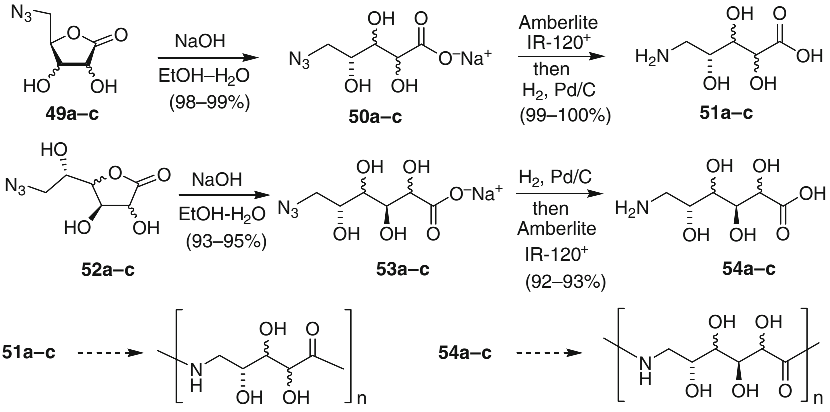
More recently, a similar synthetic strategy involving 2-azido-2-deoxy-D-xylono-1,4-lactone and 2-azido-2-deoxy-D-lyxono-1,4-lactone precursors has been applied for the synthesis of polyhydroxy-α-amino acids, namely (–)-polyoxamic acid and 3,4-diepipolyoxamic acid [70].

Aldonolactone-based fluorinated surfactants have also been reported [71].

3.2 *Synthesis of C*-Glycosyl Compounds

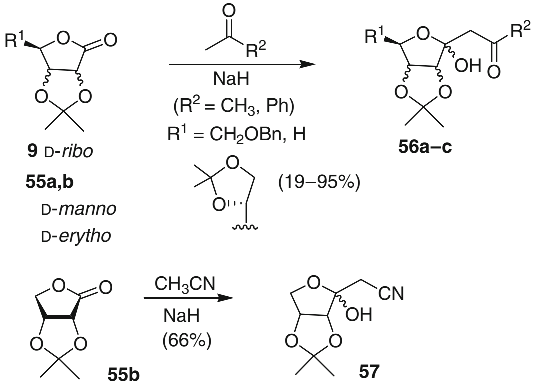
C-Glycosyl compounds are important molecular targets as they occur in Nature and have interesting biological properties (for reviews on C-glycosylation, see [72–75]). Chain extensions of aldonolactones have been employed to create C–C bond formation at the anomeric center. Claisen-type reactions of aldono-1,4-lactones (e.g., **9**, **55**) with acetone or acetophenone (Scheme 17) generate hemiacetals of type **56a–c** [76]. Similarly, lactone **55b** reacts with CH_3CN/NaH to give hemiacetal **57**.

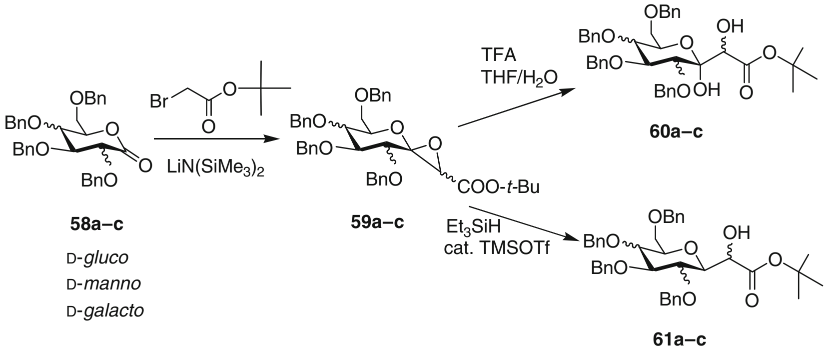
Using the enolate of *tert*-butyl bromoacetate with 1,5-lactones **58** (Scheme 18) led directly to exocyclic epoxides **59**, which were subsequently transformed into compounds **60** [77]. Alternatively, cationic reduction of epoxides **59a–c** provided *C*-glycosyl compounds **61a–c**. Upon esterification of the latter as



Scheme 16 Synthesis of 5-amino-6-deoxy- or 6-amino-6-deoxyaldonic acid monomers

Scheme 17 *C*-Glycosylation by Claisen-type reaction of aldono-1,4-lactones with acetone, acetophenone, or acetonitrile





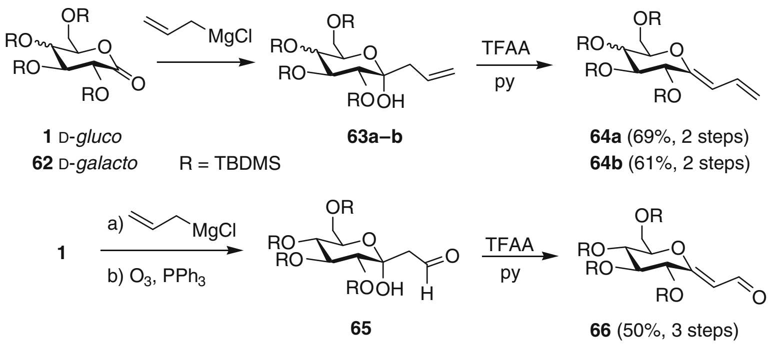
Scheme 18 Claisen condensation of aldono-1,5-lactones leading to exocyclic epoxides and further conversion into *C*-glycosyl derivatives

trifluomethanesulfonates, reaction with primary amines furnished the corresponding *C*-glycosylamino esters.

Olefination of protected aldonolactones is a convenient approach to *C*-glycosylation that furnishes *C*-glycosylidene derivatives, often referred to as "*exo*-glycals" [78]. Activated olefins, such as 1-*C*-dichloromethylene [79], 1-*C*-methoxycarbonylmethylene [80], and 1-*C*-cyanomethylene derivatives [81], have been obtained by direct Wittig-type olefination of aldonolactones. Hydrogenation of the *C*-glycosylidene compounds produces the corresponding *C*-glycosyl derivatives with high stereocontrol. However, *exo*-glycals resulting from partially protected aldonolactones, and that possess free hydroxyl groups appropriately located in the sugar ring, were shown to undergo 1,4-addition within the activated double bond to give bicyclic derivatives [82]. This propensity for activated *exo*-glycals to act as Michael acceptors permits the synthesis of *N*-glycosyl β-amino esters through stereoselective 1,4-addition of benzylamine, followed by reduction [83]. The latter compounds can be manipulated as standard amino acids and can enter into peptide synthesis. The synthesis of a variety of tri- and tetrasubstituted *exo*-glycals was accomplished from tetra-*O*-benzyl-D-glucono-1,5-lactone applying a modified Julia olefination procedure [84].

Another method for the alkylidenation of aldonolactones uses addition of organometallic reagents [78]. For example, Lin et al. [85] described an efficient route to conjugated anomeric dienes or aldehydes based on the reaction of aldono-1,4- and aldono-1,5-lactones (**1**, **62**) with allylmagnesium chloride (Scheme 19), giving allyl hemiacetals (e.g., **63a**, **b**). Hemiacetal can be dehydrated [e.g., with $(CF_3CO)_2O$] to produce dienes **64a**, **b**, or ozonolyzed (e.g., to give **65**).

C-Glycosyl aromatic compounds are particularly relevant owing to their presence in a variety of biologically important natural products, including antibiotics (for reviews concerning the synthesis and biological profile of C-glycosyl aromatic compounds, see [86–89]). Based on the method of Sulikowski and co-workers [90], Li et al. [91] developed an efficient one-pot procedure for the synthesis of a series of



Scheme 19 *C*-Glycosyl derivatives by addition of allylmagnesium chloride to aldonolactones

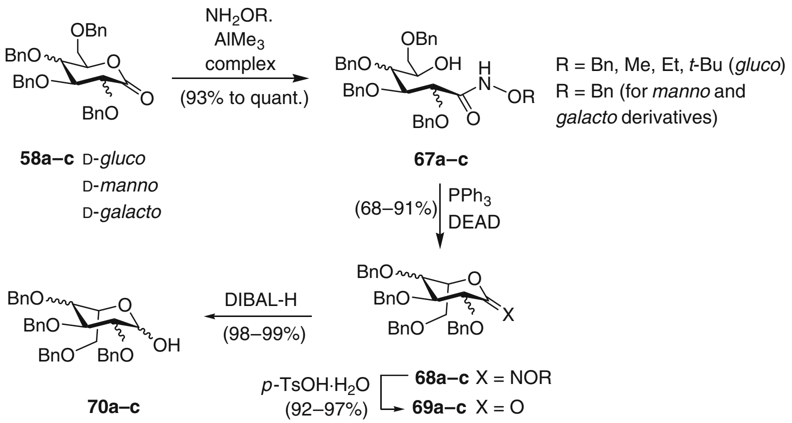
C-aryl glycals in 75–92% yields. It consisted in the addition of aryllithium reagents to variously protected 2-deoxy-aldono-1,5-lactones, followed by treatment with a mixture of pyridine (Py), 4-(Dimethylamino)pyridine (DMAP), and trifluoroacetic anhydride (TFAA).

3.3 Synthesis of L-Aldoses

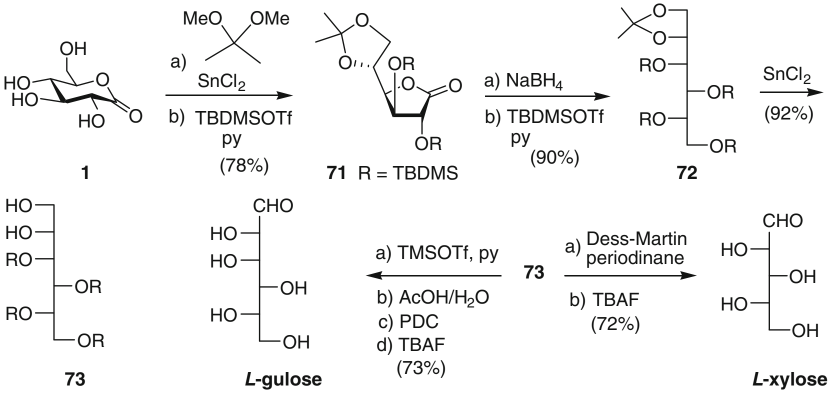
L-Aldoses are scarcely available from natural resources. However, their utility as building blocks for natural products and analogs has prompted the search for efficient methods for their synthesis. Lipták and co-workers [92] have prepared L-glucose through standard manipulations starting from D-gulono-1,4-lactone. The synthetic pathway included conversion of the lactone into 1,2,3,4,5-penta-*O*-benzyl-D-gulitol, 1,2,3,4,5-penta-*O*- acetyl-D-gulitol, or 1,2,3,4,5-penta-*O*-benzoyl-D-gulitol, oxidation at C-6 to the corresponding aldehydes, and further deprotection with concomitant pyranose ring closure. Yields in L-glucose ranged from 34 to 53% overall yield, the best one being obtained from the penta-*O*-acetyl-D-gulitol derivative.

A general and effective four-step procedure for the conversion of D-hexono-1,5-lactones into L-hexoses was developed [93]. It involved alkoxyamination of tetra-*O*-benzyl-aldono-1,5-lactones **58a–c** mediated by Me_3Al to provide the corresponding δ-hydroxyalkoxamates **67a–c**, which were then engaged into an intramolecular cyclization under Mitsunobu displacement conditions (Scheme 20). This cyclization occurred mainly via *O*-alkylation, affording the corresponding oxime derivatives **68a–c** in good yields, all with the expected inversion of configuration at C-5. At this stage, the acid-catalyzed hydrolysis of the oximes to the parent L-glycono-1,5-lactones **69a–c** provided, after reduction with diisobutylaluminum hydride (DIBAL-H), the corresponding tetra-*O*-benzyl-L-hexoses **70a–c**.

A relatively short route has been presented to convert D-glucono-1,5-lactone (**1**) into L-xylose and L-gulose [94] (Scheme 21). Acetalization of **1** gave **71**, the



Scheme 20 Conversion of D-hexono-1,5-lactones into L-hexoses via δ-hydroxyalkoxamate derivatives



Scheme 21 Synthesis of L-aldoses from D-glucono-1,5-lactone

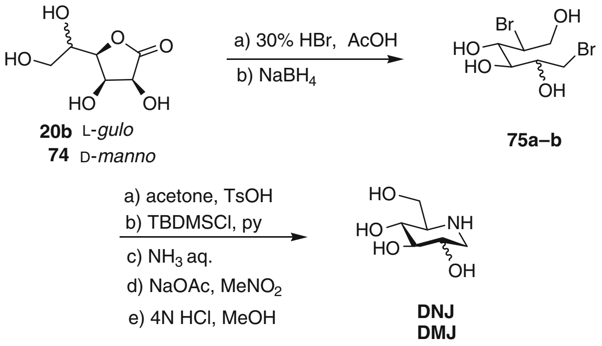
reduction of which with NaBH$_4$ and subsequent silylation afforded **72**. Deacetylation with SnCl$_2$ gave **73** which was converted either into L-gulose or L-xylose applying standard reactions.

3.4 Synthesis of Iminoalditols and Analogs

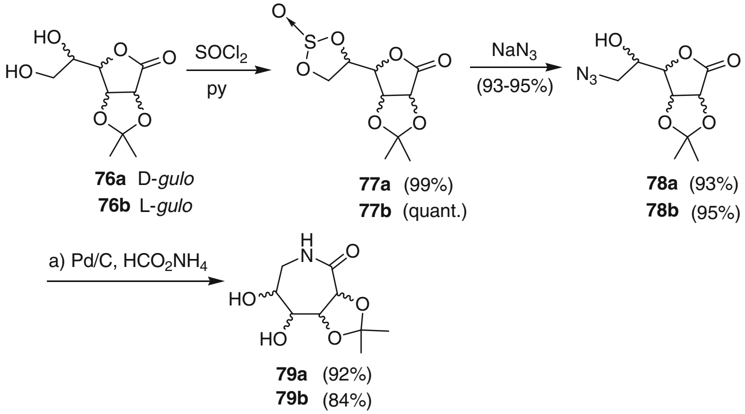
Imino sugars (or imino-dideoxyalditols) are alditols in which the ring ethereal moiety has been replaced by an amino group. These sugar mimetics are potential therapeutic agents, particularly due to their ability to act as glycosidase inhibitors [95].

Among them are found the naturally occurring 1-deoxynojirimycin (DNJ) and 1-deoxymannojirimycin (DMJ) [96]. Practical syntheses of DNJ and DMJ start from L-gulono-1,4-lactone (**20b**) and D-mannono-1,4-lactone (**74**), respectively [97]. Key intermediates are 2,6-dibromo-2,6-dideoxy-D-alditol derivatives **75a** and **75b** obtained by 2,6-dibromination of the starting lactones, followed by reduction with $NaBH_4$ [98, 99]. Then a five-step sequence involving selective partial protection, introduction of an amine functionality, and intramolecular *N*-alkylation, lead to DNJ and DMJ, respectively (Scheme 22).

Related imino alditols such as azepanes or lactam derivatives have been obtained and have shown to be glycosidase inhibitors [96, 100]. Both D- and L-gulonolactone have been converted into polyhydroxylated 1,6-aldonolactams of type **79** in a sequence of straightforward functional transformations, including sulfinylation of the corresponding aldonolactone-derived acetonides **76** that gave 5,6-cyclic sulfites **77** (Scheme 23) [101]. The latter reacted with sodium azide



Scheme 22 Synthesis of 1-deoxynojirimycin (DNJ) and 1-deoxymannojirimycin (DMJ)

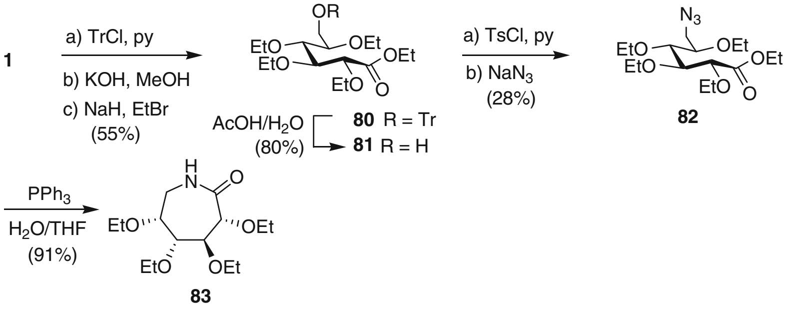


Scheme 23 Synthesis of di-hydroxylated 1,6-aldonolactams via aldonolactone-derived sulfites

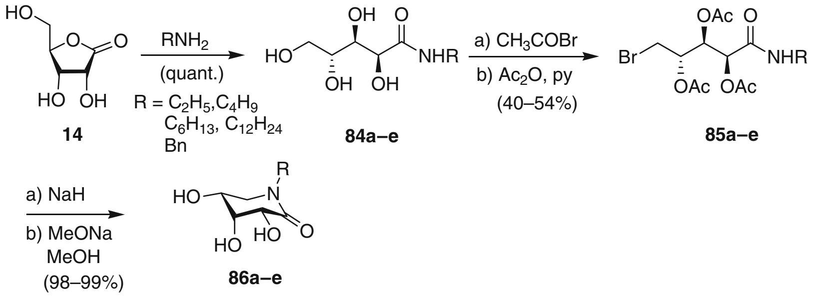
giving 6-azido derivatives **78**. In situ reduction of **78** and *N*-cyclization led to the targeted azepanes **79**.

A concise synthesis of tetra-*O*-ethyl aldonolactam **83** starting from **1** has been reported [102]. After protection of its primary alcoholic moiety as a trityl ether, saponification and treatment with EtBr generated **80**. Acidic hydrolysis liberated **81** that was esterified (tosylate). The latter was displaced with NaN_3 to give azide **82**. Reduction of **82** resulted in lactam **83** (Scheme 24).

Quite often *N*-alkylated imino sugars exhibit stronger glycosidase inhibitory activity than the corresponding non-alkylated derivatives [96, 103]. The synthesis of a series of hydroxylated *N*-alkyl aldonolactam derivatives was recently accomplished in a four-step sequence and good overall yields starting from D-ribono-1,4-lactone (**14**) [104]. Treatment of **14** with primary amines, and subsequent selective bromination of the resulting amides **84** and acetylation, provided the corresponding bromoamide derivatives **85**. The latter were then submitted to intramolecular cyclization to afford the corresponding *N*-alkyl ribonolactams, the transmethanolyse of which led to the final compounds **86** (Scheme 25).



Scheme 24 Synthesis of a tetra-*O*-ethylaldonolactam from D-glucono-1,5-lactone



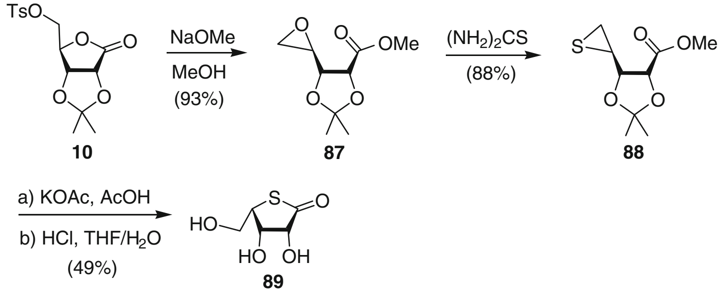
Scheme 25 Synthesis of a *N*-alkylated aldonolactam from ribono-1,4-lactone

3.5 Synthesis of Thiosugars

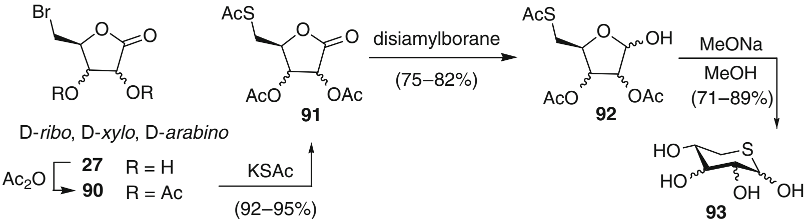
Thiosugars constitute another class of carbohydrate analogs presenting interesting biological and pharmacological properties [105, 106].

4-Thio-L-lyxono-1,4-lactone (**89**) has been prepared starting from 2,3-*O*-isopropylidene-5-*O*-tosyl-D-ribonolactone (**10**, D-*ribo*). **10** was converted first into epoxide **87** (Scheme 26) and then into episulfide **88** on treatment with thiourea. Regioselective opening of the thiirane ring of **88** and simultaneous lactonization, followed by removal of the protecting groups, furnished enantiomerically pure **89**. A similar synthetic pathway was employed for the synthesis of 4-thio-D-ribono-1, 4-lactone starting from D-gulono-1,4-lactone [107].

Beaupère and co-workers have proposed a short synthesis of 5-thio-D-pentopyranoses **93** applying a sequence of simple reactions starting from 5-bromopentono-1,4-lactones of type **27** (Scheme 27) [108, 109]. The latter were acetylated and subsequently converted into their corresponding 5-*S*-acetyl-5-thio derivatives **91**. Reduction of **91** into lactols **92** was followed by deprotection, furnishing the desired pentose derivatives **93** in good overall yields.



Scheme 26 Synthesis of 4-thio-L-lyxono-1,4-lactone from 2,3-*O*-isopropylidene-5-*O*-tosyl-D-ribonolactone



Scheme 27 Synthesis of thio-D-pentopyranoses from 5-bromo-D-pentono-1,4-lactones

3.6 Synthesis of Bioactive Natural Products

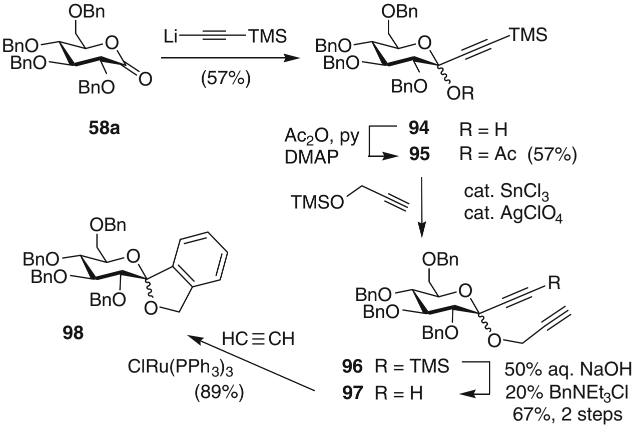
Selected examples of the synthesis of natural product starting from aldonolactones are presented in this section.

Spirocyclic *C*-aryl glycosides are central structural skeletons of papulacandins that constitute a family of novel antifungal antibiotics isolated from a strain of *Popularia sphaerosperna*. They have shown potent in vitro antifungal activity against *Candida albicans*, *Candida tropicalis*, *Pneumocystis carinii*, among other microorganisms [110].

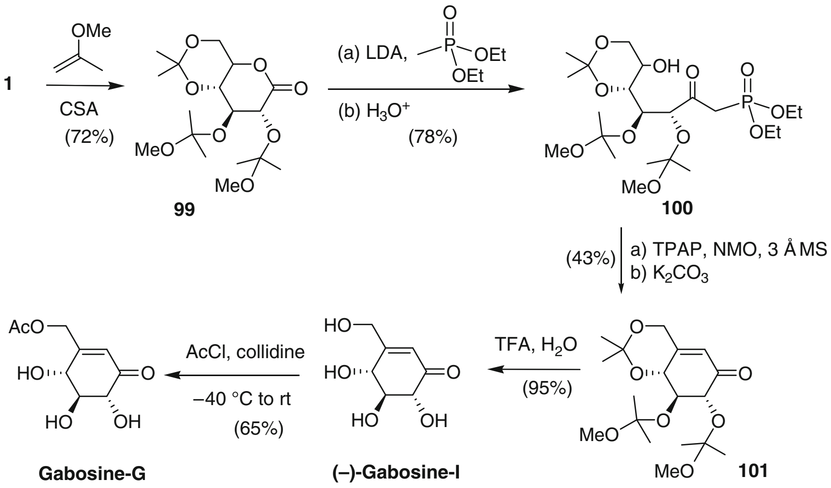
One route to spirocyclic *C*-glycosyl aromatic compounds is based on the addition of functionalized organolithium reagents to D-glucono-1,5-lactone (for example [111, 112, 113]). For instance addition of 2-(trimethylsilyl)ethynyllithium to tetra-*O*-benzyl-D-glucono-1,5-lactone (**58a**) gave the hemiacetalic 1-*C*-ethynyl derivative **94** as an anomeric mixture (Scheme 28). Acetylation of the tertiary hydroxyl group was followed by Lewis acid-mediated propargylation to give diyne **96**. Desilylation of **96** followed by cyclotrimerization in the presence of Wilkinson's catalyst gave the desired spiroketal core **98** in 89% yield.

Spirocyclic *C*-ribosyl aromatic compounds have also been derived from D-ribono-1,4-lactone by a similar strategy. In this case a mild cylopentadienyl ruthenium complex was used as catalyst for the cycloaddition step [114].

Gabosines which have been isolated from *Streptomyces* strains constitute a family of keto carbasugars, most of them possessing a trihydroxylated cyclohexenone structure. Because of their interesting bioactivities, a large number of synthetic approaches to these compounds have been proposed (for example [115, 116]). The shortest route (four to five steps) to gabosines I and G was accomplished starting



Scheme 28 Synthesis of a spirocyclic *C*-glycosyl aromatic compounds from tetra-*O*-benzyl-D-glucono-1,5-lactone



Scheme 29 Synthesis of (–)-gabosine I and gabosine G from D-glucono-1,5-lactone

from D-glucono-1,5-lactone (Scheme 29) [117]. Thus, acetalization of **1** with 2-methoxypropene resulted in the mixed acetal derivative **99** which underwent nucleophilic addition by the anion of diethyl methylphosphonate to afford the β-ketophosphonate **100**. The latter compound was subsequently submitted to a one-pot tetrapropylammonium perruthenate (TPAP) oxidation/K_2CO_3-mediated intramolecular Horner-Wadsworth-Emmons olefination, providing enone **101** in 43% yield. Other oxidation/cyclization conditions were less efficient. Deprotection of **101** furnished (–)-gabosine I which, in turn, could be acetylated regioselectively to give gabosine G.

3.7 *α,β-Unsaturated Aldonolactones*

Sugar-based lactones comprising an α,β-unsaturation are carbohydrate chiral building blocks with biological potential. Rauter and co-workers have reported the first syntheses of α,β-unsaturated lactones linked/fused to sugars and the field was broadly covered in a recent review [118–120]. Concerning monocyclic derivatives, i.e., α,β-unsaturated aldonolactones, a readily available 2,3-unsaturated aldonolactone is L-ascorbic acid (Vitamin C). Its chemistry and usefulness as chiral synthon has been reviewed very recently [121]. It is a versatile starting material for the synthesis of L-hexoses [122, 123]. Both aldono-1,4-lactones and aldono-1,5-lactones have the tendency to undergo β-elimination on acylation to give butenolides or pyranoid α,β-unsaturated aldonolactones, respectively [1]. 2,3-Unsaturated aldono-1,4-lactones are also easily obtained from 2-bromo-2-deoxyaldono-1,4-lactones through a mild reductive elimination of the C-2 bromine and a *trans*-vicinal acetoxy group that uses of sodium sulfite in methanol [124, 125]. 2-Deoxysugar lactones are intermediates for ulosonic acids [126–128].

Most of the methodologies applied to prepare pyranoid α,β-unsaturated lactones start with glycals [129–132]. The Lichtentaler's group developed a one-pot procedure consisting in the oxidation of glycals and 2-acyloxyglycal esters with *m*-chloroperbenzoic acid in the presence of boron trifluoride etherate [133–136]. Another major contribution to this field was realized by Chmielewski and co-workers. Their method was based on the oxidation of protected glycals with hydrogen peroxide in the presence of molybdenum trioxide catalyst to the corresponding anomeric hydroperoxides, which could then be readily converted into the pyranoid unsaturated lactones on treatment with acetic anhydride/pyridine [137–140]. This group has explored the ability of sugar-based α,β-unsaturated lactones to react as Michael acceptors or as dipolarophiles in cycloaddition reactions, for the synthesis of important molecular targets, including iminosugars and natural compounds of biological interest (for example [141–146]).

4 Bicyclic Carbohydrate-Based Lactones

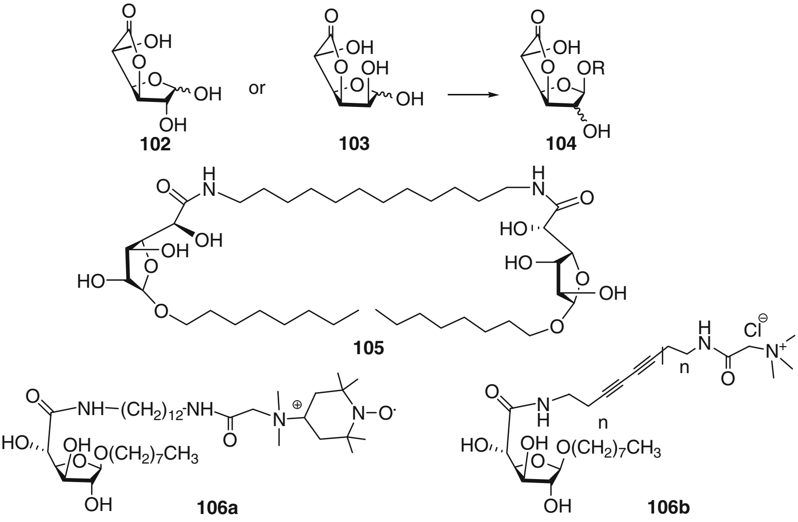
Bicyclic carbohydrate-based lactones can be divided into three classes: (1) lactones involving a carboxy group present on the sugar moiety (uronic and sialic acid lactones), (2) lactones involving a carboxy group formed by derivatization of a sugar hydroxyl group (carboxyalkyl ethers and glycosides), and (3) lactones involving a carboxy group present on a *C*-branched appendage.

When the lactone function of such bicyclic systems is consumed in a ring opening reaction, the main carbohydrate cyclic backbone is maintained in the product, unlike aldonolactones. Selected recent examples will be given in this section.

4.1 Uronic Acid Derived Lactones

The occurrence of uronic acid provides another means of easy access to bicyclic lactones, which can be used for the synthesis of various targets, such as surfactants or pseudo glycopeptides.

Alkyl furanosides can be obtained stereoselectively from the readily available D-glucofuranurono-6,3-lactone **102** arising from D-glucuronic acid, or from D-mannofuranurono-6,3-lactone **103**, which is obtained by acidic hydrolysis of alginic acid (Scheme 30) [147–149]. The lactone function of alkyl glucosides **104** can be opened by amines leading to new amphiphilic derivatives [42]. Pseudo macrocyclic bolaamphiphiles **105** are accessible by treatment of the lactone with a long-chain diamine [150]. Selective monoacylation of diamines can be followed by functionalization



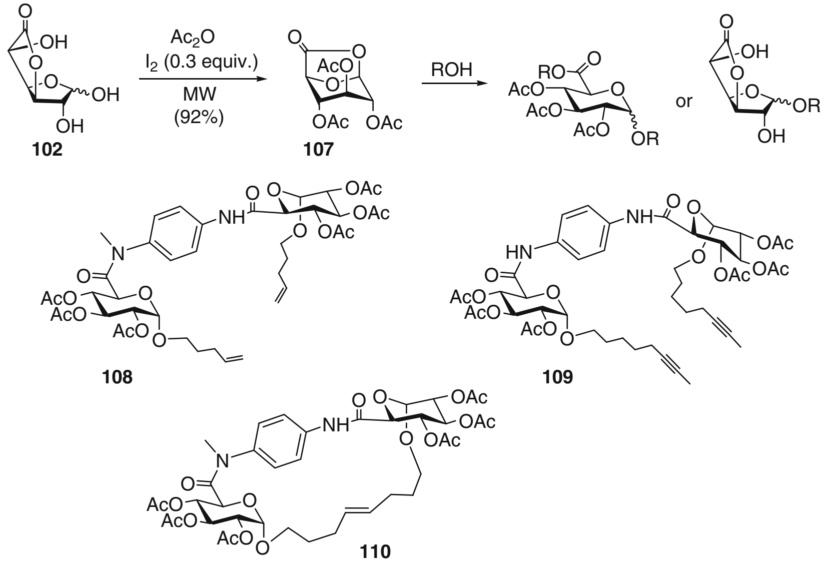
Scheme 30 Bolaphiles derived from uronic acid 6,3-lactones

of the second amino group with different functional moieties, such as a nitroxide for ESR studies (e.g., **106a**) or a cationic glycine betaine for making bolaphiles (e.g., **106b**). Variations of the self-assembly properties of the latter compound was studied as a function of the length and nature of the alkyl chain spacer connecting both polar heads [151–153].

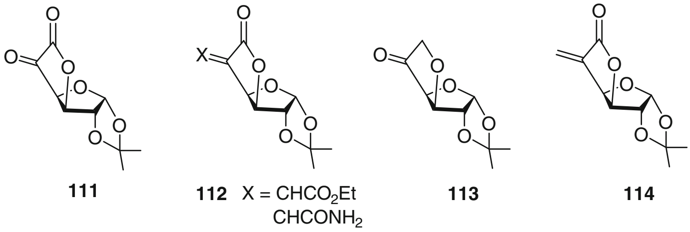
If the anomeric hydroxyl group is involved in the lactone ring (6,1-lactones), such as in compound **107**, the lactone is rapidly opened in the presence of a Lewis acid (Scheme 31). As in Hoffmann's systems arising from [4 + 3] cycloaddition methodology [154, 155], such lactones can be seen as tethered anomeric acetates acting as intramolecular leaving groups. Stereoselective glycosylations can thus be achieved with different selectivities depending on the nature of the substituent at C-2 and on the reaction conditions [catalyst, microwave irradiation (MW)]. In some cases, concomitant esterification of the released carboxylic acid is observed (Scheme 34) [156–158]. When the released carboxylic group reacts with diamines, more elaborated systems such as dienes **108** or diynes **109** can be obtained and used in subsequent intramolecular ring-closing metathesis to form glycophanes such as compound **110** [159].

Rauter and coworkers demonstrated that C-5-alkylidene derivatives **112** of D-hexofuranurono-6,3-lactone can be obtained by Wittig olefination of the α-ketolactone **111** (Scheme 32) [160]. The related α-methylene lactone **114** was prepared in three steps from 3,6-anhydro-1,2-*O*-isopropylidene-α-D-*xylo*-5-hexulofuranose **113** via Wittig reaction and allylic oxidation.

In a similar manner, sialic acids are liable to lactone formation. In some cases the observed lactones have been suggested to possess enhanced biological



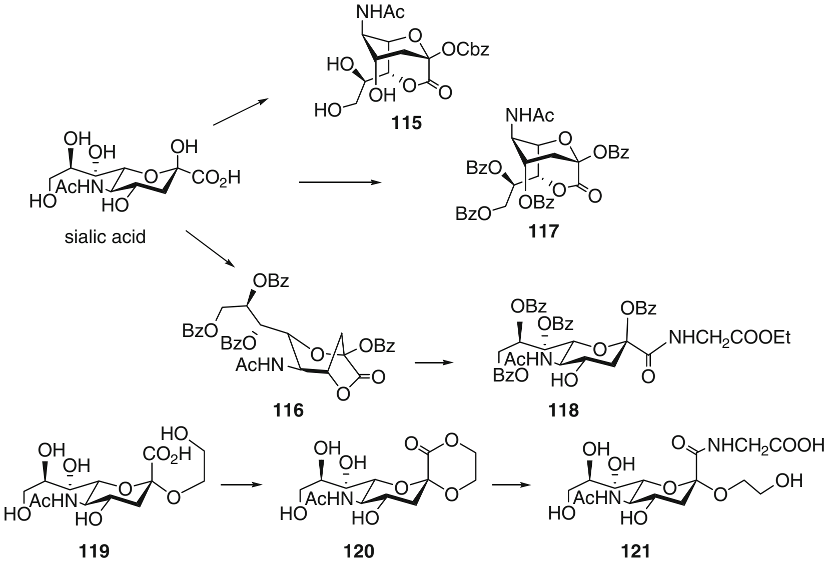
Scheme 31 Opening of glucuronic acid 6,1-lactone



Scheme 32 Alkylidene derivatives of hexuronic acid 6,3-lactone

properties with respect to the corresponding open hydroxyacids [161–163]. Sialic acid 1,7-lactone **115** is readily obtained [164]. It is present in many glycoproteins [165, 166].

Under various acetylation conditions, sialic acid leads to either 1,4-lactone **116** or to the 1,7-lactone **117** depending upon the equatorial or axial orientation of the carboxyl group (Scheme 33). In the presence of a more hindered acylating agent, e.g., CbzCl, an activated acyl intermediate can be formed and quantitative chemoselective 1,7-ring closure into compound **115** has been observed. Lactone **116**, as well as lactone **120** arising from the glycol glycoside **119**, were suggested to be the intermediates in the formation of NeuAc-aminoacid hybrids **117** and **121**. These compounds were designed as potential sialidase inhibitors [161, 167].



Scheme 33 Sialic acid lactones and derivatives

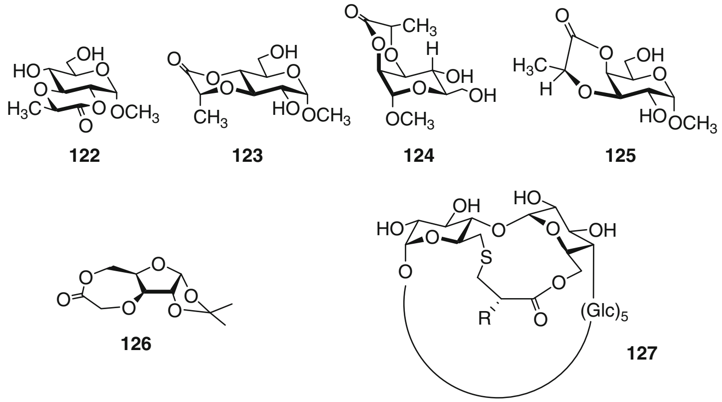
4.2 Lactonized Carboxyalkyl Ethers and Glycosides

4.2.1 Non-Anomeric Carboxyalkyl Ethers

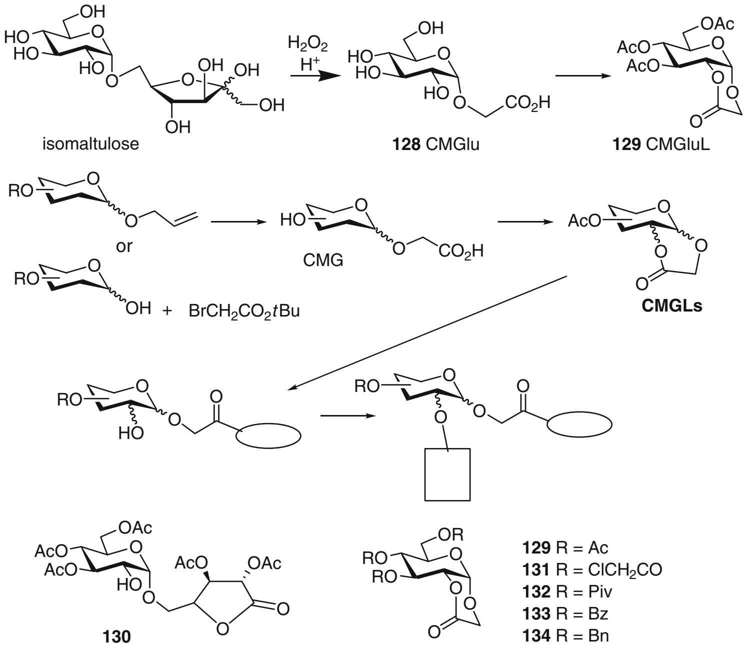
Various carboxyalkyl ethers at non-anomeric positions have been shown to give bicyclic systems which link positions 2,3 or 3,4 of sugars with various configurations through lactone formation. Examples are **122** and **123** (*gluco*), and **124** (*manno)* and **125** (*galacto*), which were derived from 3-*O*-(1-carboxyethyl) substituted methyl glycosides [168, 169] (Scheme 34). Another example is the bicyclic caprolactone **126**, derived from 1,2,5,6-di-*O*-isopropylidene-α-D-glucofuranose in six steps [170]. Modified cyclodextrins of type **127**, that involve lactonization of a carboxymethyl ether residue, have also been reported [171].

4.2.2 Anomeric Carboxymethyl Glycoside Lactones

Queneau and coworkers have developed the chemistry of lactones involving the carboxymethyl residues linked to the anomeric hydroxy group and to OH-2 in several sugars [172–176]. Isomaltulose (Scheme 35) is obtained by bioconversion from sucrose and has been shown to be an interesting starting material for various applications [177–182]. Like isomaltulose, trehalulose, another glucose-fructose disaccharide, and the hydrogenated derivative of isomaltulose, Isomalt®, were all shown to lead to the same compound **128** (CMGGlu) by oxidation [183–185].



Scheme 34 Non-anomeric bicyclic lactones from carboxyalkyl ethers



Scheme 35 Access to carboxymethyl glycoside lactones

Acetylation of the latter compound led to bicyclic lactone **129**. Another lactone **130** was also observed as side product when the oxidative degradation of the fructose moiety of isomaltulose was incomplete [186].

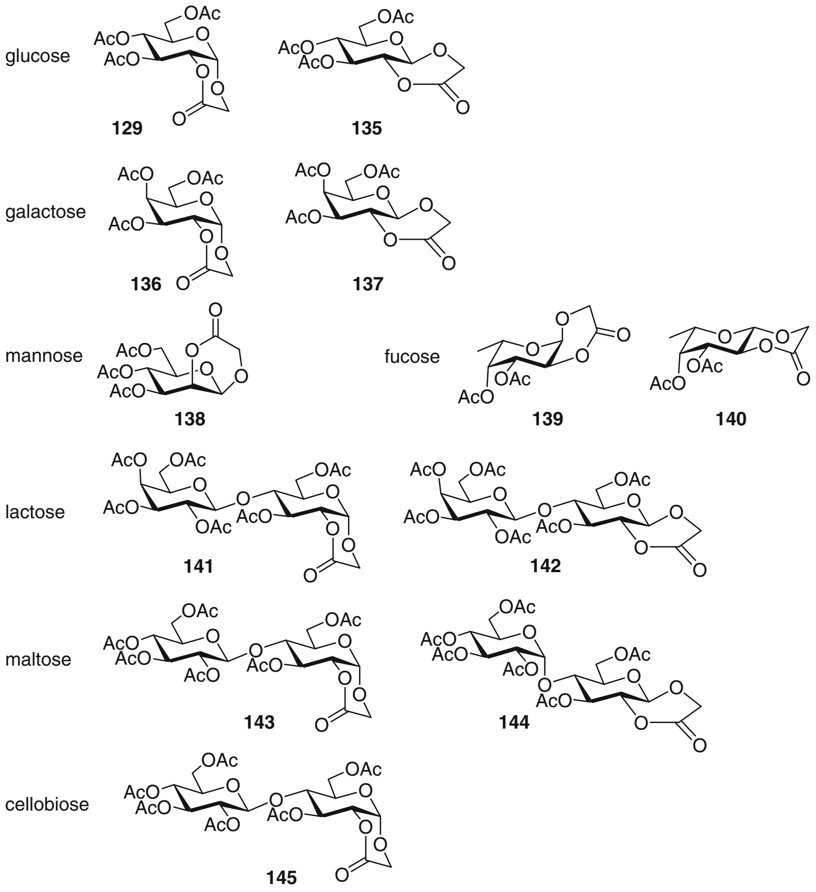
The scope of the method was extended to bicyclic lactones other than the α-D-gluco one arising from isomaltulose. The oxidation of allyl glycosides and the anomeric alkylation of various sugars with *tert*-butyl bromoacetate allowed many structural variations, leading to a full toolbox of carbohydrate-containing synthons in both their anomeric forms, in most cases, including disaccharides [186, 187]. Moreover, the selective opening of the lactone ring of these compounds releases the free 2-OH position which is available for a second functionalization, leading to 1,2-bisfunctionalized carbohydrate derivatives. An explanation for these observations is that a mixed anhydride is formed by reaction of CMG wit Ac_2O, followed by nucleophilic attack of OH-2. A similar structure, derived from β-lactoside, had been suggested [188] and a comparable system has been reported in a recent patent [189]. Not only were acetylated products prepared, but also chloroacetyl, pivaloyl (Piv), or benzoyl lactones **131–133**. The allyl glycoside route also permitted the preparation of lactones bearing another protecting group such as benzylated lactone **134** [186].

Non-protected aldoses or those peracetylated on all positions except the anomered hydroxy group react with *tert*-butyl bromoacetate (DMF, K_2CO_3) giving the corresponding *O*-glycosides [190, 191]. A significant selectivity for α anomers was observed for the reaction on the partially acetylated sugars, whereas some β selectivity (α:β from 1:1 to 1:2) was observed from free sugars. Galactose gives a more complex mixtures in which the α-furanosides are the major products [192]. Lactones **129–145** have been prepared according to this route with subsequent treatment with acetic anhydride in Py (Scheme 36).

4.2.3 Use of CMGLs

Alcohols react with carbomethoxy glycoside lactones (CMGLs) under either basic or acidic catalysis. However, the method is limited to acetylated targets, since deprotection of the acetyl groups cannot be achieved without substantial cleavage of the newly formed ester. Amines give stable amides (Scheme 37). Pseudo glycoamino acid hybrids of type **146** [184, 185], pseudo disaccharides **147**, and nucleotide sugars **148** [193] were thus obtained. With the idea that attaching a carbohydrate moiety can provide increased polarity and water solubility, other types of compounds were prepared by this method, such as polymerizable compounds of type **149–151**, and glycoporphyrins **152** designed as photosensitizers for cancer photochemotherapy [194, 195]. Pseudo glycolipids **153** were also prepared by this method [196], and more recently new glycoprobes of type **154** for membranes nonlinear imaging have been derived from lactones **129** and **141** [197].

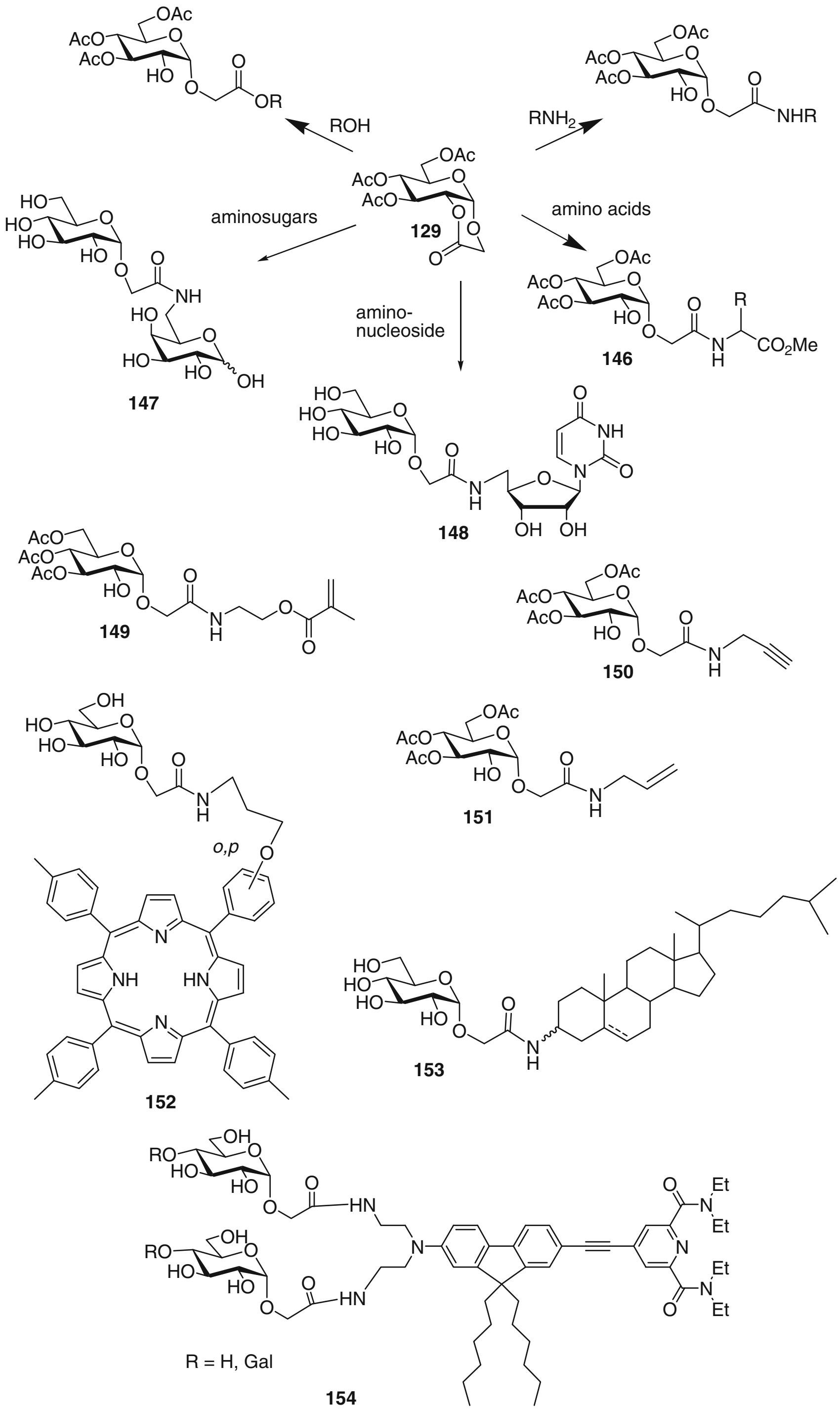
Further functionalization at OH-2 was also explored [187]. From monosaccharidic (α-gluco, **129**) and disaccharidic (α-malto, **143**) CMGLs, several types of bisfunctionalized systems were synthesized by reaction with allylamine or propargylamine. For example, compound **155** was prepared and used in a synthesis of the nucleotide sugar analog **156** (Scheme 38). In the context of studies on the



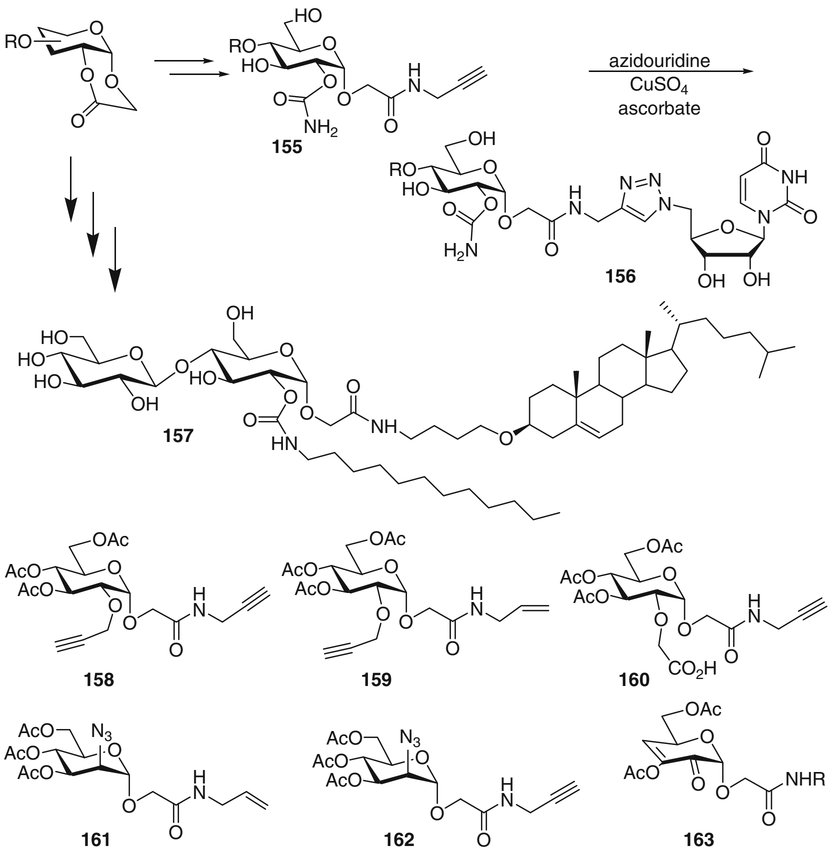
Scheme 36 Mono- and disaccharidic carboxymethyl glycoside lactones

physicochemical behavior of synthetic glycolipids [198–204], new bisfunctionalized compounds such as **157** were recently obtained and found to possess very peculiar hysteretic thermotropic properties [205]. Reactions at OH-2 included carbamatations, etherifications leading to diynes, enynes, and carboxy-ynes **158**–**160** [187]. Substitution by an azide after intermediate triflate formation led to azido alkenes or alkynes **161** and **162**, respectively. The reactivity of the latter compounds as AB monomers is presently being studied. Oxidation of OH-2 generates enones **163** [206].

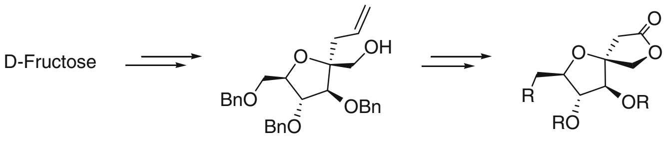
1-*C*-Allyl sugars have been transformed into spirobicyclic lactones which are the analogous synthons allowing the formation of *C*-glycosyl conjugates. For example, Araújo et al. prepared the intermediate **165** by *C*-allylation of the fully benzylated D-fructose followed by oxidation of the allyl group (Scheme 39) in the context of the evaluation of sugar-fused γ-butyrolactones and lactams as new potential γ-aminobutyric acid (GABA) receptor ligands [207].



Scheme 37 Examples of conjugates obtained from carboxymethyl glycoside lactones



Scheme 38 Bisfunctional compounds at C-1 and C-2 from CMGLs



Scheme 39 *C*-Glycosyl anomeric lactone from fructose

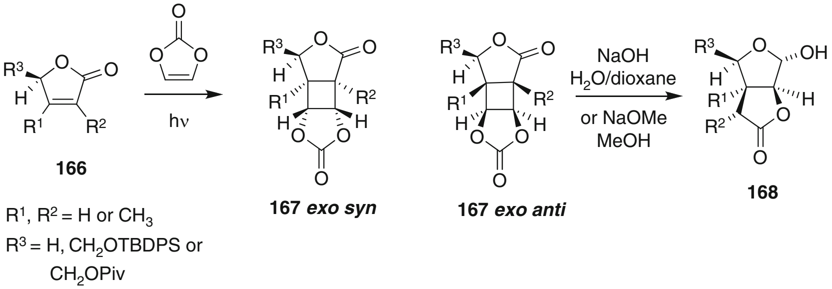
4.3 Fused C-Branched Lactones

Five-membered lactones (γ-butyrolactones) fused to carbohydrates have proven to be convenient synthons towards branched-chain sugars through opening of the lactone unit. Veláskes et al. [208] described the synthesis of γ-butyrolactones

2,3-fused to ribonucleosides by radical intramolecular addition in nucleosides comprising an α,β-unsaturated ester moiety at C-2 or at C-3 of the furanose ring. These bicyclic derivatives were further converted into 2-*C* or 3-*C*-branched chain nucleosides by opening of the lactone moiety with isobutylamine. Font and co-workers [209, 210] made use of homochiral butenolides as precursors for a stereoselective synthesis of γ-butyrolactones 2,3-fused to lyxofuranose units. Thus, photocycloaddition of vinylene carbonate to substituted butenolides (compounds type **166**, Scheme 40), gave selectively the corresponding *anti* cycloadducts **167** in moderate yields. The latter, when treated under basic conditions (0.5 M NaOH in water/dioxane or MeONa in MeOH), underwent rearrangement to afford the target bicyclic compounds **168** in modest to moderate yields.

The intramolecular cyclopropanation of 4,6-di-*O*-protected glycals (such as **169**) has been explored as a key step for the synthesis of advanced intermediates for bislactone natural products [211] (Scheme 41). The glycal-fused cyclopropane **171** was obtained by copper-catalyzed intramolecular cyclopropanation of the glycal-derived diazoacetate **170** in very good yield. It could then be converted into furanose-fused butyrolactone **175** in few steps, including selective monodeprotection to the alcohol **172** and further iodination. The resulting iodine derivative **173** was subjected to a zinc-mediated reductive ring opening cascade to furnish aldehyde **174**. Its desilylation provided bicyclic lactone **175** as a convenient precursor for xylobovide, canadensolide and sporothriolide bisfuranolactones.

With respect to five-membered lactones fused to hexopyranose units, some approaches have been reported so far and the exploitation of their synthetic potential has led to the access of new carbohydrate derivatives. Bicyclic derivatives of this type are key intermediates in the synthesis of the epimer at C-3 of the sugar moiety contained in miharamycins [212, 213]. The latter are antibiotics known to inhibit strongly *Pyricularia oryzae*, which produces the rice blast disease. These compounds are also considered to be a potential bioterrorism agent (Scheme 42). Hence, the 3,3-spiroepoxide **176** was converted into the 3-*C*-cyanomethyl derivative **177**, the hydrolysis of which led to spontaneous cyclization in the presence of



166

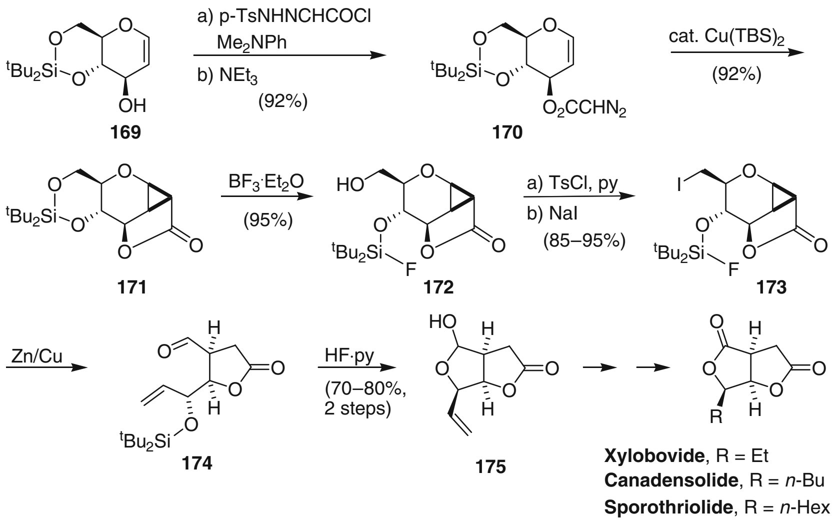
167 ***exo syn***

167 ***exo anti***

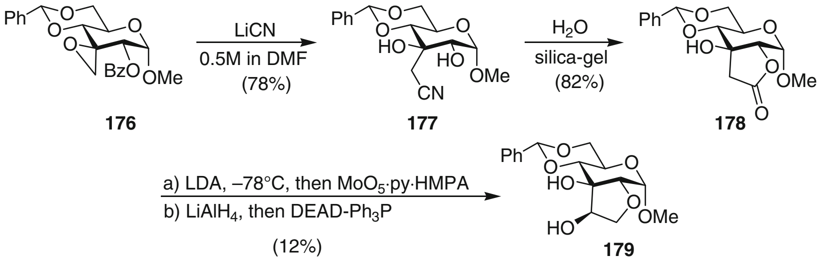
168

R^1, R^2 = H or CH_3
R^3 = H, $CH_2OTBDPS$ or CH_2OPiv

Scheme 40 Synthesis of furanose-fused γ-butyrolactones by photocycloaddition of vinylene carbonate to substituted butenolides



Scheme 41 Synthesis a furanose-fused butyrolactone from a glycal-derived cyclopropane



Scheme 42 Sugar moiety of miharamycins from hexopyranoside fused butyrolactones

silica gel, giving the sugar-fused lactone **178**. A stereoselective hydroxylation of the latter compound followed by reduction led to the desired miharamycin sugar moiety analog **179**.

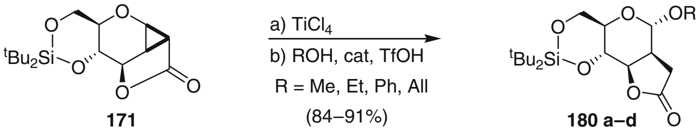
The previously mentioned glycal cyclopropanation method was also applied to the synthesis of γ-butyrolactones 2,3-fused to glycopyranosides (Scheme 43) [214]. Hence, ring opening of the cyclopropane derivative **171** by $TiCl_4$, which was followed by in situ addition of alcohol, furnished glycoside-fused butyrolactones **180a–d**, in high yields and good diastereoselectivity (α/β ratio ranging from 6:1 to 15:1).

More recently, another methodology for sugar-fused butyrolactones employing glycal-derived cyclopropane precursors has been described by Chandrasekaran and co-workers (Scheme 44) [215]. In this case, hexofuranose- or hexopyranose-1,2-fused were cyclopropanated into compounds of type **181**. After saponification with

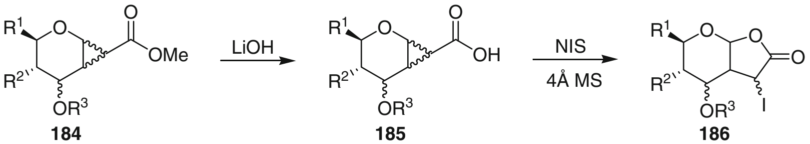
LiOH, giving **182**, iodination with *N*-iodosuccinimide (NIS) provided **183** resulting from homoiodolactonization.

On their side, Yin and Linker [216] made use of a 2-*C*-branched hexopyranoside, the synthesis of which was achieved by addition of dimethyl malonate to tri-*O*-benzyl-D-glucal (IUPAC name: 3,4,6-tri-*O*-benzyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol, Scheme 45) [217]. Thus, saponification of the 2-*C*-[bis(methoxycarbonyl)]methyl derivative **184** to the corresponding malonic acid **185** was followed by heating in refluxing toluene. This led to decarboxylation and lactonization giving **186**. The method was optimized and applied to the synthesis of pentoses and disaccharides.

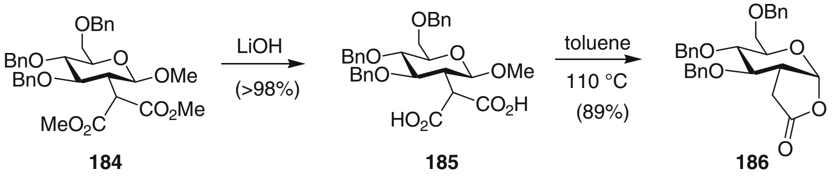
Sugar-derived α,β-unsaturated lactones are relevant motifs considering their ability to act as functionalized substrates for a variety of transformations. Some of them are bioactive [218–222]. An early synthesis of the enantiomer of (+)-altholactone, a natural product with cytotoxic and antitumor activities (for a review on the bioactivity of styryllactones see [223, 224]), involves the preparation of a furanose-fused α,β-unsaturated δ-lactone intermediate **189** [225]. Starting from a α-D-*xylo*-pentodialdofuranose derivative **187**, a Reformatsky reaction with ethyl bromoacetate introduces the carboxylic side chain necessary for intramolecular lactonization (Scheme 46).



Scheme 43 Pyranoside 2,3-fused-γ-butyrolactones from a glycal derived cyclopropane



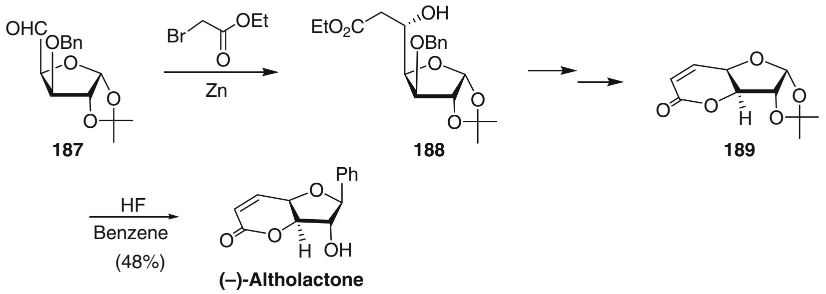
Scheme 44 Synthesis of sugar-1,2-fused iodobutyrolactones from sugar-1,2-fused cyclopropanated esters



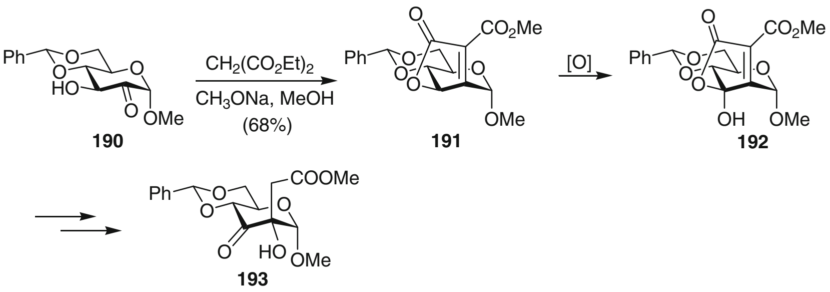
Scheme 45 Synthesis of a hexopyranose-1,2-fused butyrolactone from a 2-*C*-malonyl glucoside

A pentopyranoside-fused butenolide is the key intermediate for the synthesis of the natural micotoxin patulin [226, 227]. Its synthesis involves Wittig olefination of a 3,4-di-*O*-protected arabinopyran-2-uloside, followed by protecting group removal and dehydration (Scheme 47). In other research, the glucopyranosid-2-uloside **190** was converted into the butenolide derivative **191** by aldol condensation with diethyl malonate and transesterification [228]. The latter was shown to be prone to autoxidation, leading to **192**. Subsequent Michael addition with hydroxide ion, followed by decarboxylation, furnishes *C*-branched-chain sugar **193**.

An elegant stereocontrolled route for pyranose-fused butenolides starting from easily synthesized protected furan-3-uloses (compounds of type **194**) has been reported [229, 230] (Scheme 48). It consisted of the synthesis of 3-*C*-branched α,β-unsaturated esters (**195**) by Wittig olefination, followed by acid hydrolysis. Within this latter step, cleavage of the protecting groups (PG), intramolecular transesterification, and furanose-pyranose isomerization occurred, furnishing directly the target bicyclic compounds (**196**, **197**) in good overall yields. This approach was convenient for achieving in a few steps both pento- and hexopyranose-based bicyclic systems comprising the butenolide moiety anchored at C2-C3 or at C3-C4 of the sugar ring, depending on the configuration around the C3-C3' double bond. The feasibility and scope of this methodology were then investigated for the preparation



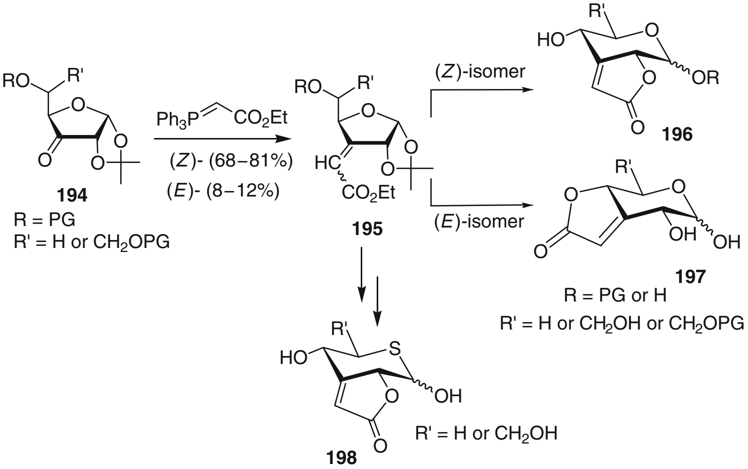
Scheme 46 Synthesis of the non-natural enantiomer of (+)-altholactone via a furanose-fused unsaturated δ-lactone



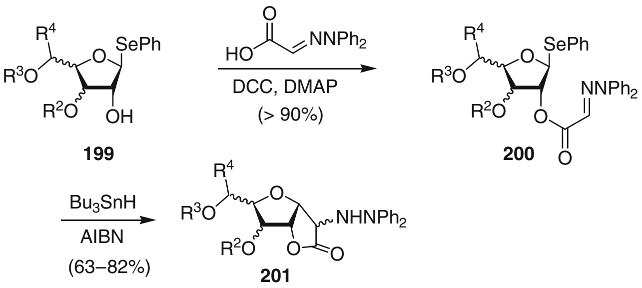
Scheme 47 Synthesis of a 2-*C*-branched-chain sugar via a pyranose-fused butenolide

of 5-thiopento or hexopyranose analogues of type **198** [231]. Thus, after introduction of an additional sulfhydryl functionality at C-5 at the intermediate α,β-unsaturated esters, acid hydrolysis also allowed ring expansion to the thiopyranose form with accompanying butenolide formation, generating new highly functionalized and potential biologically interesting bicyclic thiosugar-based systems.

Fused *C*-glycosyl lactones are also suitable synthons for further elaboration into more complex *C*-glycosyl compounds, including glycoconjugates. In one of the few published methods to afford these bicyclic lactones, protected 1-phenylseleno glycosyl donors possessing a free OH-2 (compounds of type **199**) were converted into the corresponding 2-hydrazonoesters **200**. The latter were then subjected to radical cyclization (Scheme 49) [232] giving α-hydrazino lactones **201** that could be transformed into the corresponding *C*-glycosyl amino acids through standard functional manipulations.



Scheme 48 Synthesis of butenolides fused to pento- or hexopyranoses and thiosugar analogs from furanos-3-uloses



Scheme 49 Synthesis of furanose-fused *C*-glycosyl α-hydrazino lactones from phenyl-1-seleno glycosyl donors

5 Conclusion

Lactones derived from carbohydrates are building blocks of high synthetic potential. Next to the readily available aldonolactones and uronic acid lactones, some bicyclic systems have recently emerged as useful synthons. Examples of applications encompass functional derivatives such as polymers, as well as more elaborated compounds of physico-chemical or biological relevance.

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Heterogeneously-Catalyzed Conversion of Carbohydrates

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Abstract Polyfunctionality of carbohydrates and their low solubility in conventional organic solvents make rather complex their conversion to higher value added chemicals. Therefore, innovative processes are now strongly needed in order to increase the selectivity of these reactions. Here, we report an overview of the different heterogeneously-catalyzed processes described in the literature. In particular, hydrolysis, dehydration, oxidation, esterification, and etherification of carbohydrates are presented. We shall discuss the main structural parameters that need to be controlled and that permit the conversion of carbohydrates to bioproducts with good selectivity. The conversion of monosaccharides and disaccharides over solid catalysts, as well as recent advances in the heterogeneously-catalyzed conversion of cellulose, will be presented.

Keywords Carbohydrates, Dehydration, Heterogeneous catalysis, Hydrolysis, Oxidation

Contents

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Abbreviations

BMIM	1-Butyl 3-methyl imidazolium
ChCl	Choline chloride
DMSO	Dimethylsulfoxide
HMF	5-Hydroxymethylfurfural
HMS	Hexagonal mesoporous silica
IL	Ionic liquid
PMO	Periodic mesoporous organosilica
PS	Polystyrene
TBD	Triazabicyclo[4.4.0.]dec-5-ene
TOF	Turn over frequency

1 Introduction

Biomass represents a huge reservoir of renewable carbon whose production is estimated to 180 billion metric tons per year [1–6]. Carbohydrates represent 75% of biomass and are now industrially used not only for the synthesis of a wide range of safer chemicals but also for the production of biofuels. The chemical transformation of carbohydrates to higher value added chemicals is rather complex, mainly because of the polyfunctionality of these molecules. Therefore, in order to avoid the formation of side products, assistance of protective and deprotective agents is generally required in conventional organic pathways [7–9]. However, if such a strategy allows the formation of chemicals with high purity, the economical and environmental viability of these processes limit their application to high-value added compounds such as drugs.

Catalysis represents a possible tool to convert selectively carbohydrates through environmentally friendlier processes. Homogeneous catalysts are widely used in industry mainly because of their high activity, thus allowing a minimization of energy, cost, and labor. However, these catalytic processes present some problems such as the cost of their removal from the reaction products and the generation of waste. Biocatalysis appears as a promising alternative. Indeed, enzymes are much more selective than homogeneous catalysts and generally allow reactions to proceed at low temperature. In this context, numerous carbohydrates are now industrially converted through enzymatic processes. However, the purification work-up and the stability of enzymes represent, in some cases, serious limitations. Moreover, the activity of enzymes depends on the origin of the raw materials.

Solid catalysts offer complementary advantages over homogeneous catalysts such as easy removal from the reaction media (possible recycling), high thermal stability, and the possibility to design a continuous process [10–12]. However, activities of solid catalysts are usually lower than those of homogeneous catalysts mainly because of important diffusional limitations. Material chemistry gives today access to a wide range of different elaborated solid catalyst structures, usually well defined at the nanoscale. In this context, various solid catalysts were specifically designed for the selective conversion of carbohydrates and more and more elegant works are now emerging in the literature.

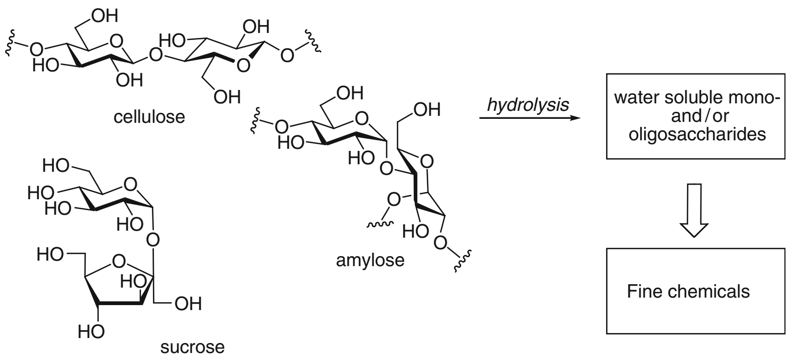
Here we report an overview of the different heterogeneously-catalyzed pathways designed for the selective conversion of carbohydrates. On the basis of these results, we shall try to determine the key parameters allowing a better control of the reaction selectivity. Water being commonly used as solvent in carbohydrate chemistry, we will also discuss the stability of solid catalysts in the aqueous phase. In this review, heterogeneously-catalyzed hydrolysis, dehydration, oxidation, esterification, and etherification of monosaccharides and polysaccharides are reported.

2 Heterogeneously-Catalyzed Hydrolysis of Carbohydrates

The design of solid catalysts for the hydrolysis of carbohydrates is now considered as one of the most challenging topics since this reaction opens a direct access to different chemicals [8, 13] of increasing value [14–20].

Hydrolysis of carbohydrates such as cellulose, starch, or sucrose to monosaccharides and/or oligosaccharides involves a cleavage of the glycosidic bonds as shown in Scheme 1. Hydrolysis of polysaccharides was discovered in 1811 by Constantine Sigmund Kirchhof using homogeneous acid catalysts and enzymes [21]. An example of utilization of a solid catalyst in this reaction remained unheard of for a long time. Indeed, it was necessary to wait more than one century (1990) to see the first report involving a solid catalyst.

This acid-catalyzed cleavage of the glycosidic bonds is rather complex and often suffers from a lack of selectivity mainly due to side dehydration or recombination reactions of monosaccharides. In the existing literature, four different classes of solid catalysts are reported: (1) cation-exchange resins, (2) siliceous-based materials, (3) metal oxides, and (4) sulfonated amorphous carbons.



Scheme 1 Hydrolysis of carbohydrates

2.1 Hydrolysis in Water

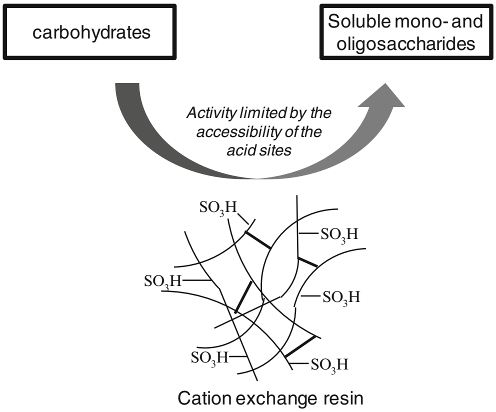
2.1.1 Cation-Exchange Resins

Strongly acid cation-exchange resins bearing sulfonic acid sites were found to be particularly efficient in the hydrolysis of sucrose [22–24]. Indeed, at 298–343 K, it has been shown that very high conversion of sucrose (97%) and selectivities (97%: 48.5% fructose and 48.5% glucose) can be obtained [22]. It should be noted that cation-exchange resins were inactive in the hydrolysis of cellulose. This inactivity of cation-exchange resins was ascribed to the poor accessibility of the grafted sulfonic sites to cellulose caused by the important steric hindrance of the resin framework.

Proceeding on the same line, Hagerdal et al. reported that perfluorinated resin supported sulfonic sites (NAFION 501) can hydrolyze disaccharides [25]. In particular, these authors studied the effect of the addition of sodium chloride in the hydrolysis of cellobiose, a subunit of cellulose much more resistant to hydrolysis than sucrose. They observed that the presence of sodium chloride in water dramatically increased the conversion of cellobiose. Indeed, in the presence of 10 wt% of sodium chloride, 80% of cellobiose was converted at 95°C after 6 h. For comparison, when 1% of sodium chloride was added, only 50% of cellobiose was hydrolyzed. It should be noted that without addition of sodium chloride only 15% conversion was achieved, thus pushing forward the key role of sodium chloride on the reaction rate. Effect of salt on the reaction rate was attributed to a change of the pH caused by the release of proton in the reaction medium (due to an exchange of the supported proton by sodium).

Yoshioka et al. investigated the catalytic activity of polystyrene–polypropylene fibrous cation-exchange resins in the hydrolysis of sucrose [26]. Owing to their higher surface area than that of traditional cation-exchange resins, the accessibility of the catalytic sites to sucrose was greatly improved. Therefore, polystyrene–polypropylene-based cation-exchange resin was more active than conventionally used

Scheme 2 Hydrolysis of carbohydrates over cation-exchange resins



crosslinked cation-exchange resins (rate constant of 12.7 × 10^{-3} mL s^{-1} $m_{equiv}{}^{-1}$ vs 0.8 mL s^{-1} $m_{equiv}{}^{-1}$ for the crosslinked cation exchange).

In a similar way, Mizota et al. grafted polymer chains functionalized with sulfonic sites over a polystyrene-type polymer. As observed above, the flexibility of the polymer chains allowed better accessibility of the catalytic sites and this solid acid catalyst was ten times more active than the conventionally used cross-linked resin in the hydrolysis of sucrose (Scheme 2) [27].

Accessibility of the catalytic sites to carbohydrates being the key of the process, Nasef et al. reported in 2005 the hydrolysis of sucrose over newly prepared radiation-grafted poly(tetrafluoroethylene-*co*-perfluorovinyl ether)-*graft*-polystyrene sulfonic acid (PFA-*g*-PSSA) membranes [28]. These new membranes were prepared by simultaneous radiation-induced grafting of styrene onto poly(tetrafluoroethylene-*co*-perfluorovinyl ether) (PFA) films using γ-radiation followed by sulfonation with chlorosulfonic mixture. Authors have shown that these sulfonic acid membranes exhibited a higher activity than commercially available crosslinked cation-exchange resins. The calculated activation energy was found to be 81.3 kJ mol^{-1}. This value was higher than that obtained in the hydrolysis of sucrose with commercial cross-linked ion-exchange resins (59 kJ mol^{-1}). Interestingly, they found that an increase of the loading of sulfonic sites (i.e., the proton concentration) on the membrane surface from 28 to 63% enhanced the catalytic activity from 7.5 × 10^{-3} to 27.5 × 10^{-3} min^{-1}. It was suggested that this increase of activity might be ascribed to (1) an increase of the amount of accessible sulfonic sites and (2) an increase of the catalyst hydrophilicity, thus improving the polymer chains mobility and therefore accessibility of the catalytic sites.

More recently, El Modhy et al. investigated the hydrolysis of sucrose over Kappa carrageenan/acrylic acid graft-copolymers (kC-*g*-AAc) prepared by γ-radiation. They showed that the catalytic activity of the kC-*g*-AAc was dependent on the reaction temperature [29]. As expected, at 80°C, the activity was higher than at 30°C because of lower diffusional resistance.

In 2007, Chambré et al. investigated the hydrolysis of sucrose over cross-linked cation-exchange resins [30]. By means of DSC analysis, they confirmed that the catalytic activity of crosslinked ion-exchange resins were dependent on the amount of cross-linked agent, the proton exchange capacity, the particle size and the nature of the polymeric matrix. The investigated resins have a polymeric matrix based on an acrylic acid backbone cross-linked with divinyl-benzene (Purolite C106 EP). Interestingly, they showed that the reaction rate with such cation-exchange resin is 18 times higher than those obtained with homogeneous acid catalysts. This greater activity of resins was ascribed to a higher local "concentration" of proton than in the case of homogeneous catalysts. Therefore, it was suspected that the catalytic hydrolysis of sucrose would be a concerted mechanism involving several protons. Interestingly, they showed that weakly acid cation-exchange resins (carboxylic acid form) are surprisingly more active than strongly acid sulfonic ones [31]. The difference of activity between weakly and strongly acid resins might be explained by the difference in proton exchange capacity which is about twice higher than in the case of weakly acid resins.

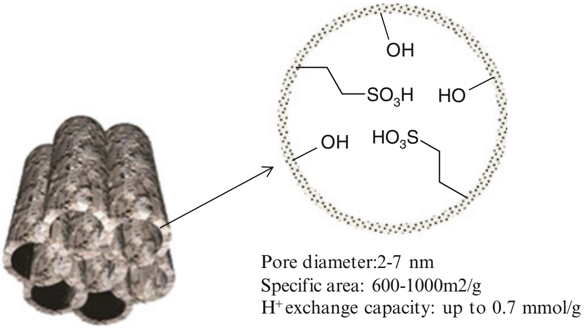
2.1.2 Siliceous-Based Catalysts

The results presented above highlighted that accessibility of the catalytic sites is a key parameter for efficient heterogeneously-catalyzed hydrolysis of carbohydrates. If "flexible" cation-exchange resins are particularly efficient, their instability at temperatures higher than 130°C still represents a major drawback. In order to circumvent this issue, attention has been directed towards porous siliceous-based catalysts. These inorganic solid supports exhibit a large surface area, large pore openings, and are more stable at higher temperature than organic resins.

In 1994, Laketic et al. investigated for the first time the hydrolysis of sucrose over dealuminated-Y-zeolites with different Si/Al ratio (27, 55, 110). The best activity was observed with the highest dealuminated zeolite (Si/Al = 110, rate constant = 1.28 L mol^{-1} min^{-1} at 30°C; [32]). As expected, the reaction obeys first order kinetics. Up to 90% conversion was obtained after 9 h of reaction at 70°C. Interestingly, little side-products were formed as the selectivity in glucose was higher than 90%.

Although zeolites are stable in water, their narrow pore openings considerably limit their utilization in carbohydrate chemistry. In most cases, only the external surface is accessible to reactants. For these reasons, many investigations have focused on mesoporous silica-supported sulfonic sites (Fig. 1). The presence of uniform channel with large pore openings (2–9 nm) offer notable advantages over zeolites.

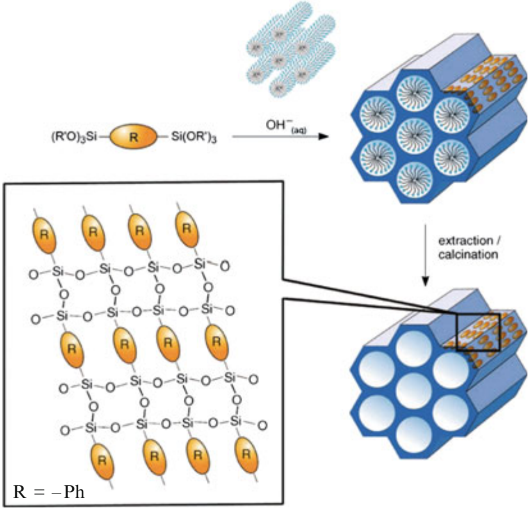
As expected, mesoporous silica-supported sulfonic sites were able to catalyze the hydrolysis of cellobiose. Indeed, at 448 K, 90% of cellobiose was hydrolyzed within 30 min of reaction with an apparent activation energy (E = 130 kJ mol^{-1}) similar to that of reactions promoted by homogeneous organic acid catalysts [33]. The hydrolysis reaction rate is proportional to the concentration of hydrated



Pore diameter:2-7 nm
Specific area: 600-1000m2/g
H^+exchange capacity: up to 0.7 mmol/g

Fig. 1 Mesoporous silica-supported sulfonic sites

Fig. 2 Mesoporous benzene-silica with crystal like pore walls. Figures reproduced with the permission of Prof M. Fröba [34]



protons. Interestingly, these hydrated protons, located on the siliceous surface, are unable to promote the dehydration of glucose, thus explaining the high selectivity of this process for glucose production. Mesoporous silica-supported sulfonic sites indisputably offer remarkable tools to hydrolyze carbohydrates with high selectivity, but their instability in water represents an important limitation.

Remarkably, in 2002, Inagaki and co-workers reported that, starting from 1,2-bis (triethoxysilyl)benzene as a siliceous precursor, mesoporous benzene-silica with crystal-like pore walls (Ph-PMO) can be prepared (Fig. 2) [35]. Owing to their crystallinity, these new hybrid organic-inorganic materials were much more stable in water than the amorphous mesoporous silica-supported sulfonic sites described above [36–39].

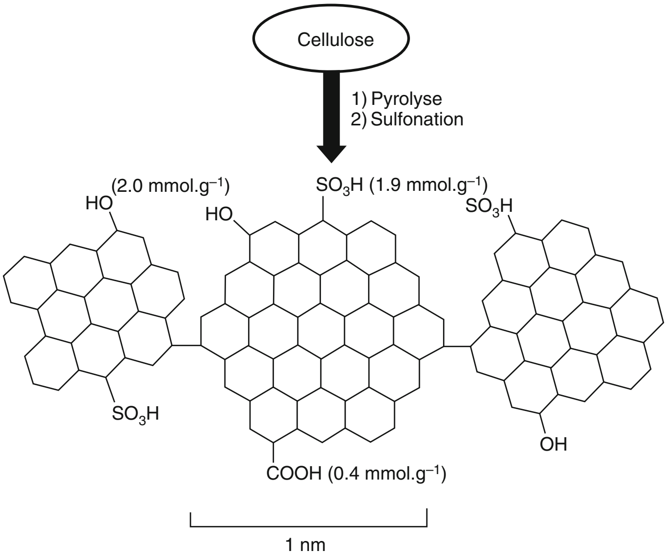
Following this discovery, Fukuoka and co-workers reported that functionalization of Ph-PMO with sulfonic acid sites (Ph-PMO-SO_3H) offers a highly robust solid acid catalyst in water. Taking advantage of the large pore opening of these materials (2–3 nm), they investigated the catalytic activity of Ph-PMO-SO_3H in the hydrolysis of sucrose and starch [40]. Ph-PMO-SO_3H was compared to Nafion, Amberlyst-15, and a siliceous material-supported sulfonic site (SiO_2–SO_3H). Over Ph-PMO-SO_3H, high conversion of sucrose, similar to that obtained with Amberlyst-15 (80% conversion of sucrose at 353 K after 4 h of reaction) was achieved. As observed above with mesoporous siliceous framework, fructose and glucose were formed as sole products and no side reactions took place. Interestingly, owing to the crystallinity of the siliceous pore walls, the Ph-PMO-SO_3H catalyst has been successfully recycled in water without notable change of activity. Under the same conditions, Nafion and SiO_2–SO_3H exhibited lower catalytic activity while no reaction was observed with HZSM-5, further demonstrating the usefulness of the Ph-PMO-SO_3H catalyst. Remarkably, Ph-PMO-SO_3H was also efficient for the hydrolysis of starch at 403 K. In this case, 65% yield of glucose was obtained.

2.1.3 Metal Oxides

In 2008, Domen et al. investigated the catalytic activity of layered transition-metal oxides ($HNbMoO_6$) and their derivatives like exfoliated nanosheet materials ($HTiNbO_5$) in the hydrolysis of sucrose and cellobiose [41]. The catalytic performances of these catalysts have been compared to conventional solid acid, including cation-exchange resins (Nafion NR50 and Amberlyst-15), H-type zeolite (H-ZSM5; JRC-Z-5-90H, Si/Al = 90), and niobic acid (Nb_2O_5, nH_2O). Over all tested acid solid catalysts (also including sulfuric acid), the hydrolysis rate of cellobiose was significantly lower than that of sucrose. Indeed, the rate of glucose production was in the range of 0.05–1.18 mmol g^{-1} h^{-1} from cellobiose vs 0.1–24.1 mmol g^{-1} h^{-1} from sucrose. Interestingly, no acid-catalyzed degradation of fructose and glucose has been observed. Among all solid catalysts assayed, the layered $HNbMoO_6$ catalyst exhibited the best activity (calculated rate based on the glucose production = 24.1 mmol g^{-1} h^{-1}). The high activity of this catalyst was attributed to the ease of intercalation of carbohydrates into the acidic interlayer gallery.

2.1.4 Sulfonated Amorphous Carbons

These carbonaceous catalysts can be obtained by the sulfonation of incompletely carbonized organic compounds [42]. Note that starch and cellulose can be used as carbon precursor [43, 44]. After the incomplete pyrolysis of the carbon precursor, the SO_3H groups have been introduced by sulfonation with sulfuric acid (Scheme 3). After this treatment, the presence of phenolic hydroxyl, carboxylic acid, and sulfonic groups at the surface of these amorphous carbonaceous materials has been demonstrated.



Scheme 3 Possible structure of the sulfonated carbonaceous material formed upon pyrolysis and sulfonation of cellulose

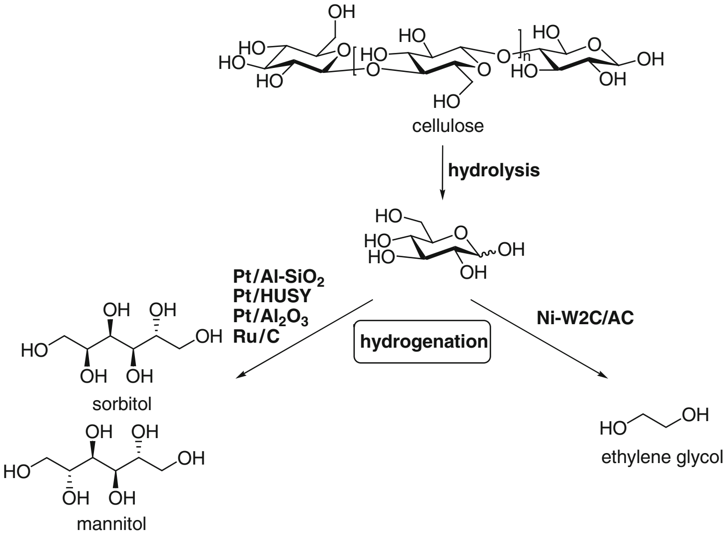
Yamaguchi et al. studied the hydrolysis of cellulose in the presence of amorphous carbon bearing SO_3H, OH, and COOH groups prepared from microcrystalline cellulose powder [45, 46]. Surprisingly, despite their low acid density, these authors showed that the sulfonated amorphous carbon was active in the hydrolysis of cellulose. Indeed, after 3 h of reaction at 100°C, white cellulose powder could not longer be observed in suspension and 68% of it was hydrolyzed into glucose (4%) and water-soluble β-1,4-glucan (64%). Under the same conditions, other acid catalysts such as niobic acid, H-mordenite, Nafion, or Amberlyst-15 did not yield glucose from cellulose. The high catalytic activity of the sulfonated carbonaceous material was attributed to (1) its ability to adsorb the β-1,4-glucan, (2) its large effective surface area in water, and (3) the presence of $-SO_3H$ groups tolerant to hydration. It was also shown that the catalyst activity and selectivity closely depend on the amount of water. When the amount of water was similar to the solid catalyst weight, a maximum yield of glucose was obtained. A lower amount of water mainly drives the reaction towards the formation of water-soluble β-1,4-glucan. Reaction temperatures higher than 373 K resulted in the formation of numerous byproducts such as levoglucosan, maltose, and levulinic and formic acids.

In 2009, Onda et al. studied the catalytic activity of sulfonated activated carbon prepared from active carbon and concentrated sulfuric acid [47]. The hydrolysis was performed under hydrothermal conditions at 423 K in a steel autoclave lined with Teflon. After 24 h of reaction, sulfonated carbon afforded high yield of glucose (40 C-%, i.e., based on the total weight consumption of carbon) and nearly no SO_4^{2-} elution was observed which clearly indicated that the process was heterogeneously catalyzed. As observed above, under hydrothermal conditions, the glucose yield closely depended on the reaction temperature and best results have been obtained at 433 K (43 C-%). At higher temperature (453 K), the yield of glucose markedly decreased from 43 C-% to 3 C-% due to the formation of insoluble side products.

2.2 *Hydrolysis of Cellulose in Water and Under Hydrogen*

Hydrolysis of cellulose has also been investigated under pressure of hydrogen with the aim of directly converting the in situ produced glucose into higher value added chemicals (Scheme 4). Fukuoka et al. have investigated a tandem reaction involving (1) a hydrolysis of cellulose to glucose and (2) a reduction of glucose to sorbitol and mannitol [48, 49]. At 190°C, with a pressure of 50 bar of hydrogen and in the presence of HZSM-5 as solid catalyst, the yield of glucose was very low (4%). This low yield was ascribed to a strong solid-solid interaction between cellulose and the catalyst. Under the same conditions, Pt and Ru supported on different supports (HUSY, SiO_2–Al_2O_3, Al_2O_3) were more active in the conversion of cellulose. The Pt/γ-Al_2O_3 catalyst gave 31% yield of hexitols (sorbitol 25% and mannitol 6%). The Ru/C catalyst afforded 22% yield of hexitols (sorbitol and mannitol in a molar ratio of about 3.6:1) at 38% conversion (in 5 min at 518 K and 60 bar H_2). Importantly, hexitol yield increased to 39% upon prolonging the reaction time to 30 min (85% of conversion) [50].

Deng et al. have also performed the hydrolysis of cellulose in the presence of metals (Fe, Co, Ni, Pd, Pt, Rh, Ru, Ir, Ag, and Au) supported over carbon nanotube (CNT) [51]. From commercial cellulose (crystalline, 85%), Ru supported catalysts (Ru = 1 wt%) was found to be the most efficient for the formation of hexitols



Scheme 4 Catalytic hydrolysis of cellulose under hydrogen

(yield = 40% at 185°C under 50 bar of hydrogen and after 24 h of reaction). Supported cellulose samples with different crystallinities (33–85%) have been prepared. With a decrease in the crystallinity of cellulose the relative amount of sorbitol was augmented. Over the Ru/CNT catalyst, and for cellulose with a crystallinity of 33%, sorbitol yield reached 69%.

Ji et al. have shown that nickel-promoted tungsten carbide catalysts can also directly convert cellulose to ethylene glycol in a one step process [52, 53]. These Ni-W_2C/AC catalysts exhibited a remarkable higher selectivity for ethylene glycol than Pt/Al_2O_3 and Ru/C. Indeed, after 30 min of reaction at 518 K under 60 bar of H_2, cellulose was completely converted into water-soluble polyols over a 2% Ni-30% W_2C/AC-973 catalyst (61% yield in ethylene glycol).

2.3 *Hydrolysis of Cellulose in Ionic Liquids*

The depolymerization of cellulose has been investigated in ionic liquid such as 1-butyl-3-methylimidazolium chloride (BMIMCl). ZSM-5 zeolite, SiO_2–Al_2O_3, sulfated ZrO_2, γ-Al_2O_3, Nafion, and Amberlyst (15, 35, 70) have been mainly investigated as solid acid catalyst [54]. In BMIMCl, Amberlyst 15 and 35 exhibited a remarkable activity and, after 5 h of reaction at 373 K, 48% of cellulose was converted to monosaccharides and disaccharides. Furthermore, after 1.5 h of reaction, cello-oligomers with a degree of polymerization around 30 can be conveniently isolated with high yields (90%) on precipitation by addition of water.

2.4 *Summary*

Heterogeneously-catalyzed hydrolysis of carbohydrates is governed by several parameters. The most important of them is the accessibility of the catalytic sites and the stability of solid catalysts in water.

Cation-exchange resins are very attractive for this reaction mainly because of their availability on a large scale. Best results were obtained with “flexible” resins. However, their instability at temperatures higher than 110°C represents an important obstacle for their industrial use. Owing to their high surface area and their stability in water, sulfonated mesoporous benzene-silica with crystal-like pore walls (Ph-PMO-SO_3H) are now emerging as promising solid catalysts for the hydrolysis of carbohydrates.

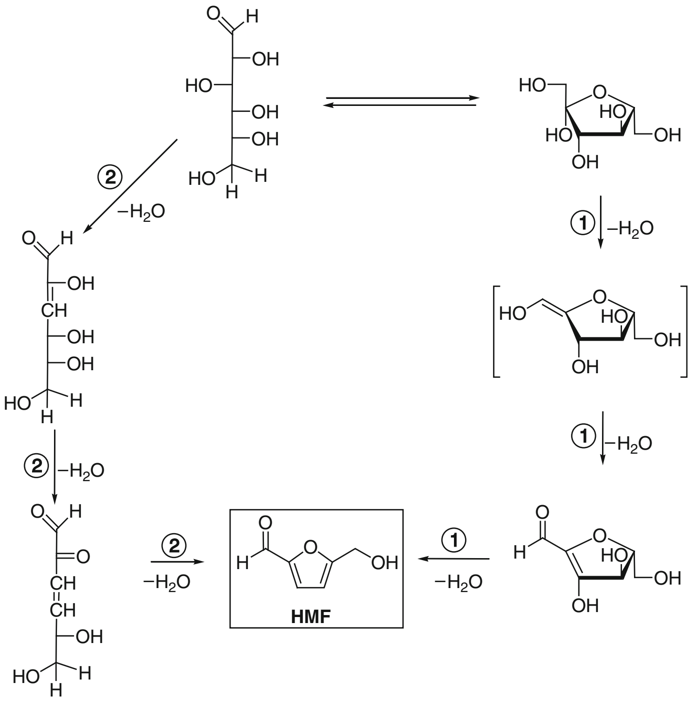
The most spectacular solid catalyst reported in the literature is probably the sulfonated carbon. Indeed, in contrast to all other solid catalysts, sulfonated carbon was able to hydrolyze, in water, cellulose to soluble 1,4-β-glucan with high yield. The presence of hydroxyl groups on the carbon surface was found to be crucial and allows a better adsorption of cellulose on the catalyst surface. However, the amount of catalyst used is unacceptable for an industrial application and much effort is still needed.

3 Heterogeneously-Catalyzed Dehydration of Carbohydrates to 5-Hydroxymethylfurfural

Catalytic dehydration of hexose polysaccharides to 5-hydroxymethylfurfural (HMF) is a highly valuable reaction. Indeed, from HMF, new generations of biofuel (e.g., dimethylfurane) and a wide range of intermediates and fine chemicals can be obtained [55–59]. Comprehensive reviews related to the utilization of HMF can be found in the literature [60–64]; see also Chap. by M. Moser.

HMF has been discovered for the first time in 1895 by Düll and Kiermeyer who independently introduced a method of synthesis of HMF that they named "oxymethylfurfurol" [65, 66]. Later, Haworth and Jones studied the mechanism of this reaction and showed that the formation of HMF involved a triple dehydration of hexoses [67]. Other studies performed by Van Dam, Kuster and Antal showed that the dehydration of hexoses (especially fructose and glucose) involved two possible pathways (Scheme 5) [63, 68, 69]. The path "1" involves the dehydration of ring systems (fructopyranose or glucopyranose), while the path "2" is based on acyclic derivatives (glucose and fructose open chain).

HMF is more easily produced from fructose than from glucose. From the viewpoint of organic chemistry, the synthesis of HMF seems rather simple



Scheme 5 Conversion of hexoses to HMF

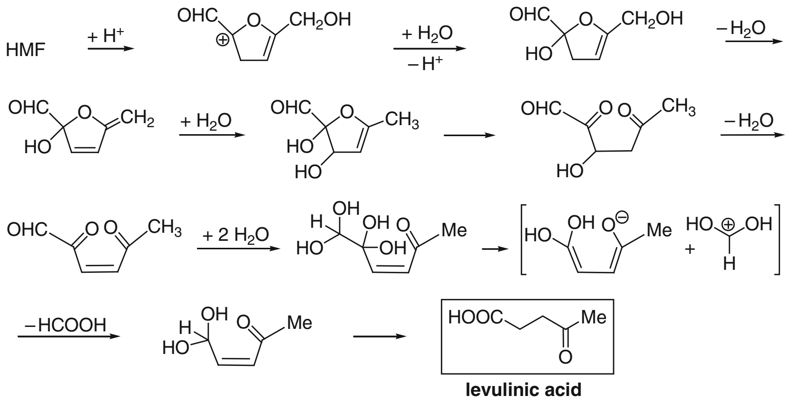
(Scheme 5). However, this reaction is not as easy as it looks since numerous side reactions may occur. Antal et al. showed that four different classes of reactions can take place from hexoses: (1) their dehydration leading to the formation of HMF, (2) their fragmentation, (3) their isomerization, and (4) their condensation leading to the formation of insoluble polymers and humins [58, 69]. Later, Van Dam and Cottier showed that at least 37 products can be produced, thus showing the complexity of this reaction. In particular, they highlighted that HMF can react with water, leading to the formation of undesirable side products such as levulinic and formic acids [68, 70].

In 1991, Cottier et al. classified the acid catalysts, known to be active for the production of HMF, in five groups: organic acids, inorganic acids, organic and inorganic salts, Lewis acids, and others [60]. As reported in Table 1, heterogeneous catalysts are rarely used for the production of HMF mainly due to the difficulty to design a water-tolerant solid catalyst.

If water represents an attractive solvent for the conversion of carbohydrates, the formation of HMF in water is rather complex, mainly due to the possible rehydration of HMF yielding levulinic and formic acids (Scheme 6). The mechanism related to the rehydration of HMF was discussed first by Pummerer in 1935 [71] and then by Horvath et al. in 1985 [72]. Conversion of HMF to levulinic acid is

Table 1 Catalysts used for the dehydration of polysaccharides

Organic acids	Oxalic acid, levulinic acid, maleic acid, *p*-toluenesulfonic acid
Inorganic acids	Phosphoric acid, sulfuric acid, hydrochloric acid, iodine, or hydroiodic acid generated *in situ*
Salts	$(NH_4)_2SO_4/SO_3$, pyridine/PO_4^{3-}, pyridine/HCl, aluminum salts, Th and Zr ions, zirconium phosphate, Cr, Al, Ti, Ca, In ions, $ZrOCl_2$, $VO(SO_4)_2$, TiO_2
Lewis acids	$ZnCl_2$, $AlCl_3$, BF_3
Others	Ion-exchange resins, zeolites



Scheme 6 Conversion of HMF to levulinic and formic acids

initiated by the addition of a molecule of water to the furan moiety of HMF. Note that, during this reaction, humic acids can also be formed as by-products.

With the aim of overcoming (1) the instability of solid catalysts in water and (2) the instability of HMF in the presence of water, other solvents such as dimethylsulfoxide and ionic liquids have also been explored.

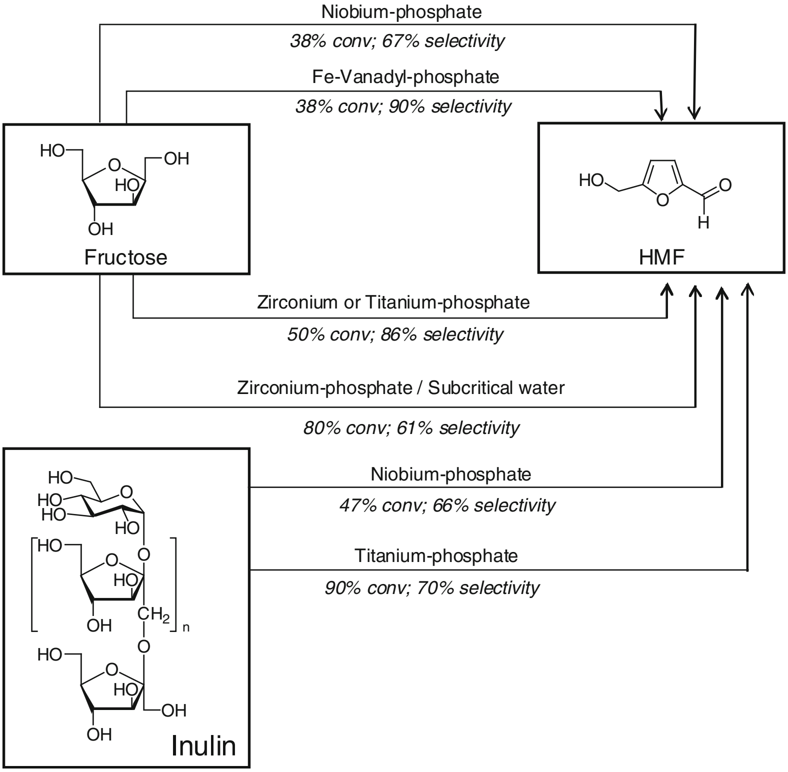
3.1 Production of HMF in Water

In 2008, Xiuyang et al. made an in-depth experimental study on the glucose decomposition in High Temperature Liquid Water (HTLW) from 180 to 220°C [73]. Interestingly, at 220°C, 100% of glucose was consumed within 90 min without addition of any catalyst. Analysis of the crude revealed that the main products of the reaction were HMF, levulinic acid, humic matter, and two unidentified soluble compounds. The maximum yield of HMF was obtained after 30 min of reaction (32%).

3.1.1 Phosphate-Based Solid Catalysts

In 1999, Carlini et al. investigated the ability of niobium-based phosphate to catalyze the selective dehydration of fructose, sucrose, and inulin to HMF (Scheme 7) [74]. Starting from fructose and using a column reactor packed with niobium phosphate catalyst, 67% selectivity to HMF was obtained at 38% conversion. This catalyst was stable in the presence of water and was successfully reused without notable change of activity. Interestingly, from sucrose and inulin, the niobium-based catalysts afforded HMF with 66% selectivity at 47% conversion. A significant improvement of both the catalyst activity and the HMF selectivity was achieved when the HMF was continuously extracted from the water phase with methylisobutylketone (MIBK). Indeed, under these conditions, HMF was produced with 98% selectivity at 60% conversion of fructose. Using the same procedure, but from inulin, HMF was obtained with 72% selectivity at 70% conversion.

Titanium and zirconium phosphates as well as pyrophosphates have also been investigated in the conversion of fructose and inulin to HMF (Scheme 9) [75]. Among all the investigated catalysts, cubic zirconium pyrophosphate and γ-titanium phosphate exhibited the best activity and selectivity, displaying a selectivity of HMF of 86% at 50% conversion. Starting from inulin, HMF was obtained with 70% selectivity at 90% conversion over γ-titanium phosphate. Despite both Brønsted and Lewis acid sites being involved in the reaction, authors pointed out that Lewis acid sites played the most important role. Indeed, an increase of the Lewis acid site strength increases the yield of HMF. As described above with niobium phosphate-based catalysts, a significant improvement of the HMF yield was achieved when the HMF was continuously extracted from water with MIBK (selectivity higher than 95% for a conversion in the range of 70–95%).



Scheme 7 Dehydration of fructose and inulin over phosphate-based catalysts

Vanadyl phosphate ($VOPO_4$ $2H_2O$), a layered material containing Lewis and Brønsted acid sites, was also tested as an acid catalyst in the dehydration of fructose to HMF (Scheme 7) [76]. These catalysts afforded HMF with a selectivity of 80% at 46% conversion of fructose. Other catalytic systems, obtained by partial substitution of VO^{3+} groups with trivalent metals (Fe^{3+}, Cr^{3+}, Ga^{3+}, Mn^{3+}, Al^{3+}), were also investigated. It has been shown that when Fe-substituted vanadyl phosphate was employed a selectivity of 90% to HMF was obtained at 38% conversion without the formation of secondary products such as levulinic and formic acid. This catalyst was also proved to be efficient for the conversion of inulin into HMF with the same selectivity as with fructose.

Later, Yoshida et al. reported the dehydration of fructose to HMF in a batch-type reactor under subcritical water (sub-CW) and with different zirconium phosphate solid acid catalysts at 240°C (Scheme 7) [77]. Over amorphous zirconium phosphate, 80% of fructose was converted after 120 s affording HMF with a selectivity of 61%. Interestingly, no side product stemming from the rehydration of HMF was detected in this case. However, soluble polymers and furaldehyde were detected as side products. Remarkably, zirconium phosphate solid catalysts were stable under subcritical water conditions and were reused without any loss of their activity.

3.1.2 Metal Oxides

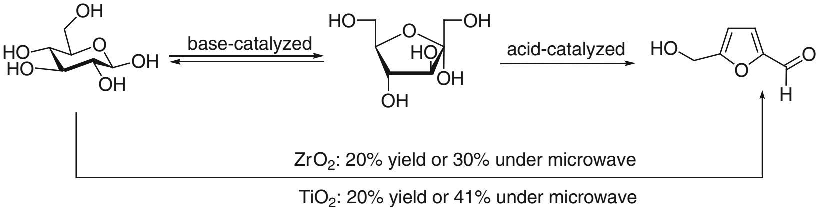
Production of HMF from glucose was also evaluated using titanium and zirconium oxides as solid acid catalysts in hot compressed water (473 K) [78–80]. Interestingly, it was found that the ZrO_2 catalyst acts as an acido-basic catalyst. Therefore, ZrO_2 was able to promote a tandem reaction involving (1) the isomerization of glucose to fructose and (2) the dehydratation to fructose to HMF (yield of HMF = 20%; Scheme 8).

In the presence of anatase TiO_2, the glucose conversion was significantly enhanced from 20 to 80% along with a HMF yield of 20% at 80% of conversion. Note that rutile TiO_2 was inactive. Interestingly, combining microwave activation with TiO_2 or ZrO_2 solid catalysts, the rehydration of HMF to levulinic and formic acids was suppressed. In the presence of ZrO_2, the HMF yield was ca. 30% at 65% conversion. When titanium oxide was used the yield of HMF reached 41% at 90% conversion.

3.1.3 Zeolites

Owing to the possibility of tuning (1) their acidic and basic properties, (2) their surface hydrophilicity, and (3) their adsorption and shape-selectivity properties, catalytic activity of zeolites was investigated in the production of HMF from carbohydrates. Whatever the hexose used as starting material, acidic pillared montmorillonites and faujasite were poorly selective towards HMF, yielding levulinic and formic acids as the main products [81–83].

As observed above, in order to quench HMF produced in situ, dealuminated H-form mordenites were investigated in a water/MIBK mixture (1/5) [84, 85]. In this case, a maximum conversion of fructose of 54% (along with 90% selectivity to HMF) was obtained over an H-mordenite with a Si/Al ratio of 11. HMF was continuously extracted with a flow of MIBK circulating in a countercurrent way through a catalytic heterogeneous reactor containing the H-mordenite zeolite. On the continuation of their efforts, the same authors then set up a new continuous solid-liquid-liquid reactor where the zeolite was now in suspension in the aqueous phase while the HMF was continuously extracted with MIBK in a countercurrent way to the aqueous phase and catalyst feed.

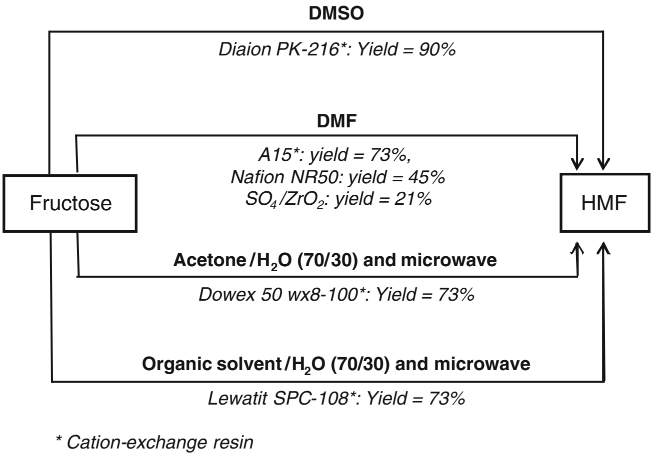


Scheme 8 Tandem isomerization/dehydration of glucose over ZrO_2 and TiO_2

3.2 Production of HMF in Organic or Organic/Water Solvents

With the aim of solubilizing carbohydrates while avoiding the side rehydration of HMF to levulinic and formic acids, dimethylsulfoxide (DMSO) has been particularly investigated as a possible solvent (Scheme 9). Over cation-exchange resins (Diaion PK-216), Nakamura et al. showed that 90% yield of HMF can be obtained from fructose in DMSO after only 300 min of reaction [86]. In DMSO, the resin was highly stable and no change of activity was observed after 900 h of reaction. This spectacular improvement of the HMF yield observed in DMSO was attributed to the ability of DMSO to dissolve the released water, thus avoiding the undesirable rehydration of HMF [87–90]. If good yield to HMF was obtained in DMSO, this process is still subject to strict limitations due to (1) the difficult extraction of the reaction products from the DMSO phase and (2) the possible formation of sulfurized side products stemming from the acid-catalyzed degradation of DMSO.

N,*N*-Dimethylformamide was also used as solvent in the production of HMF either from glucose or fructose (Scheme 9) [91]. In the presence of Amberlyst 15, Nafion NR50, SO_4/ZrO_2, Nb_2O_5 nH_2O, H-ZSM5, or H-Beta zeolites, no HMF was obtained from glucose at 373 K even after 3 h. Under the same conditions, fructose was successfully dehydrated in the presence of Amberlyst 15, Nafion NR50, or SO_4/ZrO_2, leading to HMF with 73, 45, and 21% yield, respectively. In order to favor the conversion of glucose to HMF, authors added both an acid and basic catalyst in the same reaction pot. Remarkably, with the concomitant presence of Mg-Al hydrotalcite and Amberlyst-15 catalysts, glucose was successfully converted to HMF within 3 h of reaction at 373 K (38% selectivity of HMF at 64% conversion). As observed above with ZrO_2 and TiO_2 (see Sect. 3.1.2), the basic catalyst promotes the isomerization of glucose to fructose while the acid catalyst enhances the dehydration of fructose to HMF.



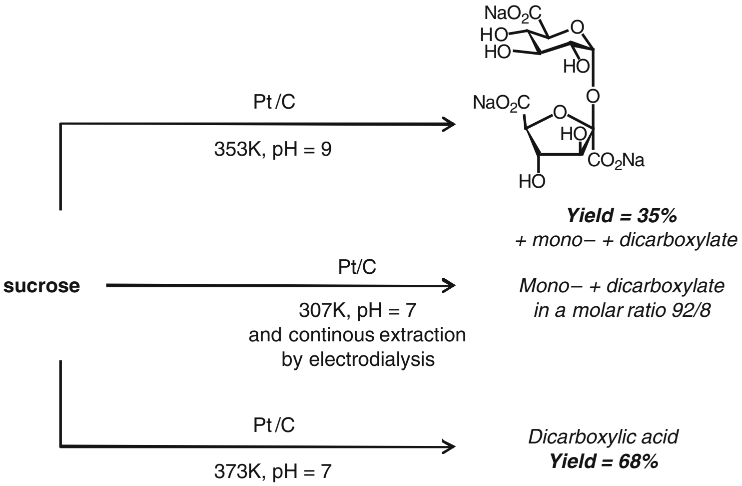
Scheme 9 Dehydration of fructose in organic and organic/water solvents

Mixtures of organic solvent and water have also been studied (Scheme 11). In this context, Watanabe and coworkers studied the catalytic dehydration of fructose to HMF at 150°C in acetone-water mixtures and in the presence of a cation-exchange resin catalyst (Dowex 50wx8-100) [92]. The use of acetone–water (70:30 w/w) as reaction medium resulted in a yield of HMF of 73% at 94% conversion. Moreover, under these conditions, the catalyst was stable for at least five catalytic runs. Assistance of microwave not only increased the selectivity to HMF but also had a beneficial effect on the reaction rate. In this context, Gaset et al. studied the activity of Lewatit SPC-108 (cation-exchange resin) in a mixture of organic solvent (MIBK or diethyl ketone or benzonitrile or butyronitrile or dichloroethylether or nitropropane) and water (from 1/7 to 1/12 by volume) at a temperature around 85–90°C Under these conditions, HMF has been obtained with a yield of 70–80% [93, 94].

3.3 Production of HMF in Ionic Liquids

According to the nature of their counter anion, ionic liquids (ILs) can dissolve a large amount of carbohydrates. In 2003, Moreau and co-workers reported the acid-catalyzed dehydration of fructose in a microbatch reactor at 80°C using 1-butyl-3-methyl imidazolium tetrafluoroborate ($BMIM^+BF_4^-$) (hydrophilic), and 1-butyl-3-methyl imidazolium hexafluorophosphate ($BMIM^+PF_6^-$) (hydrophobic) (Scheme 10) [95].

When the reaction was carried out in $BMIM^+BF_4^-$ in the presence of Amberlyst-15 (cation-exchange resins), 50% yield of HMF was obtained within 3 h (80% after



Scheme 10 Catalytic oxidation of sucrose over Pt/C

24 h). In the hydrophobic $BMIM^+PF_6^-$, it was necessary to add DMSO as a co-solvent in order to ensure a better solubility of fructose. Compared to neat DMSO, reactions performed in ILs afforded HMF with similar yield but with much shorter reaction time.

Interestingly, Qi, Smith, and co-workers reported that addition of an organic solvent such as acetone, DMSO, methanol, ethanol, ethylacetate, or supercritical carbon dioxide to $BMIM^+Cl^-$ allowed the reaction to proceed at room temperature. For instance, in the presence of Amberlyst 15 as solid acid catalyst, authors showed that addition of 5 wt% of acetone to $BMIM^+Cl^-$ yielded, at room temperature, HMF with 86% selectivity at 90% conversion. Further investigations revealed that addition of an organic solvent to $BMIM^+Cl^-$ allowed one to overcome important mass transfer at room temperature due to the high viscosity of $BMIM^+Cl^-$ [96].

König and co-workers also reported that Amberlyst 15 can promote the dehydration of carbohydrates to HMF using safe concentrated low melting mixtures consisting of choline chloride (ChCl) and about 50 wt% of carbohydrates. From fructose, glucose, sucrose, and inulin, HMF was produced with 40, 9, 27, and 54%, respectively within 1 h of reaction at a temperature around 100°C. Montmorillonite has also been used as a solid acid catalyst affording HMF with 49, 7, 35, and 7% yield from fructose, glucose, sucrose, and inulin, respectively [97].

4 Heterogeneously-Catalyzed Oxidation of Carbohydrates

Oxidation of carbohydrates can be achieved by either chemical or biochemical processes [98, 99]. Owing to their cation sequestering properties, the resulting carboxylic derivatives find potential applications in the detergent industries [100, 101]. Although homogeneous catalysts are often used in oxidation processes, utilization of solid catalysts has proved to be a feasible alternative [102].

4.1 Oxidation of Sucrose

Platinum supported on carbon (Pt/C) was tested as solid catalysts in the oxidation of sucrose using molecular oxygen as oxidant (Scheme 10). The reaction was carried out in water and under atmospheric pressure. The support strongly influences the reaction and Pt/C was found more efficient than Pt/Alumina at 353 K. Over Pt/C, at a pH of 9, mono-, di-, and tricarboxylate derivatives were mainly obtained with a tricarboxylate yield of 35% [103].

In 1994, Kunz et al. studied the oxidation of sucrose in the presence of Pt/C at 307 K and neutral pH [104]. Under these conditions, the positions 6, 6′, and 1′ of sucrose were mainly oxidized and a mixture of monocarboxylic and dicarboxylic acids (56/44) has been produced. Note that when the oxidized products were continuously removed by electrodialysis in order to avoid their subsequent oxidation a mixture of monocarboxylic and dicarboxylic acids with a molar composition of 92/8 was recovered [105].

At neutral pH and using Pt/C as solid catalyst, Edye et al. have shown that the dicarboxylic acid of sucrose can be obtained with 68% yield at 373 K [106, 107]. In contrast to the previous results obtained at pH 7.0, in this study the hydroxyl groups at C(6) and C(6′) were oxidized and no oxidation of $HOCH_2(1')$ had occurred.

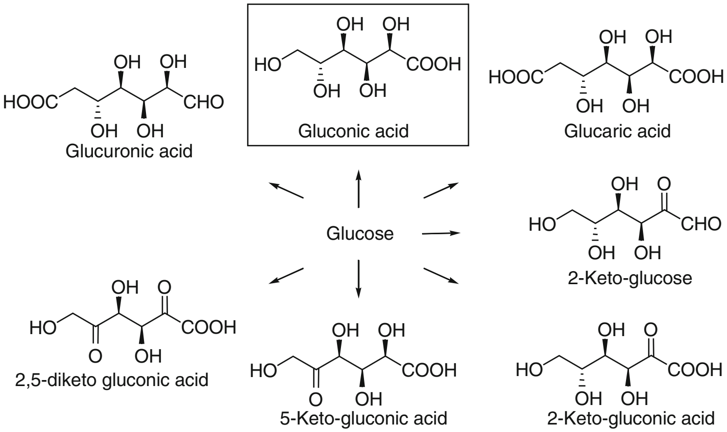
4.2 Oxidation of Glucose over Monometallic Solid Catalysts (Pt or Pd)

As depicted in Scheme 11, D-glucose can be converted to several oxidized products. In this section we will only discuss the heterogeneously-catalyzed oxidation of D-glucose to D-gluconic acid since this compound is one of the most valuable oxygenated derivatives obtained from glucose. Indeed, D-gluconic acid is now widely used as an intermediate in food and pharmaceutical industries [108].

Dirkx et al. clearly showed that, during the oxidation process, a strong deactivation of the solid catalyst, attributed to the formation of platinum or palladium oxides, occurred [109].

Effect of the pH (2–9) on the oxidation of D-glucose to D-gluconic acid was also investigated in the presence of 5 wt% of Pt/C [110]. Below pH 7 a poisoning of the catalyst was observed. Indeed, the conversion reached 45% at neutral pH and 28% only at pH 5, along with a selectivity to D-gluconic acid of 22 and 36%, respectively. At basic pH 9 the selectivity to D-gluconic acid was 75% for 85% conversion.

Hattori et al. patented the oxidation, under O_2 atmosphere, of D-glucose to D-gluconic acid using Pd/C. At 323 K and pH 9.5, gluconic acid was produced with 99% selectivity [111]. Later, in 1993, Besson et al. reported the oxidation of a concentrated solution of glucose (1.7 mol L^{-1}) using Pd/C catalysts with particle



Scheme 11 Products obtained from the oxidation of glucose

sizes larger than 3 nm, which gave complete conversion of glucose within 6 h whereas the conversion stopped around 66% over palladium with a particle size smaller than 2 nm [112]. This phenomenon was attributed to the poisoning of the palladium particles with oxygen, the smallest particles being the most prone to over-oxidation.

4.3 Oxidation of Glucose over Bimetallic Solid Catalysts

Fuertes et al. patented the effect of promoters such as bismuth on the catalytic activity of Pd/C. The reaction was performed with D-glucose using Pd-Bi/C (5 wt% Pt, Bi/Pt = 0.1), air as oxidant at 35°C, and pH 8.8 (aqueous solution of sodium hydroxide at 30%) [113]. The Pd-Bi/C catalyst was prepared by deposition of bismuth on the surface of palladium particles (1–2 nm) via a redox surface reaction [110, 114, 115]. The rate of D-glucose oxidation was 20 times higher over Pd-Bi/C (Bi/Pd = 0.1) than over Pd/C [116]. Similarly, the selectivity to D-gluconate was greatly improved (99.8% at 99.6% conversion). In addition, the catalyst exhibited an excellent stability since, after recycling, no leaching of bismuth and no deactivation of the catalyst was observed. This was attributed to the ability of bismuth to prevent the overoxidation of palladium particles mainly because of its stronger affinity for oxygen as evidenced by calorimetric measurements.

Karski and co-workers found that thallium acts also as a "promoter" and prevents the poisoning of the palladium particle with oxygen. Indeed, a bimetallic system which contained 5 wt% of Th led to 100% selectivity to gluconic acid at 95% conversion [117]. On their side, Bönneman et al. reported that charcoal-supported Pd-Pt catalysts prepared from a colloidal solution of Pd-Pt/$NOct_4Cl$ exhibit a superior activity and selectivity than industrial heterogeneous Pd-Pt-based catalysts [118].

4.4 Oxidation of Glucose over Gold-Based Solid Catalysts

Gold supported over carbon (Au/C) was investigated in the oxidation of D-glucose to D-gluconic acid using molecular oxygen as oxidant (P_{O2} = 1–3 bar). This reaction was conducted at 323–373 K in water over a pH range of 7–9.5 [119]. Remarkably, under these conditions, no isomerization of glucose to fructose was observed and a total selectivity to D-gluconate was obtained at 100% of conversion. Whereas conventionally used Pd-based or Pt-based catalysts were inactive under acidic conditions, Au/C is still active at a pH as low as 2.5. At a pH of 9.5, Au-M/C and Bi-M/C (with M = Pd or Pt) exhibited similar selectivity to gluconate but Au-based catalysts were always more active. Remarkably, as compared to Pd or Pt/C, Au/C is much more stable since no deactivation occurs, thus allowing the recycling of the Au/C catalyst.

On the basis of these results, a series of Au/C catalysts with different Au particle size (3–6 nm) were prepared using different reducing agents [120]. Authors found that Au/C with the smaller particle size (3 nm) was the most active solid catalyst in the oxidation of glucose. This relationship between the gold nanoparticle sizes and the catalyst activity was attributed to differences of adsorption of glucose on gold. As the metal particle size decreases, the relative proportion of active gold atoms located on corners and edges of the particles increases, thus increasing the oxidation rate of glucose. Influence of the reaction conditions ($T = 30$–$90°$C, pH 7.0–9.5) has also been examined using the most active Au/C catalyst (3 nm particle size). Best results were obtained at 50°C and a pH of 9.5. Note that, contrary to what was previously observed, when decreasing the pH of the reaction to 7, the reaction rate drops significantly. It was suggested that a partial poisoning of the catalytic sites caused by the increasing amount of gluconic acid in the reaction medium is the cause, the smaller the particle sizes the more sensitive they are toward their poisoning.

In 2005, Rossi and coworkers investigated the effect of the carbon support on the activity of Au/C catalysts in the oxidation of glucose under atmospheric pressure of oxygen at 323 K and a pH of 9.5 [121]. Au nanoparticles (in a range of 1–6 nm) dispersed on carbon XC72R (specific area 254 m^2 g^{-1}, pore volume 0.19 mL g^{-1}) were more active than Au nanoparticles dispersed on carbon X40S (specific area 1,100 m^2 g^{-1}, pore volume 0.37 mL g^{-1}). However, if the nature of the carbon support played a role on the catalyst activity, authors pointed out that the major role was played by the size of the Au nanoparticles, the smaller particles being the most active.

In 2006, Beltrame et al. investigated the catalytic activity of a colloidal solution of gold in the selective oxidation of D-glucose to D-gluconic acid. This reaction was performed at 303–333 K in water, at atmospheric pressure and with different glucose and oxygen concentrations at a pH of 9.5 [122]. The results showed that the reaction rate was proportional to the oxygen concentration.

In 2006, Mirescu et al. obtained gold colloids by reducing tetrachloroauric acid (HAuCl) with sodium borohydride ($NaBH_4$) in the presence of polymers as stabilizing supports [123]. Using chitosan (Au/chitosan), high selectivity in (99%) D-gluconic acid was obtained at 40°C and a pH of 9. Unfortunately, this catalyst was unstable. Interestingly, titanium oxide supported gold was far more active than the Au/chitosan catalyst. Au/TiO_2 was also highly stable and, even after 17 runs, no loss of activity and selectivity was observed.

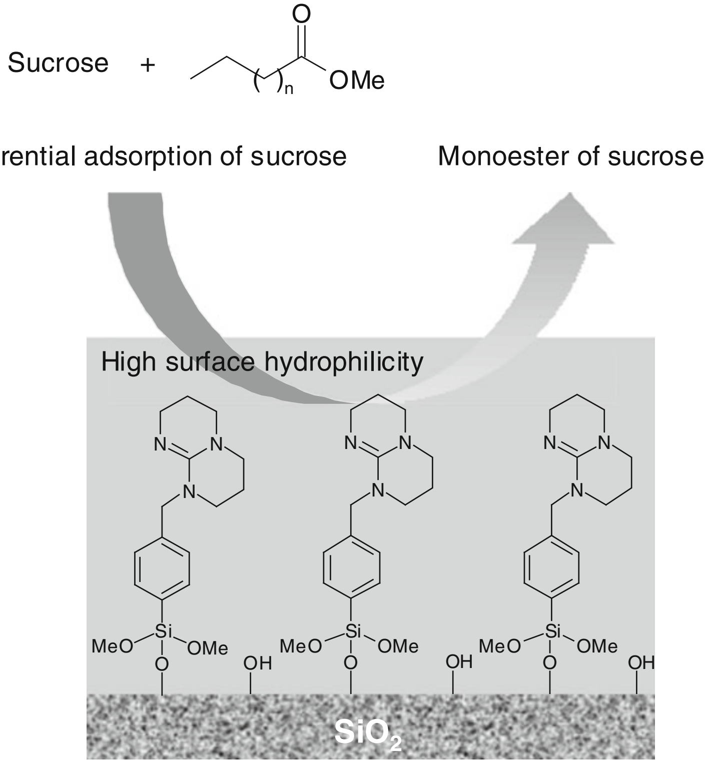
5 Heterogeneously-Catalyzed Esterification of Carbohydrates

Esterification of carbohydrates with fatty esters is an important reaction that provides an important class of safer non-ionic surfactants. These biodegradable surfactants are widely used in the detergent, cosmetic, pharmaceutical, and food industries [124–127].

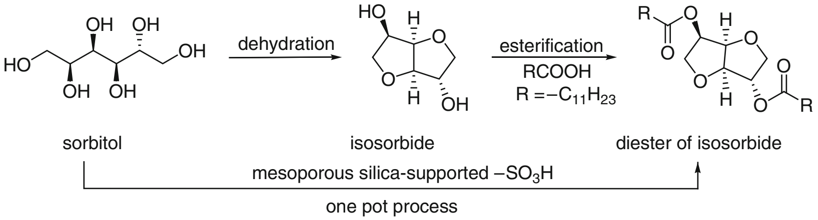
For environmental and economical reasons, sucrose esters are now receiving more and more attention [128]. Sucrose esters can be synthesized through an esterification or transesterification process. To date, most processes used for the esterification of sucrose involve homogeneous catalysts or enzymes and examples of solid catalysts are still scarce.

In 2005, Jerome and co-workers investigated the selective monoesterification of sucrose with various fatty methyl esters, in the presence of a strongly basic guanidine (triazabicyclo[4.4.0.]dec-5-ene (TBD)) grafted either over silica (HMS-TBD) or a polystyrene support (PS-TBD) (Scheme 12) [129].

The reaction was performed at 110°C under nitrogen atmosphere and using a concentrated solution of sucrose in DMSO (2 M). Starting from a sucrose/fatty ester molar ratio of 1, the HMS-TBD solid catalyst afforded the corresponding sucroesters with more than 90% yield along with a monosucroester selectivity of 68%. Under similar conditions, the PS-TBD solid catalyst was found to be 12 times less active (TOF = 2.1 h^{-1}) than HMS-TBD (TOF = 25 h^{-1}). Moreover, at total conversion, the PS-TBD solid catalyst was less selective to monosucroesters (48%). This difference of selectivity between PS-TBD and HMS-TBD was ascribed to a difference of surface hydrophilicity. Indeed, owing to a greater hydrophilicity, the amount of sucrose adsorbed on the siliceous surface is more important than in the case of the PS-TBD catalyst, thus creating an excess of sucrose on the HMS-TBD



Scheme 12 Selective esterification of sucrose over silica-supported strongly basic guanidine sites



Scheme 13 Acid catalyzed conversion of sorbitol to dilauryl isosorbide

surface and favoring the formation of monosucroesters. It should be noted that using a fourfold excess of sucrose, the corresponding monosucroesters were obtained with 80% selectivity.

Jacobs and coworkers reported the catalytic activity of a mesoporous silica-supported sulfonic sites in the esterification of sorbitol with lauric acid [130]. This reaction affords in a one step process the dilauryl isosorbide (dehydration of sorbitol/esterification). In contrast to zeolites, it is found that mesoporous silica-supported sulfonic sites afford the corresponding dilauryl isosorbide with 95% selectivity at 33% conversion (Scheme 13).

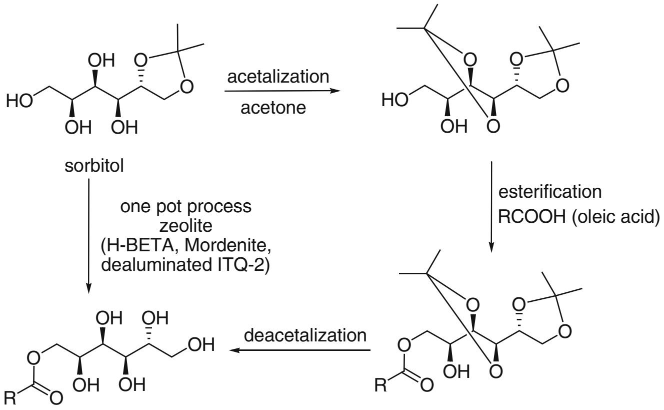
In order to avoid the acid-catalyzed dehydration of sorbitol to isosorbide, Corma et al. reported a new innovative three-step cascade route involving (1) an acetalization of sorbitol, (2) an esterification of sorbitol, and (3) a deacetalization of sorbitol esters (Scheme 14) [131]. In this case, esters of sorbitol were obtained. At 408 K, between 70 and 90% of conversion of sorbitol was obtained. Activity of the zeolites employed (H-Beta, mordenite, and dealuminated zeolite ITQ-2) was dependent on both their acidity and pore structure. The modernite catalyst has emerged as the most efficient.

Cation-exchange resin such as Amberlyst 15 has been used for the esterification of isosorbide with *n*-octanoic acid [132], giving the corresponding diesters in 98% yield.

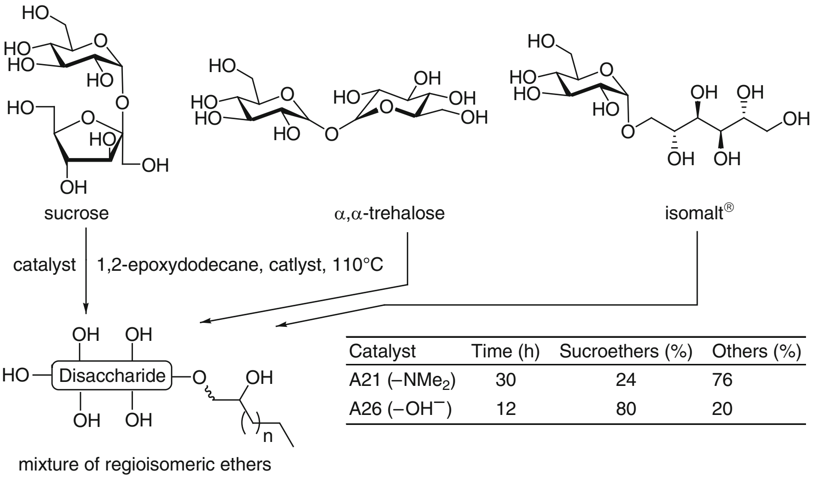
6 Heterogeneously-Catalyzed Etherification of Carbohydrates

As compared to the esterification of sucrose, catalytic etherification of sucrose provides another family of non-ionic surfactants that are much more robust than sucrose esters in the presence of water. Synthesis of sucroethers can be achieved according to two processes: (1) the ring opening of epoxide in the presence of a basic catalyst and (2) the telomerization of butadiene with sucrose using a palladium-phosphine catalyst.

Utilization of heterogeneous catalysts which are able to promote the etherification of carbohydrate is scarce. Usmani and co-workers reported the etherification of sucrose with poly(vinyl alcohol) in the presence of molecular sieves in DMSO [133]. This reaction afforded the corresponding sucrose ethers with a degree of



Scheme 14 Acid catalyzed three-step cascade route for the synthesis of ester of sorbitol

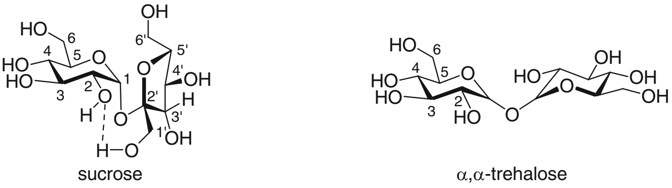


Catalyst	Time (h)	Sucroethers (%)	Others (%)
A21 (–NMe_2)	30	24	76
A26 (–OH^-)	12	80	20

Scheme 15 Heterogeneously-catalyzed etherification of disaccharides over anion-exchange resins

substitution of 3.4–5.4. In 2004, Barrault, Queneau, and coworkers reported the ring opening of 1,2-epoxydodecan with sucrose in the presence of basic anion exchange resins [134]. The best results were obtained using basic anion exchange resin (A26 OH^-) (Scheme 15). This reaction can also be conducted in water and the corresponding sucroethers are obtained with more than 85% yield. However, the catalytic process is much less selective to monoethers of sucrose in water than in DMSO. Indeed, at total conversion, monoethers of sucrose were obtained with 68% selectivity in DMSO vs only 36% in water.

The regioselectivity of the reaction was also investigated by means of NMR and HPLC studies. These investigations clearly showed that the etherification reaction



Position of the fatty chain

	2	3	4	6	1'	3'	4'	6'
Sucrose	**41%**	1%	5%	7%	25%	14%	4%	4%
Trehalose	24%	9%	30%	**37%**	-	-	-	-

HPLC analysis over-NH_2 column

Scheme 16 Regioselectivity of the reaction

mainly takes place at the C(2) of sucrose (41%). This regioselectivity was ascribed to the greater acidity of this position owing to the presence of a strong hydrogen bond (Scheme 16).

7 Conclusion

With the rapid development of material sciences, new solid catalysts are now emerging that offer attractive solutions for the selective conversion of carbohydrates into higher value added chemicals. Although ionic liquids have been reported to be promising solvents for carbohydrates, their toxicity and relatively high costs still represent a limitation to their application. More satisfying are heterogeneously-catalyzed processes conducted in water and using hydrophobic solid supports such as carbon or organic polymers.

As compared to conventional petrochemicals, the significant hindrance of carbohydrates induces many diffusional limitations and activity of solid catalysts is obviously strictly governed by the accessibility of the catalytic sites. In this context, the porosity of commonly used siliceous-based catalysts or metal oxides is not crucial since, because of the steric hindrance of carbohydrates, the catalytic reaction mainly takes place on the catalyst surface. In the case of organic polymers, utilization of flexible polymeric chains considerably improves the accessibility of the catalytic sites.

Oxidation of carbohydrates is probably the most efficient heterogeneously-catalyzed process since very high yield and selectivity are reported for reactions over solid catalysts. Despite important recent advances, the conversion of carbohydrates to HMF still requires further investigations. For reactions, in water, the yield of HMF is still too low due to the significant formation of side products. Today, several procedures for the conversion of monosaccharides, disaccharides, oligosaccharides, and starch in water into high value added materials are available. With cellulose, its heterogeneously-catalyzed conversion into useful products remains a challenge. Indeed, the low solubility of cellulose in water requires overcoming important solid-solid interactions with the catalyst. Up to now, the most efficient strategies consist in the utilization of sulfonated carbon or in the assistance of hydrogen in order to convert directly the in situ produced glucose to sorbitol, mannitol, or ethylene glycol. Fermentation processes are for the moment much more efficient than solid catalysts. In this context, the rapid progress of biocatalysis is expected to offer new tools for the design of efficient solid catalysts. In particular, combination of biocatalysis with heterogeneous catalysis is now emerging as a feasible approach for the valuation of cellulose, and, through that, of left-overs of the agriculture.

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Palladium-Catalyzed Telomerization of Butadiene with Polyols: From Mono to Polysaccharides

Sandrine Bouquillon, Jacques Muzart, Catherine Pinel, and Franck Rataboul

Abstract The telomerization of butadiene with alcohols is an elegant way to synthesize ethers with minimal environmental impact since this reaction is 100% atom efficient. Besides telomerization of butadiene with methanol and water that is industrially developed, the modification of polyols is still under development. Recently, a series of new substrates has been involved in this reaction, including diols, pure or crude glycerol, protected or unprotected monosaccharides, as well as polysaccharides. This opens up the formation of new products having specific physicochemical properties. We will describe recent advances in this field, focusing on the reaction of renewable products and more specifically on saccharides. The efficient catalytic systems as well as the optimized reaction conditions will be described and some physicochemical properties of the products will be reported.

Keywords Hydrophobic starch, Octadienyl ether, Palladium, Surfactant, Telomerization, Water catalyzed reaction

Contents

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Abbreviations

CMC	Critical micelle concentration
CTAB	Cetyltrimethyl ammonium bromide
dba	Dibenzylideneacetone
DMAc	Dimethyacetamide
DMI	Dimethyl isosorbide
DPPM	Diphenylphosphine methane
DS	Degree of substitution
HLB	Hydrophilic lipophilic balance
IMes.HCl	1,3-Bis(2,4,6-trimethylphenyl)imidazolinium chloride
MEK	Methyl ethyl ketone
MIBK	Methyl isobutyl ketone
PEG	Poly ethylene glycol
POEA	Polyethoxylated tallow amine
TOMPP	Tris(2-methoxyphenyl)phosphine
TON	Turnover number
TPPMS	(*m*-Sulfonato-phenyl) diphenyl phosphine monosodium salt
TPPTS	Tris(*m*-sulfonato-phenyl) phosphine trisodium salt

1 Introduction

More than 45 million tons of starch that are extracted from seeds, roots and tubers, by wet grinding, sieving and drying are transformed using either physical or chemical processes. Chemically modified starch founds applications mainly in papermaking but also as paint or food additives. Depending on the applications, different processes are developed to perform starch modification: for the preparation of highly substituted starch, gel phase is reported. On the other hand, for the synthesis of low substituted starch, the reaction is carried out in granular phase or even under "dry" conditions. The introduction of hydrophilic or hydrophobic functions to starch induces new properties for various applications. As far as hydrophobic properties are expected, examples of modifications include esterifications with acetate, alkylsiliconate, or fatty acid esters groups [1, 2]. However these methods use unfriendly stoichiometric

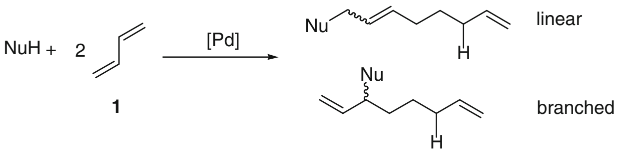


Fig. 1 Telomerization of butadiene with nucleophiles

reagents and base reactants. Etherification reactions were also described, albeit to a lower extent. Michael additions to activated double bonds were reported. The most efficient route consists of the reaction of starch with epoxyalkanes at high temperature in the presence of bases [3]. One approach consists of the telomerization reaction involving butadiene (**1**) as reactant catalyzed by homogeneous palladium complexes. This reaction has been largely developed since its independent discovery in 1967 by Takashi and Smutny [4, 5]. It consists of condensation of two molecules of diene with a nucleophile in the presence of a palladium complex (Fig. 1). The most used nucleophiles are methanol and water, leading to the formation of 1-methoxy-2,7-octadiene and 2,7-octadien-1-ol, respectively, as the main products, both having industrial applications as was recently reviewed [6].

This reaction is environmental friendly since it produces no salt, provides a 100% atom efficiency, and can be performed in water to fulfill some green chemistry principles. In this review, we wish to focus on the telomerization of mono and polysaccharides. As an introduction, recent results achieved with several polyols will be summarized.

2 Telomerization with Polyols

2.1 *In Organic Solvents*

Selective modification of polyols such as ethylene glycol, 1,3-propylene glycol, or glycerol with butadiene (**1**) has been studied [7–10]. The monosubstituted compounds are preferred due to their potential applications as surfactants, PVC plasticizers, or even in cosmetics. The telomerization of **1** with ethylene glycol yields a complex mixture including linear and branched mono- and ditelomers, as well as 1,3,7-octatriene and vinyl cyclohexene (Fig. 2) [11].

Several catalytic systems based on palladium chelated with phosphine or *N*-heterocyclic carbene were evaluated for such a reaction (Table 1) [12].

In the presence of triphenylphosphine as ligand, the main product is the monoether (45–60%) together with low amounts of ditelomers (<25%) and products issued from the dimerization of butadiene itself (vinylcyclohexene: VCH and octatriene: OCT). Both mono and ditelomers are formed as a 90:10 mixture of the linear and branched products. However, it is essential to optimize the ratio ligand/Pd from 1 to 4 to carry out the reaction (Table 1). Indeed, large excess of ligand (L/Pd = 8) or ligand defect (L/Pd = 0.25) provokes a lack of activity,

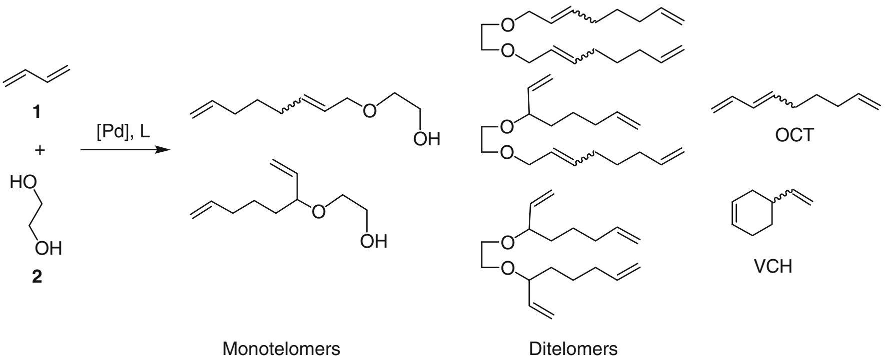


Fig. 2 Telomerization of butadiene with ethylene glycol

Table 1 Effect of the catalytic system on the selectivity of the reaction

(1) %	Ligand (equiv./Pd)	Mono	Di	VCH + OCT	TON
0.06	PPh_3 (4)	53	18	6	1,204
0.03	PPh_3 (4)	45	10	8	1,945
0.06	PPh_3 (2)	60	23	11	1,389
0.06	PPh_3 (1)	59	21	17	1,354
0.06	PPh_3 (0.25)	Decomposition of catalyst			
0.06	PPh_3 (8)	Decomposition of catalyst			
0.06	DPPM (1)	57	25	7	1,388
0.02	Imes.HCl (2)	51	41	1	4,299

Reaction conditions: palladium source = $Pd(acac)_2$, **1**/**2** = 2.5, THF, 80°C, 2 h

probably due to the instability of the catalytic system. Using bidentate phosphine DPPM as ligand yields results similar to the case of monophosphine ligand.

On the other hand, the highest reactivity is achieved in the presence of the complex prepared in situ from $Pd(acac)_2$ and N-heterocyclic carbene IMes.HCl (TON = 4.299). With this catalytic system, the dimerization of butadiene is negligible (1%). However, in that case, due to very high activity of the catalytic system, there is no selectivity towards the monotelomer, and a large amount of the ditelomer was formed (51 and 41% respectively).

More recently, optimization of the reaction conditions ([Pd] = 0.001%, Pd/Imes. HCl = 1/10, $NaOCH_2CH_2ONa$ = 0.5%, THF, 80°C) allows the formation of monoether in good chemoselectivity (60–80%) and the TON reaches 250,000 [10, 13]. This optimized system was evaluated with different diols and a high selectivity towards the monoether could be achieved with *trans*-1,2-cyclohexanediol.

In a similar approach, the telomerization of butadiene (**1**) with glycerol (**3**) was studied [7, 8]. Moreover, no additional solvent was necessary with this substrate. The corresponding monoether can be used as detergent or emulsifier while, after hydrogenation and sulfonation, the diether could be transformed to potential detergent molecule.

Thanks to the difference of reactivity between primary and secondary hydroxyl groups, mono and ditelomers corresponded only to the reactivity of the terminal alcohols (Fig. 3).

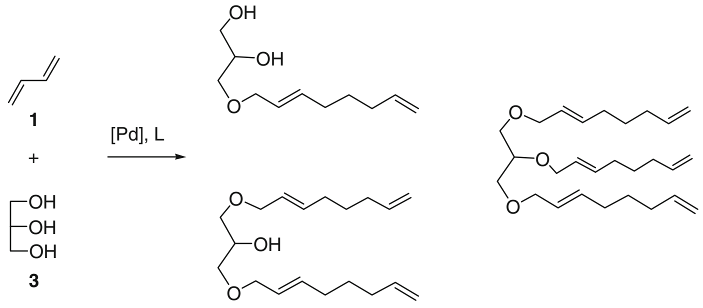
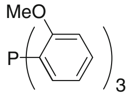
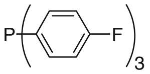
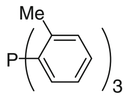
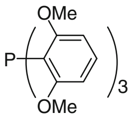


Fig. 3 Telomerization of butadiene with glycerol

Table 2 Influence of the nature of the ligand on the selectivity of the butadiene/glycerol telomerization

Ligand	t (h)/yield (%)	Monoether	Diether	Triether	TON
 TOMPP	0.5/67	58	29	14	1,520
	5/0.5	n.d.	n.d.	n.d.	14
	5/2	n.d.	n.d.	n.d.	50
	5/73	36	35	28	2,245

Reaction conditions: Pd(acac)$_2$ = 0.06 mol%, (Pd/L) = (1/5), **1**/**3** = 2.5, 80°C

Ligands such as TOMPP (tris(ortho-methoxyphenyl)phosphine) bearing electron-donating methoxy groups are advantageous to achieve high catalytic activity (Table 2). High selectivity of the mono- and diethers of glycerol can be achieved at lower butadiene/glycerol ratio (<2.5), high temperature (>90°C), and without solvent.

It was also shown that the reaction was efficient using crude glycerol resulting from the production of biodiesel but the activity is lower (TOF = 5,182 and 1,581/h for pure and crude glycerine respectively).

Recently, the Pd/TOMPP catalytic system was used in the telomerization of butadiene with a series of polyols and TON up to 10,000 was achieved with ethylene glycol or 1,3-propanediol [14].

The telomerization of the lower reactive isoprene with glycerol was achieved in the presence of palladium-carbene complex but in a dioxane/PEG solvent [15]. Under such conditions, both glycerol and PEG are converted. After 24 h, in the presence of 0.06% [Pd(acac)$_2$/IMes.Cl] (1/1.5) at 90°C, the telomerization of isoprene with glycerol (glycerol/PEG/dioxane/isoprene = 1/2.5/2.5/5) yields 70% of the linear monoether glycerol together with 29% of PEG telomer.

2.2 *Under Biphasic Conditions*

To circumvent the formation of ditelomers and to attempt recycling of the catalysts, the telomerization of polyols was studied in the presence of water using water soluble catalysts such as Pd/TPPTS (TPPTS = tris(*m*-sulfonato-phenyl) phosphine trisodium salt) [9, 12, 16, 17]. Behr et al. studied the telomerization of ethylene glycol under biphasic conditions. Under such reaction conditions, 80% of monotelomer are formed and only traces of ditelomer and butadiene dimers are detected (Fig. 4). This is attributed to the solubility of the monomer in the catalyst phase. However, the catalyst is unstable and decomposes rapidly, leading to almost inactive catalyst after three runs. This is due to TPPTS oxidation during the work-up of the reaction and can be avoided by addition of 2.5 equiv. ligand in the solution prior to each run.

In situ Pd(acac)$_2$/IMes.HCl catalyst was evaluated under biphasic conditions. The activities of this catalyst are lower compared to those obtained under monophasic conditions (963 and 2,150/h respectively) because the catalytic system is

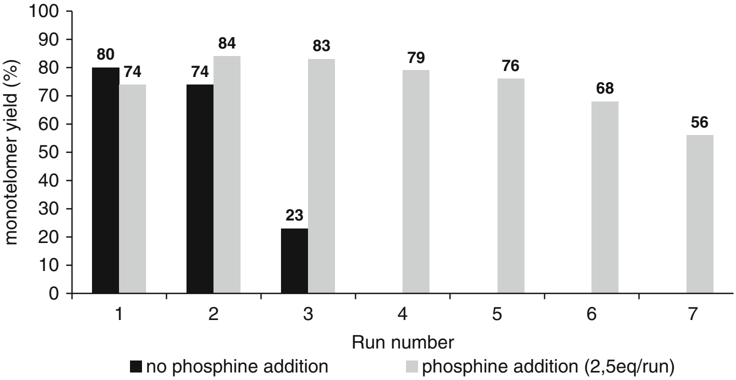


Fig. 4 Telomerization of butadiene with ethylene glycol under biphasic conditions: reuse of the catalyst

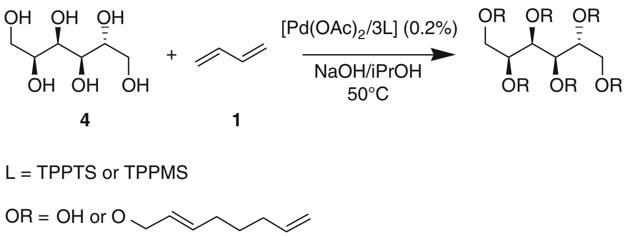


Fig. 5 Telomerization of butadiene with sorbitol

Table 3 Telomerization of butadiene with sorbitol

[Pd]%	[NaOH] (mL)	Butadiene (equiv./OH)	t (h)	DS
0.05	0.1 M (60)	1.2	16	0.78
0.1	0.1 M (60)	2.0	30	1
0.2	0.1 M (30)	3.4	64	2.5
0.2	1 M (30)	3.5	64	5

Reaction conditions: $Pd(acac)_2$/TPPTS (1/3), 50°C, aq. NaOH/*i*-PrOH = 5/1

partially soluble in organic phase. The selectivity towards the monotelomer is modest and no efficient recycling is achieved.

The aqueous biphasic approach using Pd/TPPTS complex has been applied to a range of diols as well as glycerol yielding the selective formation of the monotelomer ($>95\%$) [9, 16]. TON up to 990 was reached and the catalyst was recycled for five runs. It was shown that the addition of cyclodextrin leads to slightly higher conversions. It was proposed that an inclusion complex between cyclodextrin and butadiene was formed that increased the solubility of butadiene in the water phase. Moreover, in the presence of highly water soluble cyclodextrins such as Me-β-cyclodextrin (DS = 1.8), the palladium leaching was significantly reduced (<50 ppm).

This reaction was applied to a series of polyols issued from reduced saccharides such as sorbitol (**4**, see Fig. 5), xylitol, maltitol, isomaltitol, but in alkaline conditions [18, 19]. Depending on the reaction conditions, a very large range of DS was obtained.

Sorbitol (**4**) exhibits low reactivity, so a large excess of butadiene was used in the reaction (Table 3). Almost fully substituted sorbitol can be obtained using 1 M NaOH/*i*-PrOH solvent for 3 days. At DS = 5, the resulting product was soluble in apolar solvents such as petroleum ether [20].

3 Etherification of Protected Monosaccharides in Organic Solvents

The telomerization of butadiene (**1**) with protected pentoses has been particularly studied using 2,3,4-tri-*O*-acetyl-D-xylopyranose (**5**) [21] and 2,3,4-tri-*O*-benzyl-β-D-arabinofuranose (**8**) [22] as the telogens, in a 50-mL stainless steel autoclave reactor (Fig. 6). These reactions afford linear 2,7-octadienyl- and branched 1,7-octadien-3-yl carbohydrate derivatives as well as oligomers of butadiene.

High conversions of **5** and satisfactory yields required a large excess of butadiene but depended also on the telogen and solvent loading. For examples with the [$Pd(acac)_2$/$2PPh_3$] catalytic system (2 mol% of Pd) at 75°C for 1.5 h, the **6** + **7** yield was 31% using 3 mmol of **5** and 30 mmol of **1** in 4 mL of DMF, but increased to 58% in tripling the amount of **5** and DMF. This is due to the dependence of the butadiene concentration on the gas-liquid equilibrium since both reactions were carried out in the same autoclave. In agreement with this proposal, 96% yield was attained when performing the reaction of 3 mmol of **5** in 4 mL of DMF, using 45 equiv. of **1** instead of 10 equiv. Under the above experimental conditions, the linear:branched **6**:**7** ratio depends on the relative amounts of **1** and **5**, but is almost constant throughout the course of the reaction. The use of a range of solvents and phosphanes has shown their influence on the yields and the linear:branched ratios. Hexane, benzene, and toluene were not suitable owing to their low solubilization of **5**, while 87–98% yields were obtained with PPh_3 as ligand in DMF, CH_2Cl_2, MeCN, and THF with a **6**:**7** ratio varying from 2.6:1 to 15.6:1. As for triphenylphosphine, P(*p*-tol)$_3$ and P(*o*-tol)$_3$ afforded similar results while trialkylphosphanes led only to traces of **6** and **7**.

To examine the reactivity of **5** at lower temperatures, the $Pd_2(dba)_3{\cdot}CHCl_3/PPh_3$ system has been used as the catalyst since the reduction of the Pd^{II} pre-catalyst may be difficult under these conditions [23, 24]. At 20°C, the reaction time has to be increased from 1.5 h to 1 day to reach a good conversion of **5**: 93% of **6** + **7** with a **6**:**7** ratio = 7.3:1 have been thus obtained. Interestingly, performing the reaction under the same conditions, except for the presence of 0.1 equiv. of BuLi as additive, increased the yield to 98% and the selectivity to 19:1.

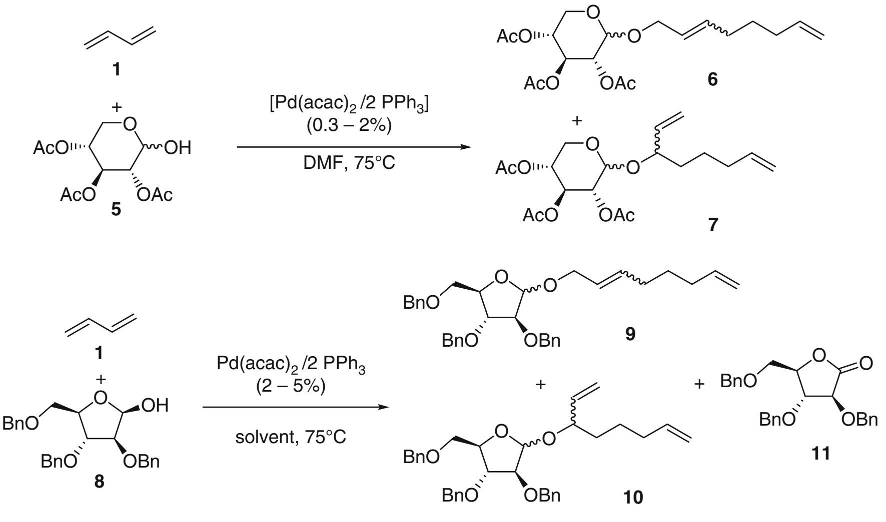


Fig. 6 Telomerization of butadiene with protected pentoses

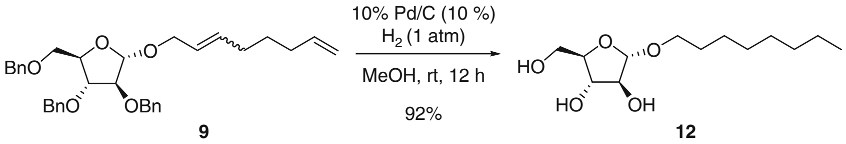


Fig. 7 Deprotection-hydrogenation of benzylated pentose

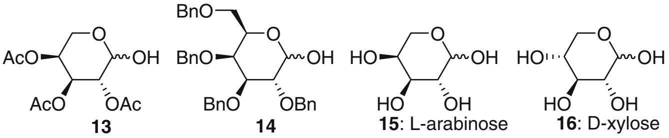


Fig. 8 Examples of aldoses used as telogens

As shown in Fig. 6, **5** as well as **6** and **7** are mixtures of α- and β-stereoisomers. The α:β ratios depend on the solvent, catalyst and traces of impurities. In the absence of palladium, the α:β ratio for **5** in CD_3CN decreases with time (2.4 after 5 min and 1.6 after 12 h). Since most experiments led to **6** and **7** having α:β ratios lower than for the starting material, it seems that the **5β** anomer of the starting material is more reactive than the **5α**.

As for **5**, the efficient transformation of **8** requires a large excess of **1**, but the strong difference is the concomitant formation of lactone **11** in DMF, THF, and especially toluene [22, 25]. The highest **9**:**10** ratio was achieved in toluene (17:1) but at the expense of the yield (23%) because of the formation of **11** as the main product (75% yield). The best results were obtained in acetonitrile, at 75°C for 24 h, with 30 equiv. of butadiene and the $Pd(acac)_2/2PPh_3$ catalytic system (2 mol% of Pd). These conditions led to a 5:1 mixture of **9** and **10** in 99% yield.

The Pd-catalyzed hydrogenolysis of the benzylated telomers **9** to obtain surfactants also leads to the reduction of the C=C bonds with formation of **12** (Fig. 7).

The telomerization of two other protected aldoses, **13** (2,3,4-tri-*O*-acetyl-L-arabinopyranose) and **14** (2,3,4,6-tetra-*O*-benzyl-D-galactopyranose) (Fig. 8), has been briefly examined: corresponding adducts were isolated with yields up to 85% from **13** in DMF [21], and 91 or 93% from **14** in CH_2Cl_2 and THF respectively [22].

4 Etherification of Unprotected Monosaccharides

4.1 In Organic Solvents

Since L-arabinose (**15**) and D-xylose (**16**) (Fig. 8) are easily extracted from wheat straw and bran [26, 27], the telomerization of **1** with these pentoses constitutes an attractive route to prepare surfactants without the use of expensive protection and deprotection steps.

Even if the anomeric hydroxyl group is the most reactive, the presence of five nucleophilic hydroxyl groups in these substrates can lead to the formation of various mono- and polyethers. Moreover, these ethers can be pyranose or furanose derivatives with linear and branched octadienyl tethers (Fig. 9).

The sugar conversion and the monoethers/polyethers ratio (mono/poly ratio) were determined at 75°C for 140 min, using [$Pd(acac)_2/3PPh_3$] as the catalytic system with a sugar/butadiene/Pd ratio = 150:900:1 in DMF [28, 29]. Under these conditions, the conversions of **15** and **16** were 31 and 39% respectively with mono/poly ratio = 5.2 and 8.1. Interestingly, the addition of triethylamine (20 equiv./Pd) increased the conversion and the selectivity towards the monoethers: 51 and 56% conversions with mono/poly ratios = 9 and 19 for **15** and **16**, respectively (Table 4). The conversion is also sensitive to the nature of the phosphane and to the Pd/phosphane ratio. Indeed, variation of only the phosphane leads to conversions varying from less than 2 to 99%, alkyl phosphanes and sterically hindered aryl phosphanes being less effective. The selectivity also depends on the phosphane (Table 4) [29].

The reactivity of **15** in other solvents (Table 5) has shown that MeCN and *t*-BuOH are suitable, but the differences in the amounts of the reagents and the reaction times preclude actually determining the optimum solvent.

Nevertheless, it appears that the selectivity seems to depend on the nature of the solvent, only monoethers being observed in low polar toluene but with a low conversion of the sugar even for a much diluted solution and a prolonged reaction time. The structure of the major monoethers has been established by peracetylation of the mixture (Fig. 10) [29, 30].

Associated to PPh_3 and NEt_3, $Pd(OAc)_2$ and $Pd_2(dba)_3{\cdot}CHCl_3$ afforded results rather similar to those obtained with $Pd(acac)_2$, while $PdCl_2$, $PdCl_2(MeCN)_2$, and $PdCl_2(PhCN)_2$ provide no more than 10% conversion of the sugar. To improve the process, a number of experiments has been carried out from **15** and **16** on reducing the catalyst loading and/or on increasing the sugar concentration. The amount of the catalyst has thus been reduced up to 0.7 mol% with an increase of the sugar concentration ≥ 1.3 M in keeping a sugar conversion $\geq 95\%$ [30].

The telomerization has also been carried out using D-glucose (**17**) as the telogen. As expected, the increase of the amount of **1** and reaction time under conditions depicted in Fig. 11 increased the relative quantity of di-and tri-octadienylglycosides

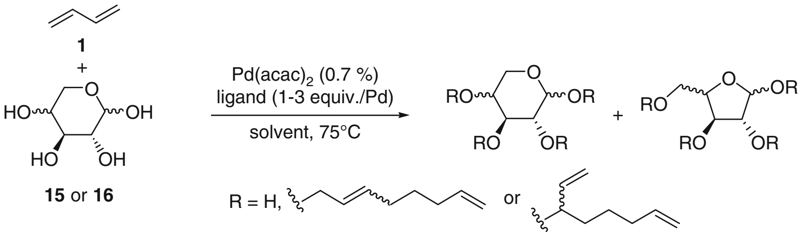
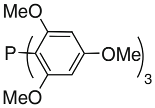


Fig. 9 Telomerization of butadiene with unprotected pentoses

Table 4 Influence of the amounts of NEt_3 and ligand, the nature of the ligand, and the reaction time on the pentose conversion and the selectivity[a]

L	Pd/L/NEt_3	Time (min)	Conv. (%)	Mono/polyether
From **15** (L-arabinose)				
PPh_3	1:3:0	140	31	5.2
PPh_3	1:3:20	140	51	9
PPh_3	1:3:150	140	58	10
PPh_3	1:2:150	140	68	3.5
PPh_3	1:2:150	320	88	3.2
P(*p*-tolyl)$_3$	1:2:150	45	97	1.2
P(*o*-tolyl)$_3$	1:2:150	45	86	2.2
P(*p*-ClC_6H_4)$_3$	1:2:150	45	69	4.6
	1:2:150	45	6	5.2
From **16** (D-xylose)				
PPh_3	1:2:0	140	39	8.1
PPh_3	1:2:20	140	56	19
PPh_3	1:2:150	45	97	2.2
P(*p*-tolyl)$_3$	1:2:150	45	99	1.2
dppe	1:2:150	45	8	–[b]
P(*n*-Bu)$_3$	1:2:150	45	<2	–[b]
Ph_2PNEt_2	1:2:150	45	95	1.2

[a] Using $Pd(acac)_2$ (0.7 mol%) as the pre-catalyst, 6.66 mmol of sugar, 40 mmol **1** in 25 mL of DMF at 75°C

[b] Only monoethers

Table 5 Influence of the nature of the solvent on the conversion of **15** (L-arabinose) and the selectivity[a]

Solvent (mL)	**15** mmol	**15**/**1**/Pd	Time (min)	Conv. (%)	Mono-/polyether	Di-/triether
DMF (25)	6.66	150:900:1	140	68	3.5	–[c]
THF (25)	3.33	75:900:1	140	0	–	–
MeCN (20)	3.33	75:900:1	140	96	0.9	16.3
CH_2Cl_2 (20)	3.33	75:900:1	180	29	4.9	–[c]
t-BuOH (15)	6.66	150:900:1	120	100	0.3	2.6
DMSO (5)	6.66	150:900:1	45	85	3.9	3
PhMe (20)	3.33	75:900:1	180	33	–[b]	–

[a] Using $Pd(acac)_2/PPh_3$ (1/2) as the catalyst at 75–80°C, **1**/NEt_3 = 1/6

[b] Only monoethers

[c] No triethers

[30]. Given the structure of the main mono-octadienylglycosides (Fig. 11), the first etherification occurs mainly with the anomeric hydroxyl of **17**. The higher reactivity of the anomeric hydroxyl has also been exemplified with the slow conversion of methyl xylopyranoside under Pd-catalyzed reaction with butadiene [31].

In the course of these optimizations, it has appeared that the amine influence disclosed above, disappeared at high sugar concentrations. This observation, which is highlighted in Fig. 12 and Table 6, with **16** as the sugar, may contribute to an

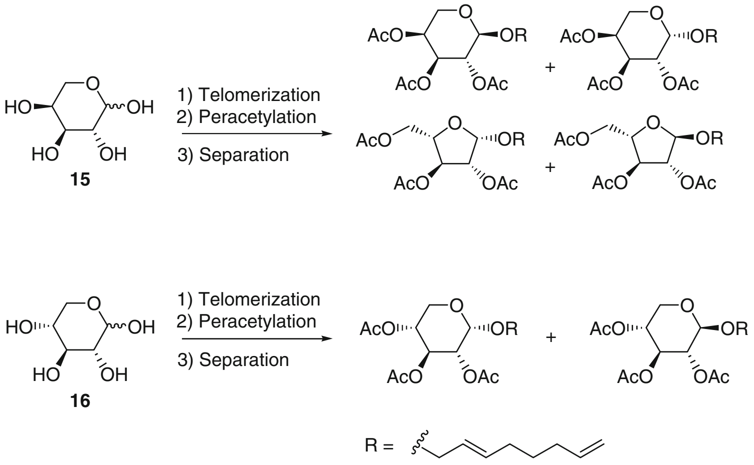


Fig. 10 Characterization of monoethers issued from arabinose and xylose

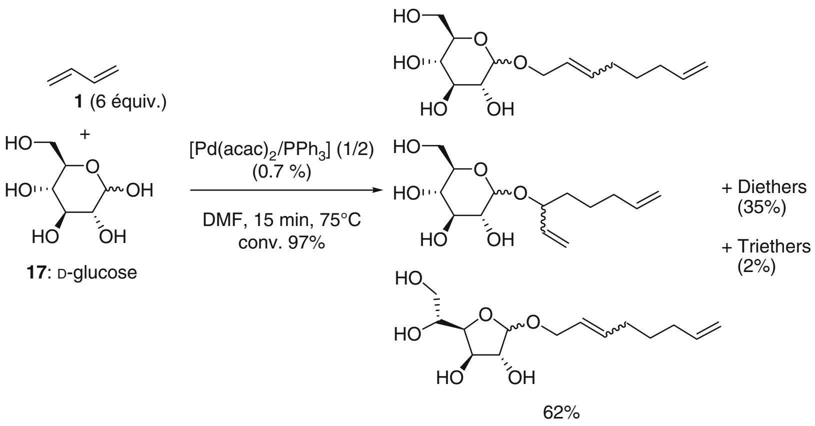


Fig. 11 Telomerization of butadiene with glucose

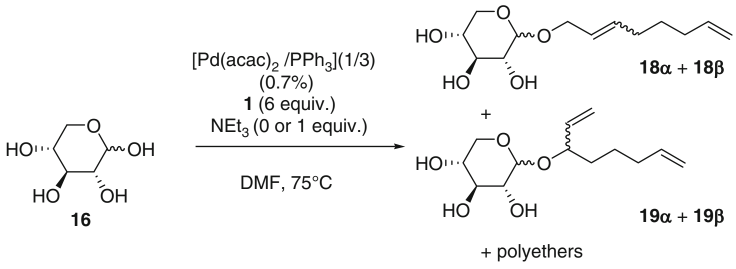


Fig. 12 Telomerization of butadiene with xylose in the presence of triethylamine

Table 6 Influence of the role of amine on the conversion of **16** and the selectivity[a]

16 (mol/L)	NEt_3 (equiv.)	Time (min)	Conv. (%)	**18** (%)	**19** (%)	Polyethers
0.27	0	135	39	22	13	4
0.27	1	135	56	42	10	3
1.34	0	135	98	45	16	37
1.34	1	135	97	46	16	36
1.34	0	15	63	44	15	4
1.34	1	15	74	51	17	6

[a] **16**/**1**/$Pd(acac)_2/PPh_3$ = 150:900:1:3 at 75°C

Table 7 Telomerization of butadiene (**1**) with D-xylose (**16**), recycling of Pd-TPPTS-KF/Al_2O_3 catalyst

Run	Conv. (%)	Yield monoether (%)
1	81	77
2	77	73
3	72	71
4	66	65
5	68	67

Reaction conditions: **1** (12 equiv.), Pd(TPPTS)n-KF/Al_2O_3 (0.07 equiv. Pd), $CH_3(CH_2)_{11}NMe_2$ (1 equiv.), DMF, 80°C, 1 h

Table 8 Telomerization of butadiene with monosaccharides using Pd/TOMPP catalyst

Sugar	Time (min)	Conv. (%)
15	12	84
16	15	66
17	25	87
D-Galactose	25	82

Reaction conditions: **1** (4 equiv.), Pd/TOMPP (0.02% Pd/OH unit), P/Pd = 4, DMAc, 80°C

easier work up, and may have economical implications. High conversions can be attained but the selectivity towards the monoethers decreased with the sugar concentration. It has also been observed that the ratio between linear and branched monoethers is quite independent of the reaction time [31].

The use of a heterogeneous catalyst prepared from $Pd(acac)_2$, $(m\text{-}NaSO_2C_6H_4)_3P$ (TPPTS), and KF/Al_2O_3, has been evaluated with the aim of obtaining recyclable catalytic systems [32]. KF/Al_2O_3 has been chosen as support of Pd^0 species, because this basic material mediates the addition of nucleophilic species to η^3-allylpalladium intermediates [33–36]. Moreover, it was previously observed that the $Pd(TPPTS)_n$-KF/Al_2O_3 thus obtained was efficient for the telomerization of **1** with methanol and phenol [37]. This catalyst allows recycling experiments leading, in five successive runs, to a global turnover number >500 for the formation of the monoethers of **16** (Table 7).

Very recently, the Pd/TOMPP catalytic system (Table 2) was developed for the efficient telomerization of several carbohydrates. The reaction was performed for 12–25 min at 80°C in DMAc as solvent. Conversions in the range 66–87% were achieved (Table 8) yielding a mixture of mono-, di-, and tritelomers. It must be stressed that no base was used in this reaction. However, deactivation of catalyst was reported due to the reactivity of anomeric hydroxyl groups [38].

4.2 In Water

Greener methodologies often involve reactions in aqueous media. The telomerization of glucose in an *i*-PrOH/H_2O mixture has been reported using 0.2% $Pd(acac)_2$/PPh_3 as catalyst for 12 h at 65°C. After hydrogenation of the resulting octadienyl ethers, a mixture of saturated monoether (14%), diether (37%), and triether (40%) has been obtained [11, 19, 39]. However, the application of these conditions to L-arabinose (**15**) was disappointing since the sugar conversion attained only 21% and a non-negligible amount of octadienol was observed [29]. Much better results were obtained using the $Pd(acac)_2$/TPPTS catalytic system in water but the presence of a base, in particular an amine, was required [40]. Under these conditions, mono-, di-, tri-, and tetraethers have been obtained in ratios depending on the nature of the base, the reaction time and the quantity of butadiene (Tables 9 and 10). Monitoring the reactions in the presence of $Me_2NC_{12}H_{25}$ over time has shown an induction period before the etherification process. This has been attributed to the formation of the active Pd^0 species. The Pd^{II} reduction can be induced by various compounds present in the mixture, water [41, 42], pentose [42], TPPTS [43], and amine [44, 45], the real reducing material remaining the matter of debate [46].

It has been reported that the use of aqueous-organic biphasic systems may enhance the selectivity (Sect. 1.2) [12, 16, 47, 48]. In fact, sugar diethers are quasi insoluble in water and can be extracted in the organic phase. When the telomerization is carried out in the presence of $Me_2NC_{12}H_{25}$ and a large excess of **1** (15 equiv., Table 9), the conditions are already biphasic: the diethers of **15** have thus been obtained in a 57% yield at 99% conversion of the telogen.

Table 9 Influence of the nature and concentration of the base, and the reaction time on arabinose (**15**) conversion and the selectivity in water

Base	Time	Conv.	Selectivity (%)			
(equiv./**15**)	(min)	(%)	Mono-ether	Diether	Triether	Tetraether
NEt_3 (0.16)	45	4	100	0	0	0
NEt_3 (0.5)	45	80	34	60	6	0
NEt_3 (1)	45	96	35	53	12	0
NEt_3 (1)	90	100	0	25	50	25
EtN(*i*-Pr)$_2$ (1)	45	63	79	21	0	0
$Me_2NC_{12}H_{25}$ (0.5)	45	67	13	52	29	6
$Me_2NC_{12}H_{25}$ (1)	45	99	4	57	37	2
KF/Al_2O_3[a]	45	94	33	48	19	–[b]

Reaction conditions: 6.66 mmol of **15** in 0.5 mL H_2O at 80°C; **15**/**1**/$Pd(acac)_2$/TPPTS = 150:2250:1:3

[a] 1.21 g of KF/Al_2O_3

[b] Not determined

Table 10 Influence of the quantity of butadiene (**1**) and the addition of a supplementary co-solvent on the L-arabinose (**15**) conversion and the selectivity

Amine	Cosolvent	**1/15** equiv.	Conv. %	Selectivity % Mono-	Di-	Tri-
$Me_2NC_{12}H_{25}$	–	15	99	4	57	37
$Me_2NC_{12}H_{25}$	–	6	96	14	63	23
$Me_2NC_{12}H_{25}$	–	3	25	40	55	5
$Me_2NC_{12}H_{25}$	$MeO(CH_2)_2OH$	15	96	8	65	27
$Me_2NC_{12}H_{25}$	$MeO(CH_2)_2OH$	6	98	21	61	18
$Me_2NC_{12}H_{25}$	$MeO(CH_2)_2OH$	3	90	42	49	9
$Me_2NC_{12}H_{25}$	AcOEt	15	7	6	94	0
$Me_2NC_{12}H_{25}$	*i*-BuCOMe	15	97	2	66	32
EtN(*i*-Pr)$_2$	$MeO(CH_2)_2OH$	15	42	97	3	0
EtN(*i*-Pr)$_2$	*i*-BuCOMe	15	66	92	8	0

Reaction conditions: 6.66 mmol of **15** in 0.5 mL H_2O and 1.25 mL of cosolvent if necessary at 80°C for 45 min; **15**/Pd(acac)$_2$/TPPTS/amine = 150:1:3:150

With 6 equiv. of **1**, this selectivity was even increased because of the relative lower amount of the triether (Table 10). Nevertheless, experiments have been performed with 2-methoxyethanol, methylisobutylketone, and ethyl acetate as a supplementary co-solvent. While ethyl acetate is not suitable, good sugar conversion was achieved in the presence of the two other co-solvents, even using a low excess (3 equiv.) of **1**. Switching to EtN(*i*-Pr)$_2$ as the base reduced the sugar conversion but raised the monoether selectivity up to 97%.

Recycling possibilities are often an advantage of reactions in aqueous media. However, attempts using either $Me_2NC_{12}H_{25}$ or KF/Al_2O_3 as the base have led to a strong erosion of the sugar conversion from the second recycling [40].

5 Telomerization with Polysaccharides

5.1 Reactivity of Sucrose

The application of sucrose derivatives as surfactants, plastics, or polymers is attractive because this pure and cheap carbohydrate is a renewable polyfunctional starting material. The telomerization of sucrose (**20**) was initially reported by Hill et al. [11, 39] using a Pd(II)/PPh_3 catalytic system in an *i*-PrOH/H_2O mixture (Fig. 13).

The sucrose octadienyl ethers have an average degree of substitution of 4–5.7 and are almost insoluble in water (Table 11). However, under such reaction conditions, the isopropanol reacted with the butadiene and 4–10% of isopropyloctadienyl ether were also observed.

The reaction can also be performed in the presence of Pd(II)/TPPTS catalytic system [49, 50]. The presence of a base is essential to achieve high conversion (Table 11). The use of co-solvent increases butadiene solubilization in the liquid

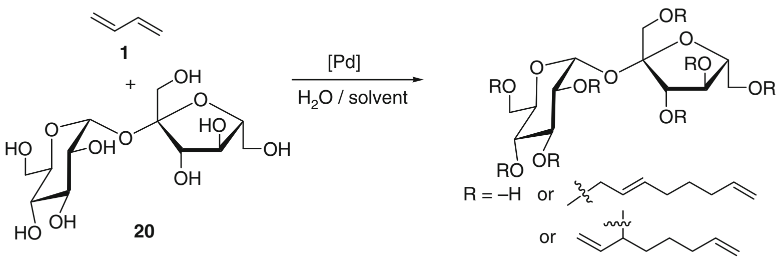


Fig. 13 Telomerization of butadiene with sucrose

Table 11 Telomerization of butadiene (**1**) with sucrose (**20**) in water-based solutions

20/1 equiv.	Solvent	Catalyst	$(Pd)_{mol.}$	T(°C) /t(h)	DS/Conv. (%)
5.4	H_2O/*i*-PrOH (1/10)	$Pd(acac)_2/PPh_3$ (1/2)	0.015	65/5	4/74
16.7	H_2O/*i*-PrOH (1/10)	$Pd(acac)_2/PPh_3$ (1/2)	0.010	65/10	5.7/33
11.8	H_2O	$Pd(OAc)_2$/TPPTS (1/3)	0.010	80/10	2.6/43
11.8	NaOH 1 M/MEK (2/5)	$Pd(OAc)_2$/TPPTS (1/3)	0.010	80/0.5	3.0/57
11.8	NaOH 1 M/*i*-PrOH (1/1)	$Pd(OAc)_2$/TPPTS (1/3)	0.010	80/0.5	2.0/32
11.8	NaOH 1 M/*i*-PrOH (2/5)	$Pd(OAc)_2$/TPPTS (1/3)	0.010	80/0.5	1.4/13
11.8	NaOH 1 M	$Pd(OAc)_2$/TPPTS (1/3)	0.010	80/0.5	2.7/41
11.8	NaOH 1 M	$Pd(dba)_2$/TPPTS (1/2)	0.010	80/2.5	4.7/78
11.8	NaOH 1 M	$Pd(OAc)_2$/TPPTS (1/3)	0.003	80/2.5	3.6/63

phase leading to higher catalytic activity. In the presence of ketone-based solvent (MIBK or MEK), the triethers constitute the main products, while in the presence of *i*-PrOH, high selectivity towards the monoether is achieved. It was shown that only palladium-based catalysts were efficient in this reaction, and no transformation occurred with nickel or cobalt–based complexes. The reaction can be further performed at 50°C using TPPTS or TPPMS as ligand. However, under similar conditions, the telomerization of maltose was unsuccessful and the substrate decomposed probably due to the basic conditions. On the other hand, the use of $Pd(OAc)_2/PPh_3$ catalytic system under neutral conditions is efficient to yield maltose ether [20].

5.2 *Reactivity of Polysaccharides*

It was shown from data summarized previously that telomerization of butadiene can occur with a large range of alcohols including reduced saccharides as well as mono- and disaccharides. It is of interest to extend such a reaction to much more complicated substrates such as polysaccharides (**21**) (Fig. 14). In that case, a low degree of substitution (average number of ether chains per glucose unit) is sufficient to modify deeply the physical properties of the organic polymer [51].

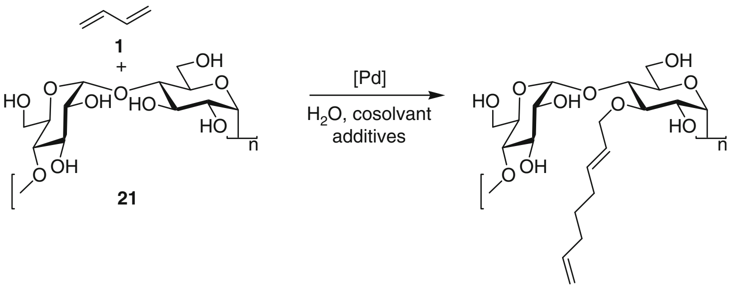


Fig. 14 Telomerization of butadiene with starch

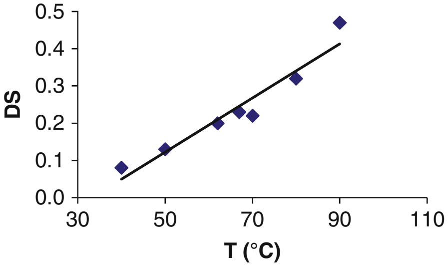
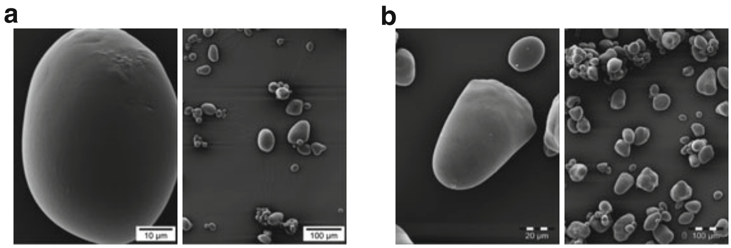


Fig. 15 Influence of the temperature on the degree of substitution for the telomerization of butadiene with starch

The transposition of the telomerization reaction to insoluble compounds is challenging, especially in the case of starch (**21**) that gelatinizes at low temperature (< 50°C). The reaction must be performed in aqueous media in order to swell the solid allowing reactivity of hydroxyl groups. The reaction was then catalyzed by hydrosoluble complexes in a NaOH/*i*-PrOH mixture [52, 53]. The influence of [NaOH] was studied to establish the best concentration that allowed high reactivity of the hydroxyl groups and good stability of the solid starch. The best result was achieved in the range 1.25–1.38% [53]. The temperature of the preparation of the octadienyl starch affects significantly not only the degree of substitution but also the texture of the solid. Indeed, native potato starch is formed of regular granules in the range of 20–100 μm having crystallized moieties. From 40°C up to 90°C, a linear improvement of the degree of substitution was observed (Fig. 15) but when telomerization was performed at temperature > 50°C, gelatinization occurred and the material was difficult to handle compared to the one prepared at 40°C (Fig. 16b, c).

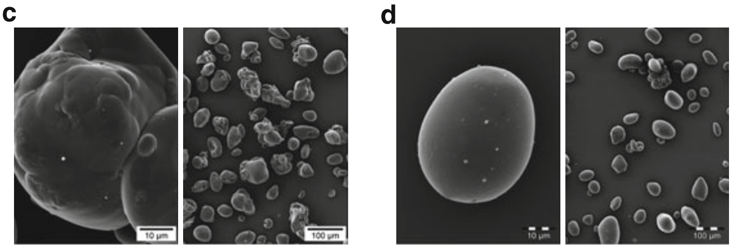
However, at this temperature very low activity was observed. The addition of Na_2SO_4 allows higher reaction temperatures without degrading the granular aspect by increasing the temperature of gelatinization of starch (Fig. 16d).

When the reaction was performed at 50°C in the presence of Na_2SO_4 (12.5 wt%/starch), the granular aspect of starch was completely preserved, especially with a final slow heating rate of 0.2°C/min and similar DS of 0.07 was obtained, indicating that Na_2SO_4 did not affect the catalytic performance of the system.



Native starch

40°C



50°C without Na_2SO_4

50°C with Na_2SO_4

Fig. 16 Scanning electronic microscopy of granular starch before and after reaction at different temperatures (see text)

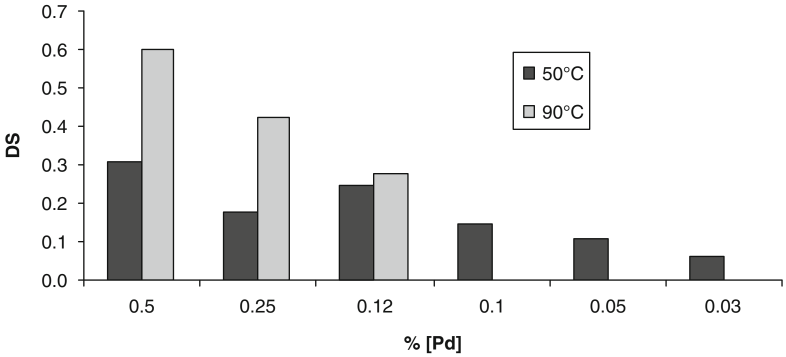


Fig. 17 Influence of the catalyst loading on the DS

The stability of the catalyst is also strongly influenced by the temperature. At 90°C, the degree of substitution was dramatically affected by the palladium content. With 0.5% of $Pd(OAc)_2$/TPPTS, the DS reached almost 0.6 while less than 0.3 was achieved with 0.12% Pd content. At 50°C, the DS was lower but the starch/catalyst ratio has a smaller impact (Fig. 17).

This low influence can be attributed to the stability of the catalyst with temperature. At 90°C, the Pd/TPPTS was unstable and decomposed progressively into palladium metal as confirmed by the formation of black particles. At 50°C, the

Table 12 Influence of the presence of *i*-PrOH on the telomerization of butadiene (**1**) with starch (**21**)

$V_{i\text{-PrOH}}$ (mL)	Time (h)	DS	Conv. (%)
20	4	0.06	80
10	4	0.03	40
5	4	0.03	40
5	24	0.05	67
0	24	0.02	30
0 (+ POEA)	24	0.07	87

Reaction conditions: 80 g **21**, 100 mL water, 20 mL **1** (0.3 equiv./glucose unit), [(π-allyl)Pd(TPPTS)$_2$]Cl = 0.04 wt% based on **21** amount or 0.4 mol% based on **1**, [Na$_2$SO$_4$] = 12.5 wt%/**21**, [NaOH] = 1.38 wt%, 50°C

catalyst was stable enough and substitution occurred with a catalytic level as low as 0.03% [52].

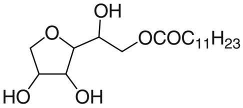
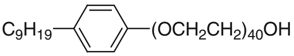
Optimization of reaction conditions was carried out with the hydrosoluble complex [(π-allyl)Pd(TPPTS)$_2$]Cl prepared from [(π-allyl)PdCl]$_2$ and two equivalent of TPPTS per Pd [54]. As low DS are expected, **1** is used as the limiting reactant (0.3 equiv./glucose unit). When the amount of co-solvent decreases, the conversion of **1** is lower but the catalyst is still active even in pure water (DS = 0.02) (Table 12) [53].

Alternatively, dimethylisosorbide was used as green solvent instead of isopropanol. Dimethylisosorbide (DMI) is a bio-sourced non-protic solvent, with a very low vapor pressure and environmentally friendly [53]. When the telomerization was carried out in the presence of 5 mL DMI or *i*-PrOH, the same conversion of butadiene was achieved after 24 h corresponding to a DS = 0.05.

In order to improve the activity in the absence of co-solvent, the use of a surfactant was studied in the presence of TPPTS-based catalyst [55]. Monflier et al. reported the hydrodimerization of **1** in the presence of surfactants in order to improve butadiene mass transfer in pure water solution [56–58]. Such an additive used in very low amount avoided the presence of an organic co-solvent. It was shown in the case of hydrodimerization that neutral or cationic surfactants played a significant role in the process. Similar behaviors were reported for the telomerization of **1** with **21**. While 30% conversion of **1** was achieved in pure water after 24 h reaction time at 50°C using 0.4 mol% of catalyst, the conversion reached 87% when polyether surfactant (POEA) was added to the reaction medium under similar reaction conditions (Table 12). It was found that the conversion is strongly affected by the nature of the surfactant (Table 13).

As far as neutral surfactants are considered, it is clear that the higher the HLB (hydrophobic lipophylic balance) of the surfactant, the higher the butadiene conversion. This can be attributed to the formation of micellar aggregates in the reaction medium which increase mass transfer between organic butadiene and aqueous phase. Considering the evaluated surfactants, the reactivity is as follows: SPAN 20 (HLB = 8–10) < P-123 (HLB = 7–9) < POEA23-16 (HLB = 10) < BRIJ 98 (HLB = 15) ≅ IGEPAL CO-890 (HLB = 16). However, it is clear that the HLB is not the only parameter since SPAN 20 and P-123 having similar

Table 13 Telomerization of butadiene with starch (**21**) in the presence of surfactants

Surfactant	HLB	DS	Conv. (%)
$C_{23}H_{45}(OCH_2CH_2)_{16}OH$ *POEA (23/16)*	10	0.05	60
$C_{18}H_{35}(OCH_2CH_2)_{16}OH$ *BRIJ 98*	15	0.08	100
 *SPAN 20*	8–10	0.01	13
$H\text{-}(OCH_2CH_2)_{20}(OCH_2CHCH_3)_{70}(OCH_2CH_2)_{70}\text{-}OH$ *P-123*	7–9	0.04	47
 IGEPAL CO-890	16	0.08	100
$C_{16}H_{33}NMe_3Br$, *CTAB*	21	0.07	93

Reaction conditions: 80 g **21**, 5 mL **1** (0.075 equiv./glucose unit). 100 mL water. [(π-allyl)Pd $(TPPTS)_2$] ([Pd] = 0.4 mol%). 8 g Na_2SO_4. 1.38 wt% NaOH. 0.05 mol/L surfactant. 50°C, 6 h

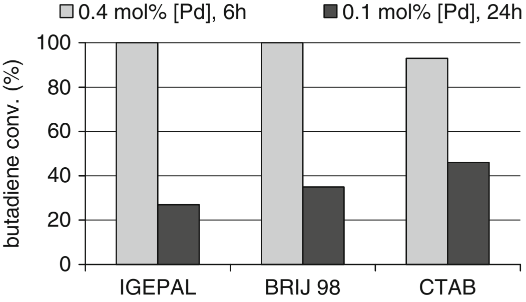


Fig. 18 Influence of the presence of surfactant on the butadiene conversion

hydrophobicity parameter exhibit different behaviors. It is supposed that SPAN bearing some hydroxyl groups can react with butadiene during the reaction, so losing its surfactants properties. In the presence of cationic surfactant CTAB, high conversion of butadiene has also been achieved (Table 13).

The influence of the nature of the surfactant has been highlighted by lowering the catalytic level to 0.1 mol% (Fig. 18). Under such conditions, the highest catalytic activity was achieved in the presence of cationic surfactant with 46% butadiene conversion after 24 h corresponding to DS = 0.06. The conversion obtained with the neutral surfactants BRIJ 98 and IGEPAL CO-890 were 31 and 27% respectively.

The role of the surfactants has been evaluated with other hydrosoluble catalysts. It was found that the activity of the system depends on the surfactant/ligand pair, the highest conversion being achieved with CTAB/TPPMS couple (Conv. = 80% ± 3% corresponding to a DS = 0.105 ± 0.005) [55].

For the reaction taking place, micelles and starch have to interact closely. The micellar aggregates increase the solubilization of butadiene within the aqueous solution. The long alkyl chains are in the center of the micelles while the positively charged polar groups are directed to the surface. At the same time, the solid starch is partially negatively charged after action of NaOH. This favors close contact between the insoluble polymer and the micelles (Fig. 19). Moreover, the water soluble catalyst is also supposed to interact at the surface of the micelles close to the butadiene and the telogen.

The catalyzed telomerization of butadiene has been applied to other polysaccharides such as inulin (**22**) (Fig. 20) which is a polyfructose extracted from Jerusalem artichokes (tuber) or from chicory (roots). This soluble polymer is easily telomerized under mild conditions and the degree of substitution is also dependent on the reaction conditions [20] (Fig. 20).

Hydrogenation of the lateral chain of telomerized polysaccharides (starch, inulin) has been carried out using homogeneous $RhCl(TPPTS)_3$ complex (0.8%) at 40°C under 30 atm. H_2 in H_2O/EtOH (5/1) mixture. Both terminal and substituted double bonds were successively hydrogenated [59].

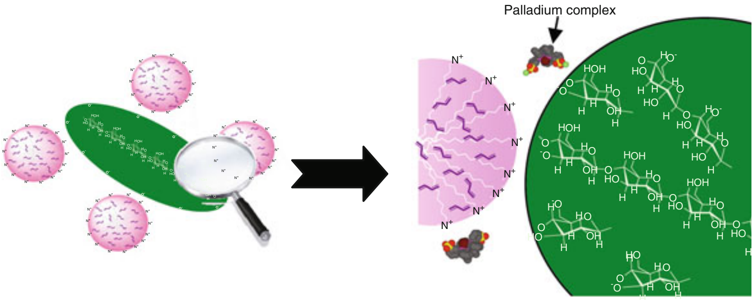


Fig. 19 Schematic representation of interactions between starch and cationic micelles

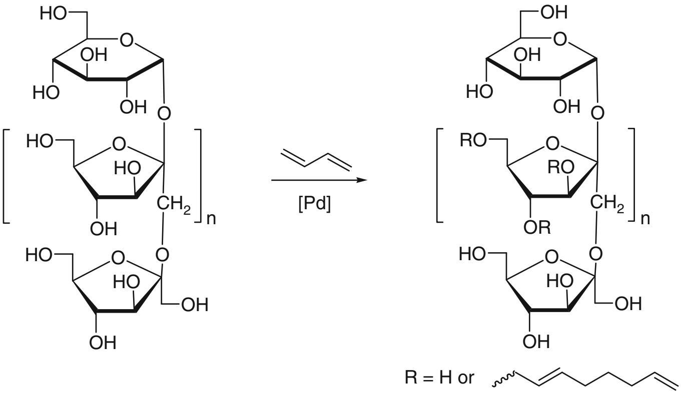


Fig. 20 Telomerization of butadiene with inulin (**22**)

6 Physicochemical Properties

Many new sugar based products present the advantage of being non-toxic and biodegradable. The products resulting from the telomerization of **1** with appropriate nucleophiles such as alcohols, amines, water, or carbon dioxide serve generally as useful intermediates in the synthesis of various natural products and fine chemicals [60–63], as precursors for plasticizer alcohols [56, 64], components of diesel fuels [65], surfactants [11, 66], corrosions inhibitors, and non-volatile herbicides [67].

Several alkyl glyceryl ethers prepared by the telomerization of **1** with glycerin (**3**) in the presence of a transition metal were evaluated. The characteristic behavior of isostearyl glyceryl ether (GE-IS) toward water, such as formation of water-in-oil emulsions containing large amounts of water, has made it applicable for use in hair- and skin-care cosmetics [68]. Glyceryl ether sulfates $R^1OCH_2CH(OR^2)CH_2OR^3$ (R^1 = linear or branched C8 alkyl, R^2 or $R^3 = R^1$ or SO_3X, X = alkali or alkyl earth metal) also show good surfactant properties with satisfactory micelle concentrations; they are mild, present good compatibility with skin, and are useful with other surfactants in hair shampoos, skin cleaners, and manual dishwashing detergents [69, 70]. Apart from the surfactant field, glycerol octadienyl ethers were also associated with fumaric acid, benzylic alcohol, and ethylene glycol to build some crosslinked polyesters having a molecular weight from 300 to 10,000 and containing 5–70% octadienyl groups [71].

The interfacial properties of neutral octadienyl pentosides (**18α**, **18β**, **23**) obtained from the telomerization of butadiene (**1**) with D-xylose (**16**) and L-arabinose (**15**) [28, 29, 32, 37, 40] have been evaluated [72] (Table 14, Fig. 21).

As pentoses are readily accessible from wheat straw and bran [26, 27], the telomerization of **1** with a bran syrup having the composition given in Table 15 led to a crude mixture containing 1% bran syrup, 67% monooctadienylethers (**18**, **23**), 31% dioctadienylethers (**24**–**26**), and 1% trioctadienylethers (Fig. 21). The physical evaluation of this mixture is given in Fig. 22 and revealed satisfactory surface-active behavior of this crude mixture although no sharp value of CMC could be determined, as can happen with complex mixtures. Continuous decrease of

Table 14 Surfactant properties of mono- and dioctadienyl pentosides and mixtures

Compounds	CMC (mmol/L)	γ_{CMC} (mN/m)[c]	a_{min} (Å^2/molecule)[b]
18β	–[b]	36[b]	–
18α	1.94	31	41.5
23	0.70	34	43.0
90% **18β** + 10% **18α**	–[b]	33.5[c]	–
Dioctadienyl xylosides mixture **24** + **25**	0.19	35	57.5
Crude mixture of xylosides telomers[a]	0.19	35	–

[a] Composition of the crude mixture: 6% xylose, 62% xylosyl monooctadienyl ethers, 27% xylosyl dioctadienyl ethers, 5% xylosyl trioctadienyl ethers (evaluated by GC)

[b] Above 1,000 mg/L the value of surface tension tends to slowly decrease but the solution becomes turbid, so that the existence of a true CMC is questionable

[c] Surface tension and area determined at a concentration of 1 mmol//L

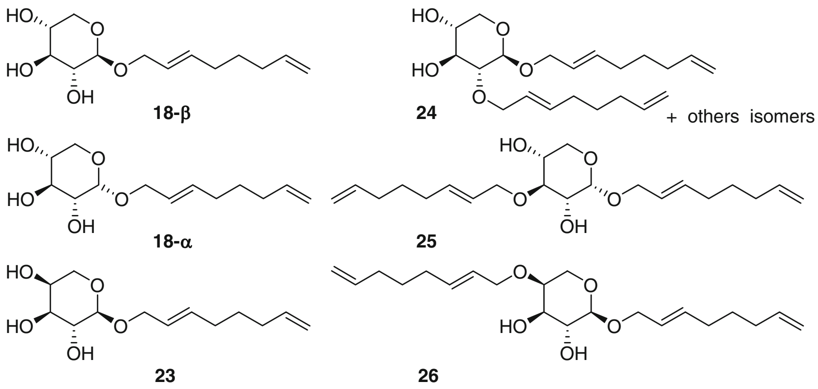


Fig. 21 Mono- and dioctadienyl pentosides

Table 15 Composition of the bran syrup (wt%)

Purity = 99.5%. Dry Material = DM = 72.6%	
L-Arabinose/DM	33.5%
D-Xylose/DM	54.2%
D-Glucose/DM	8.9%
D-Galactose + D-Mannose/DM	1.7%
Polysaccharides/DM	1.2%

surface tension down to values around 30–35 mN/m was observed over a long range of concentrations.

Thorough separations of major synthesized products were performed leading to pure monooctadienyl-xyloside (**18**) or arabinoside isomers (**23**). The study of their surface activity showed their interesting capacity of lowering surface tension down to 30–35 mN/m at relatively low concentrations in the range of 1–4 mmol/L (Table 14). Submitting crude mixtures of telomers of xylose or bran syrup to the same examination established that the surface-activity was not improved after the separation process. Therefore, for an industrial application of these surfactants, the use of the lower cost, non-separated mixture can be recommended.

Glucose octadienyl ether (DS = 2) is non-toxic with good skin compatibility [73]. The viscosity of derivative with moderate degree of substitution (DS = 1.5) reaches 2500 cPs at 25°C and potential applications as emulsifiers or defoamers are conceivable.

Sucrose (**20**) was also used for the reaction of telomerization with **1** [19, 49, 50]. Applying specific conditions, sucrose octadienyl ethers were obtained with an average degree of substitution of 4.7–5.3. These products are practically insoluble in water, clear or almost colorless, and present a viscosity of 1500–2000 cPs at 25°C [39]. These properties confer to these products the possibility of being employed as emulsifiers or defoaming agent [49]. Minimum surface tension of solution of substituted sucrose in water is 25–28 mN/m whatever the degree of substitution

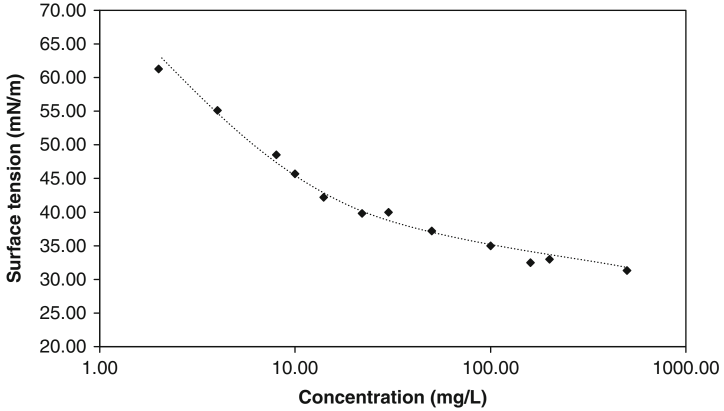


Fig. 22 Surface tension of a crude telomer mixture issued from the telomerization of **1** with bran syrup as a function of concentration

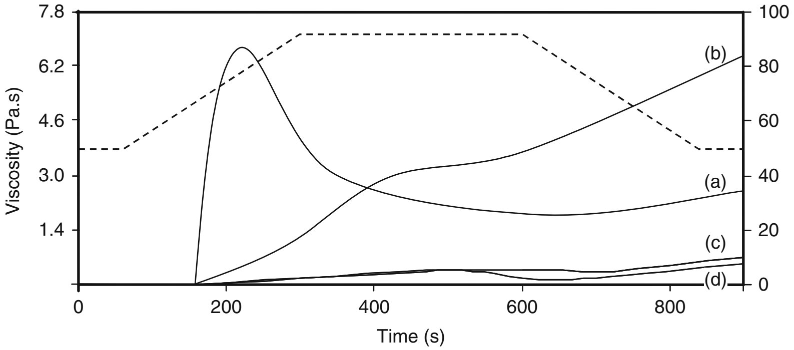


Fig. 23 Viscosity profiles of (**a**) native starch. (**b**) Native starch heated up at 50°C for 24 h. (**c**) Telomerized starch with DS = 0.055. (**d**) Telomerized starch with DS = 0.1. *Dotted line*: temperature profile

(DS < 1). However, this value is achieved for 1 g/L for the telomerized sucrose (DS = 0.4) and 0.1 g/L for the corresponding saturated compound. This was correlated with high foaming capability [20].

Some properties of substituted starches were determined [55]. The viscosity of telomerized starches (DS < 0.1) was evaluated by heating a suspension of the material in water for 15 min (Fig. 23).

The viscosity of the native starch (Fig. 23a) increases after 160 s corresponding to a temperature of 66°C due to the swelling of the starch granules. The maximum viscosity (6.7 Pa.s) is reached at 87°C when the granules lose their semi-crystallinity with a concomitant release of macromolecules. Keeping the temperature constant (90°C) involves a viscosity decrease due to the solubilization of these macromolecules as well as the disappearance of the granules. However, the viscosity starts to increase again with a decrease of the temperature (retrodegradation, t > 600 s).

Table 16 Surface properties of starches modified by octadienyl groups

DS	Total energy (mN/m)	Polar component (%)	Dispersive component (%)	Contact angle (°)
0.055	512.5	58	42	45
0.105	100	74	26	99
0.3	59	5	95	93

When a thermal treatment was applied to starch before the analysis, a very different behavior (Fig. 23b) was obtained. After such a treatment, no maximum was observed for the viscosity which increased slowly up to 82°C. In the case of starch modified with octadienyl chains (DS 0.055 (Fig. 23c) and DS 0.1 (Fig. 23d)), the viscosities were much lower than for native starch (b) in both cases. The presence of hydrophobic chains at the surface of the material could prevent the interaction of water molecules with the macromolecules after the splitting, thus avoiding the formation of a gel.

The surface polarity of telomerized starches was determined by the contact angle technique. The surface free energy of the solid was measured from the contact angles of a drop of various probe liquids with the surface of a starch tablet (Table 16).

The DS has a strong influence on the hydrophobic character of the modified starches and, as expected, increasing the DS decreases the polarity of the surface. For DS > 0.1, contact angles are greater than 90° with quite a low total surface energy, indicating a significant hydrophobicity of the material and a low wettability as previously reported for esterified starches [74–76].

7 Conclusion

While the telomerization reaction of butadiene has been known for 40 years, its application to polyols issued from the biomass is recent and continues to be under investigation. Most polyols are much less active than MeOH or H_2O that have found industrial developments. Higher catalytic loading are required, but recent studies disclosed very active catalytic systems which are promising.

Moreover, telomers of glycerol or saccharides, i.e. made from renewable materials, can be used for biodegradable applications. Owing to their skin- and eco-friendliness, they have potential interest as additive in the cosmetic industry. Alternatively, telomers of polysaccharides might find applications in the paper industry.

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Enzymatic Processing of Bioactive Glycosides from Natural Sources

Lenka Weignerová and Vladimír Křen

Abstract A number of biologically active natural products are glycosides. Often, the glycosidic residue is crucial for their activity. In other cases, glycosylation only improves their pharmacokinetic parameters. Enzymatic modification of these glycosides – both extension of the glycoside moiety and its selective trimming – is advantageous due to their selectivity and mildness of the reaction conditions in the presence of reactive and sensitive complex aglycones. Enzymatic reactions enable the resulting products to be used as “natural products”, e.g., in nutraceuticals. This chapter concentrates on naturally occurring glycosides used in medicine but also in the food and flavor industry (e.g., sweeteners). Both “classical” and modern methods will be discussed.

Keywords Alkaloids, Anthocyanidins aroma, Cardioglycosides, Enzymatic and chemical glycosidation, Enzymatic trimming, Flavor chemistry, Ginsengosides, Glycoandomization, Glycodiversification, Glycohydrolase, Glycosyltransferase, Glycyrrhetinic acid, Isoquercitrine, Morphine glucuronides, *O*-Glycosides, Rutin, Sweeteners, Vancomycin, Vitamins

Contents

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1 The Role of Glycosidic Residues in Biological Activity

Many biologically active compounds are glycosides. Glycosides are comprised of several important classes of compounds such as antibiotics, hormones, sweeteners, alkaloids, flavonoids, etc. [1]. The glycosidic residue can be crucial for their activity or can merely improve their pharmacokinetic parameters. Due to recent developments in molecular glycobiology, the relationship between the properties of aglycone vs glycoside is now clearer and – based on these findings – it is possible to develop new, more active or more effective glycodrugs. Nevertheless, it is nearly impossible to define a general pattern of the biological activities of the glycosides compared to their respective aglycons. Using well selected examples it could be possible to illustrate some general trends and show the effects and potential applications of the compounds carrying a glycosidic moiety compared to the respective aglycons.

It is generally accepted that glycosides are more water-soluble than the respective aglycons. Attaching a glycosidic moiety to the molecule increases its hydrophilicity. This effect influences the pharmacokinetic properties of the respective compounds, e.g., circulation, elimination, and their concentrations in body fluids. This modified hydrophilicity, however, mainly influences their membrane transport. Some compounds enter the cells purely because of their "solubility" in the membrane components. Glycosylation can, in some cases, restrict or inhibit the cell uptake of particular compounds. Glycosylation can strongly influence transport through such important barriers as the hemato-encephalitic barrier and block the entrance of many compounds into brain tissue. In contrast, some glucosides can be actively transported into brain tissue using the glucose-transport system. Another important barrier, in which glycosylation plays a crucial role, is the placental barrier. Here many glucuronides are blocked from entering fetal tissue, thus preventing intoxication by the metabolites of xenobiotics. On the other hand, some glycosidic moieties can interact with receptors or lectins on the cell surface, followed by their active uptake. A good example is the high affinity of β-galactosides to hepatocytes due to C-galectin occurring at a high concentration on their surface.

Carbohydrates and glycosides recently emerged as a novel class of nucleic acid binding compounds. A detailed study of the factors affecting the site-selectivity of some recently discovered antitumor antibiotics has shed new light on the role that oligosaccharides may play in nucleic acid recognition.

An important aspect of predicting the respective glycoconjugate activities is also their susceptibility towards glycosidic cleavage at various sites of application. Most glycosides are hydrolyzed in the stomach and intestine, either by the action of the acidic environment (stomach) or by the action of glycosidases (small intestine). There are, however, glycosides that are not hydrolyzed easily – e.g., α-galactosides – and such compounds are either unable to pass through the hemato-intestinal barrier or they penetrate unhydrolyzed. Non-resorbed glycoconjugates can be cleaved later in the colon or metabolized by the action of the intestinal microflora. Glycosidases are also present in other body fluids, e.g., blood serum contains lysozyme, which effectively cleaves β-*N*-acetylhexosaminides. There are, however, glycosides with specific individual biological activities that cannot be simply derived from the respective activity of the aglycon. Their final activity is then given by their overall molecular structure. Comparison of the biological activities of a given aglycon and respective glycoside can indicate some structure-effect correlations and also demonstrate the advantage of introducing glycosyl moieties into pharmacologically interesting molecules.

Exploitation of the SAR data of the glycosides (most often glycosidic antibiotics) has enabled the synthetic modification and optimization of their glycon part. Recently, however, the effective new methodology of "glycorandomization," based on the enzymatic modifications of glycosides, has enabled glycoside libraries to be prepared. This method, employing natural and mutant glycosyltransferases with wobbling specificities, has opened up new ways of preparing optimized or entirely novel glycoside antibiotics.

One of the most promising and relatively cheap ways of obtaining new physiologically active compounds without adverse effects is the modification of substances with well-known properties. Glycosylation is one of the ways that move us closer to this objective. This derivatization profoundly changes the physiological activity of various drugs. Some substances only gain their activity after glycosylation, e.g., cardioglycosides. Complex oligo-saccharides mediate or modulate a variety of biological processes [2, 3]. The carbohydrate portion of a glycoside is sometimes responsible for its recognition by cell surface receptors. The pharmacological applicability of the transformed substances is improved by better solubility, facilitating transport and improving their selective binding to the target tissues. Glycosylation often lowers toxicity without substantially compromising the respective activity.

Glycosides have one major advantage over other derivatives, as they carry a physiologically acceptable glycosyl moiety that can be cleaved in most tissues by the glycosidases present and further metabolized in a natural way without generating any harmful metabolites. Therefore, glycosylation is also an excellent method for prodrug preparation [4].

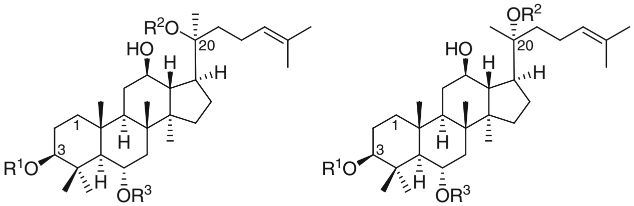
Chemical glycosylation used to be a "classical" method of choice; however, in the last 10–20 years a plethora of enzymatic methods for the synthesis [5, 6] and also selective "trimming" [7] of glycosides have been described. These enzymatic methods are especially suitable for the glycosylation and deglycosylation of natural products [8], drugs, nutraceuticals, and substances used in the food industry. It is not only the high selectivity of the enzymatic processes which makes them attractive for these industrial applications, but also the mildness of the reaction conditions and compliance with food and drug regulations.

2 Selective Trimming of Natural Glycosides with Hydrolytic Enzymes

2.1 Ginsenosides

Ginseng saponins, i.e., dammarane-type saponins, are extracted from the root of *Panax ginseng*. They have been used in various formulations in oriental countries for more than 5,000 years, especially as a tonic [9].

Ginsenoside Rb_1 is a representative of the saponins derived from **20** (*S*)-protopanaxadiol (Fig. 1). It exhibits central nervous system-depressant and antipsychotic



20 (*S*)-Ginsenoside **20** (*R*)-Ginsenoside

Ginsenoside	R_1	R_2	R_3
Rb_1	Glcβ(1-2)Glc	Glcβ(1-6)Glc (*S*)	H
Rb_2	Glcβ(1-2)Glc	Ara*p*α(1-6)Glc (*S*)	H
Rb_3	Glcβ(1-2)Glc	Xylβ(1-6)Glc (*S*)	H
Rc	Glcβ(1-2)Glc	Ara*f*α(1-6)Glc (*S*)	H
Rd	Glcβ(1-2)Glc	Glc (*S*)	H
F_2	Glc	Glc (*S*)	H
Rg_3	Glcβ(1-2)Glc	H (*R*,*S*)	H
Rh_2	Glc	H (*R*, *S*)	H
C-K	H	Glc (*S*)	H
Re	H	Glc (*S*)	Rhaα(1-6)Glc
Rf	H	Glc (*S*)	Glcβ(1-2)Glc
Rg_1	H	Glc (*S*)	Glc
Rg_2	H	H (*R*,*S*)	Rhaα(1-6)Glc
Rh_1	H	H (*R*, *S*)	Glc

Fig. 1 Structures of ginsenosides

Fig. 2 Enzymatic trimming of ginsenosides

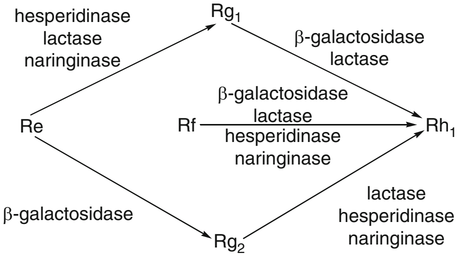
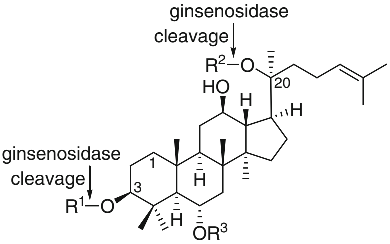


Fig. 3 Selective cleavage of glycosidic residues from ginsenosides by ginsenosidase



activity, protects against stress ulcers, increases gastrointestinal motility, and has a weak anti-inflammatory action. Rg_1 – the major saponin of **20** (*S*)-protopanaxatriol – exhibits a weak CNS-stimulant action, antifatigue activity, and blood pressure activity [10, 11].

Some other saponins have been reported to have a potentiation activity on the nerve growth factor [12], stimulate the pituitary-adrenocortical system [13], and saponins were recently shown to have favorable antitumorigenic effects [14, 15].

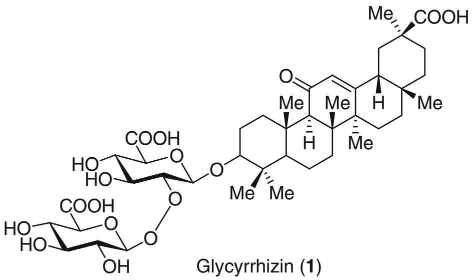
Ginsenosides are highly glycosylated and their activity often differs depending on the number of glycosyl units attached. They can be interconverted by trimming the glycosidases and this is a way in which some of the more scarce ginsenosides are produced (Fig. 2) [16–20].

Recently, a new type ginsenosidase able to hydrolyze the multiglycosides of ginsenoside was described. This enzyme (denoted ginsenosidase I from *Aspergillus* sp.) selected the ginsenoside-aglycon type and preferably cleaved Rb_1, Rb_2, Rb_3, Rc, Rd, and Rg_3 (Fig. 3) [21]. Danieli et al. [22] accomplished (regio-) selective β-galactosylation and also the β-glucosylation of ginsengoside Rg_1 using β-galactose transferase.

2.2 Glycosides of Glycyrrhetinic Acid

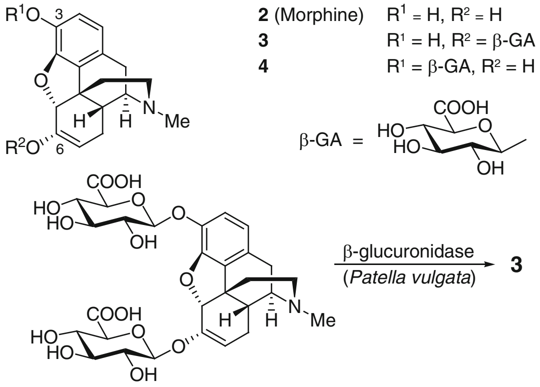
The major sweet principle of licorice root (*Glycyrrhiza glabra*), glycyrrhizin (**1**) (content ~4%), has been used as a sweetener and flavor enhancer in foods, tobacco products, and in medicine as an anti-inflammatory agent (Fig. 4).

Fig. 4 Structure of glycyrrhizin



Glycyrrhizin (**1**)

Fig. 5 Morphine glucuronides



A structure-sweetness relationship study has shown that the monoglucuronide of glycyrrhetinic acid is about five times sweeter than respective diglucuronide (**1**) and ca. 1,000 times sweeter than sucrose [23]. Replacement of the second glucuronic acid by, e.g., xylose or glucose, also resulted in an improvement of the taste and enhancement of sweetness [24]. The monoglucuronide of glycyrrhetinic acid is now commercially produced using a β-glucuronidase from the yeast *Cryptococcus magnus* MG-27 that selectively cleaves purely a single GlcA moiety [25]. Chemical hydrolysis would only yield the aglycon. This compound has also better pharmacological properties, such as an inhibitory effect against skin carcinogenesis and pulmonary tumorigenesis (in mice) [23].

2.3 Morphine Glucuronides

Morphine (**2**) is an important analgesic with a long history of usage (Fig. 5). This drug has, however, unwanted side effects. Recently it was found that one glycosidic metabolite – morphine-β-6-glucuronide (**3**) – has a quite interesting biological effect that is rather different from those of the parental drug **2** [26].

Morphine has two nucleophilic sites that may be glucuronidated, a 3-hydroxy group on an aromatic ring and an alcoholic 6-hydroxy group.

Conjugation of the 3-hydroxy group occurs in many mammalian species, while glucuronidation at the C-6 position appears to be unique in man [26, 27]. Although the analgesic potency of **3** has been known for more than two decades, the potential clinical use of this glycoside has only been recognized recently. Clinical studies in cancer patients treated with **3** indicated that useful analgesic effects are achieved without the nausea and vomiting [28] that is often caused by the morphine itself.

The enzymatic method developed by the group of Turner [29] enabled the regioselective (over 95%) hydrolysis of morphine diglucuronide by β-glucuronidase from limpets (*Patella vulgata*) (Fig. 5). This is an excellent example of selective and efficient enzymatic trimming of the glycosides yielding a more effective drug.

2.4 Isoquercitrin

The *raison d' être* for the proliferation of flavone and flavonol glycosides in nature continues to intrigue plant scientists. The ability of UV-B radiation to damage DNA, RNA, and proteins as well as to impair processes like photosynthesis is well known. Most flavonoids are very efficient antioxidants and chemoprotectants, and are therefore used in a plethora of food supplements and nutraceuticals [30]. Some flavonoids, however, have a "*Janus face*" – they could be excellent antioxidants but also have negative features.

A typical example is the flavonol quercetin (**7**), which is one of the most common flavonoids in food (typically apples, yellow onions). This flavonoid occurs in natural sources mostly in the form of glycosides, typically rutin (quercetin-3-β-rutinoside, **5**), isoquercitrin (quercetin-3-β-D-glucopyranoside, **6**), and some others. Despite the excellent antioxidant effects of quercetin, this compound has proven unwanted effects, namely, it gives a positive Ames test (potential mutagen and/or carcinogen) [31]. This (potential) mutagenicity of quercetin is partly caused by the inhibition of topoisomerase II, which can cause errors in DNA transcription and thus also mutations [32]. Pure quercetin is not used in nutraceuticals and functional food due to these unwanted effects but quercetin-3-β-D-glucopyranoside (isoquercitrin) has excellent properties, including better solubility. Its isolation from natural sources is excluded for mostly economical reasons. However, another quercetin glycoside – e.g., rutin – is highly available from various natural sources as a bulk commodity. Rutin can be selectively deglycosylated by α-L-rhamnosidase, usually from fungal sources (typically *Penicillium decumbens* or some *Aspergillus* sp.). Here it is crucial to avoid cleavage of the β-glucosyl moiety to avoid the formation of unwanted quercetin. This can be achieved by preparation the enzyme with a carefully selected producer [33] or by the selective inhibition of β-glucosidase with, e.g., δ-gluconolacton or using specific conditions (pH, temperature) (Fig. 6).

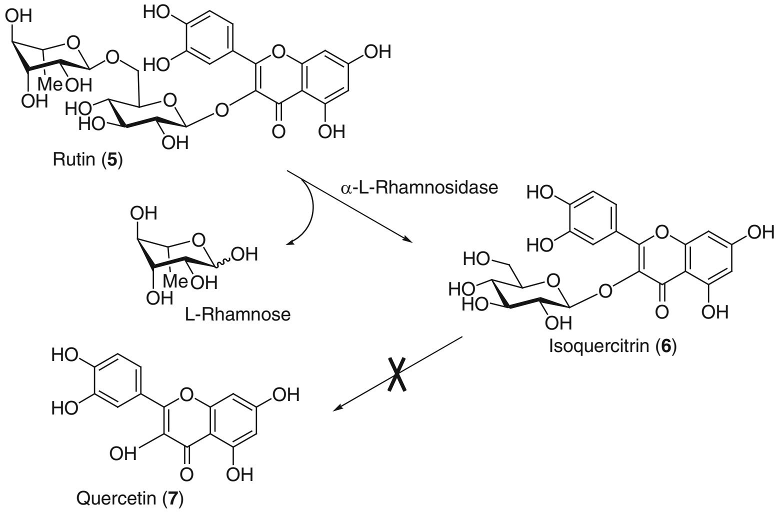


Fig. 6 Enzymatic preparation of isoquercitrin

3 Enzymatic Glycosylation of Natural Products

The enzymatic glycosylation of natural products can be performed in principle by glycosidases, glycosyltransferases, and some other glycoside-processing enzymes – sometimes called transglycosidases.

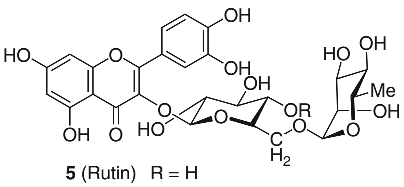
3.1 Rutin

Rutin (**5**, vitamin P) is one of the most widespread quercetin glycosides (quercetin-3-*O*-rutinoside: Fig. 7). It should be formally classified as a flavonoid, but, because of its activities (essential capillary protectant), it is included in the vitamin group. Rutin is a glycoside itself, composed of quercetin and the disaccharide rutinose [6-*O*-(β-L-rhamnopyranosyl)-D-glucose]. Its water solubility is rather low (ca. 0.1 g L^{-1}) and, therefore 4G-α-D-glucopyranosyl-rutin (**8**) was prepared using cyclodextrin glucanotransferase [34]. Its solubility was considerably increased (30,000 times higher than rutin). An improved biological activity has been predicted based on the finding that this glucoside is hydrolyzed by pig liver α-glucosidase [34].

3.2 Alkaloids

Ergot alkaloids that are produced by parasitic fungus *Claviceps purpurea* (Ergot) [35] cover a large field of therapeutic uses: as high-potency drugs in the treatment of

Fig. 7 Rutin glucopyranosides



5 (Rutin) R = H
8 R = α-Glcp

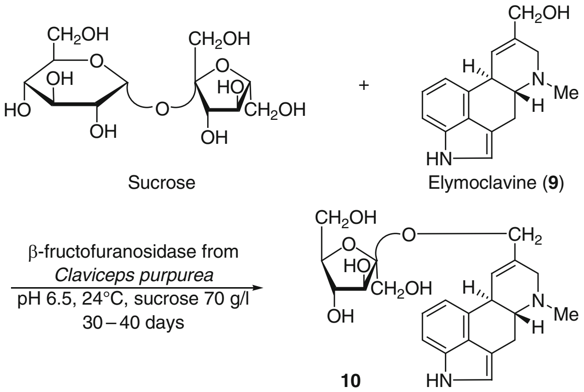


Fig. 8 Elymoclavine fructosylation

uterine atonia, postpartum bleeding, migraine, orthostatic circulatory disturbances, senile cerebral insufficiency, hypertension, hyperprolactinemia, acromegaly, and Parkinsonism [36]. New therapeutic uses have recently emerged, such as, e.g., against schizophrenia, applications based on its newly discovered antibacterial and cytostatic effects, and immunomodulatory and hypolipemic activity [37–39].

Glycosides of ergot alkaloids were isolated as naturally occurring products [40] and a large series of them has been prepared by chemical and enzymatic methods [41].

3.2.1 Ergot Alkaloid Fructosylation

The fructosylation of elymoclavine (**9**) by *C. purpurea* was described in [42] (Fig. 8). This reaction is mediated by the transfructosylating activity of β-fructofuranosidase in sucrose-containing media. Beside mono- (**10**) and difructoside, higher fructosides (tri- and tetra-) (**11**) are also formed [43] (Fig. 9).

Glycosylating *Claviceps* strains (mostly *C. fusiformis*) produce most elymoclavine in the form of β-fructofuranosides, which complicates the isolation of elymoclavine. The hydrolysis of fructosides by HCl is not suitable for a large scale process due to the aggressive nature of the acid solution and losses of elymoclavine. A more elegant method is a bioconversion employing the high invertase activity

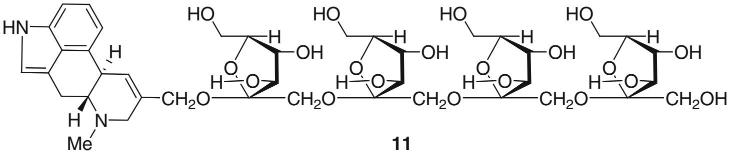


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Fig. 9 Elymoclavine tetrafructoside

of *Saccharomyces cerevisiae*. At the end of the production cultivation, a suspension of baker's yeast is added to the fermentation broth (without isolating the product). The hydrolysis is completed within 1 h (37°C) [42].

3.2.2 Ergot Alkaloid Glycosylation Using Glycosidases

The interesting physiological effects of alkaloid fructosides [41] stimulated the preparation of other glycosides, such as galactosides, glucosides, *N*-glucosaminides, and complex alkaloid glycosides.

β-Galactosylation of elymoclavine (**9**), chanoclavine (**12**), lysergol, 9,10-dihydrolysergol, and ergometrine was accomplished by β-galactosidase from *Aspergillus oryzae* using *p*-nitrophenyl-β-D-galactopyranoside or lactose as glycosyl donors [44]. This enzymatic method enabled ergometrine, containing an amidic bond, to be glycosylated for the first time.

Aminosugar-bearing alkaloids had been expected to have immunomodulatory activities and this glycosylation would also create the basis for further extension of their carbohydrate chains (introduction of aLacNAc or sialyl residue – see below). This task was accomplished by transglycosylation using β-hexosaminidase from *A. oryzae*. Representatives of each class of ergot alkaloids, e.g., clavines – elymoclavine (**9**), secoclavines – chanoclavine (**12**) and lysergic acid derivatives – ergometrine were chosen to demonstrate the wide applicability of this method [45].

Enzymatic mannosylation of the alkaloids by α-mannosidase from *Canavalia ensiformis* (Jack beans) was accomplished via two different strategies – transglycosylation using *p*-nitrophenyl-α-D-mannopyranoside or reversed glycosylation using a high concentration of mannose [46] (Fig. 10).

A series of other glycosides of ergot alkaloids was prepared by enzymatic transglycosylations using activated *p*-nitrophenylglycosides as donors [47].

3.2.3 Ergot Alkaloid Glycosylations by Glycosyltransferases: Complex Glycosides

Complex alkaloid glycosides bearing, e.g., lactosyl (Lac), lactosaminidyl (LacNAc), or sialyl (Neu5Ac) moieties were required for immunomodulation tests (see below). Because of the paucity of starting material (alkaloid monoglycosides) and because of the need of regioselective glycosylation, only enzymatic reactions were practicable.

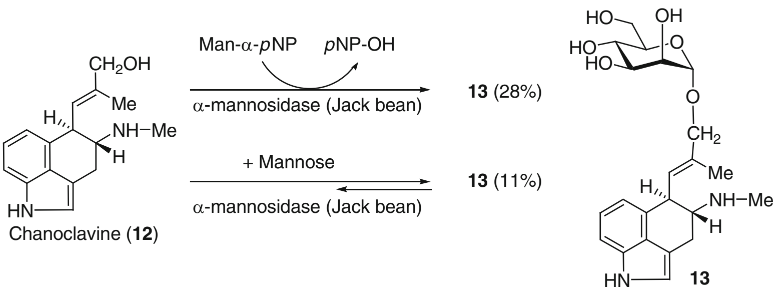

Fig. 10 Chanoclavine mannosylation using enzymatic transglycosylation and reversed glycosylation

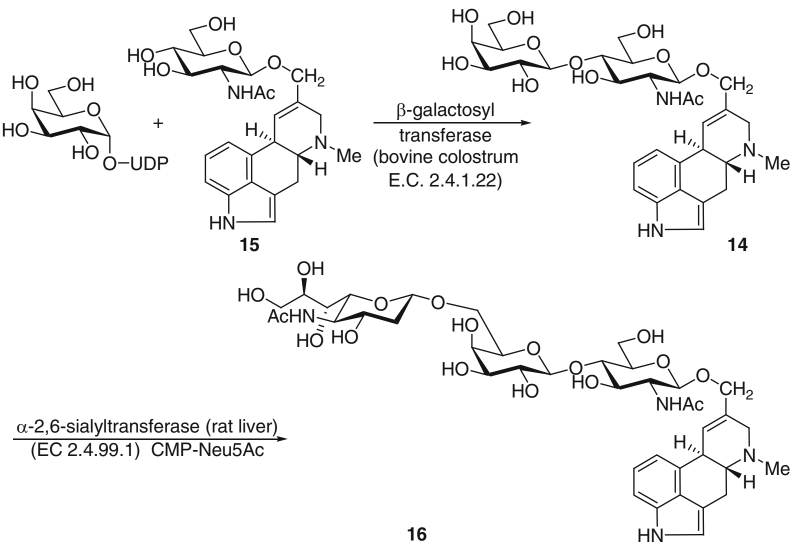

Fig. 11 Synthesis of complex ergot alkaloid glycosides using different glycosyltransferases

For the preparation of β-D-galactopyranosyl (1→4)-2-acetamido-2-deoxy-β-D-gluco-pyranosyl-(1→*O*)-elymoclavine (**14**) it was decided to extend previously prepared 2-acetamido-2-deoxy-β-D-glucopyranosyl-(1→*O*)-elymoclavine (**15**) using bovine β-1,4-galactosyltransferase. Uridine 5′-diphosphogalactose (UDP-Gal) served as a substrate [48] (Fig. 11).

β-Lactosyl elymoclavine was prepared from the respective β-glucoside using bovine β-1,4-galactosyltranferase in the presence of α-lactalbumin. β-Lac and β-LacNAc derivatives of other ergot alkaloids, e.g., 9,10-dihydrolysergol, were prepared analogously [48]. The attachment of 5-*N*-acetylneuraminic acid to β-Lac-NAc-elymoclavine (**14**) yielding **16** was accomplished using α-2,6 sialyltransferase from rat liver [48].

3.3 Glycosides of Vitamins

3.3.1 Ascorbic Acid

Ascorbic acid (vitamin C) is involved in many biological processes, such as collagen synthesis, antioxidation, the intestinal absorption of iron, and metabolism of some amino acids. The search for and preparation of its glycosides was motivated mostly by the need for more stable compounds (resistant to oxidation) having the same or better bioavailability. The first glycoside of ascorbic acid was prepared by Yamamoto [49], its structure was presumed to be 6-*O*-α-glucopyranosyl-L-ascorbic acid, and it was postulated that this glycoconjugate is formed in vivo by α-glucosidases. Its sensitivity to oxidation was the same as ascorbic acid and its biological activity was inferior to it. Later, another glycoside, e.g., 2-*O*-α-glucopyranosyl-L-ascorbic acid (**17**), was synthesized by an enzymatic regioselective transglucosylation [50] (Fig. 12). This glycoside was found to show similar bioavailability to the aglycon in vivo [51] and in vitro [52]. This compound was, however, considerably more stable in terms of oxidative stress and UV irradiation. In fact, glycoside **17** itself has no reducing power because of the substitution at the 2-OH group that is involved in the redox reactions of ascorbic acid. Oral administration of **17** (guinea pigs) resulted in a remarkable increase in ascorbate in various tissues as well as in plasma [53]. Ascorbic acid was released from **17** at the mucosal side, and was actively taken up across the intestinal membrane into the serosal side, whereas **17** itself permeated, but poorly. The hydrolysis of **17** was mediated by maltase that could be inhibited by castanospermine. Ascorbate was transported by an active uptake system. Because of its in vivo inhibitory action on melanin synthesis, ascorbate is also used as a skin-whitening agent in cosmetics [54].

3.3.2 Pyridoxine

Pyridoxine (vitamin B_6, **18**) (Fig. 13) assists in the balancing of sodium and potassium as well as promoting red blood cell production. A lack of pyridoxine can cause anemia, nerve damage, seizures, skin problems, and sores in the mouth. It is required for the production of the monoamine neurotransmitters serotonin, dopamine, norepinephrine, and epinephrine, as it is the precursor to pyridoxal phosphate, which is the cofactor for the aromatic amino acid decarboxylase enzyme.

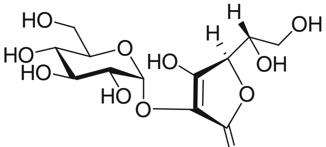

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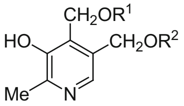
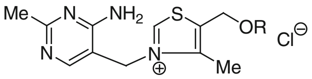
Fig. 12 2-*O*-α-Glucopyranosyl-L-ascorbic acid

Fig. 13 Pyridoxine and its glycosides prepared by enzymatic reactions



18 (Pyridoxine) $R^1 = R^2 = H$
19 $R^1 = H$, $R^2 = \beta$-Glc*p*
20 $R^1 = H$, $R^2 = \alpha$-Glc*p*
21 $R^1 = \alpha$-Glc*p*, $R^2 = H$

Fig. 14 Thiamine and its glycosides prepared by enzymatic reactions



22 (Thiamin) R = H
23 R = β-Glc*p*
24 R = α-Glc*p*
25 R = α-Glc*p*NAc

A series of glycosides of pyridoxine – 2-acetamido-2-deoxy-β-D-glucopyranosides, α/β-glucopyranosides (**19**–**21**) (Fig. 13), and α-D-mannopyranosides, and one α-D-galactopyranoside were prepared using a library of glycosidases [55]. Free sugar (mannose) or *p*-nitro-α/β-glycosides were used as donors. The regioselectivity of glycosidases towards two different primary hydroxyl groups of pyridoxine were studied and it was found to be strongly dependant on the enzyme source. The Trincone group [56] described a high-yield preparation of pyridoxine isomaltoside, in which *exo*-α-glucosidase from *Aplysia fasciata* was applied with maltose as a donor.

Recently, the enzymatic preparations of various pyridoxine and retinol glycosides were published by Divakar's group [57, 58]. Although the syntheses of various pyridoxine and retinol glycosides were presented (glucosides, galactoside, mannoside, fructosides), only one glycosidase (β-glucosidase from sweet almond, purified enzyme – one band on SDS–PAGE) was used. All of these papers suffer from many problems – often repeating previously published experiments without proper citations and questionable reproducibility (failing to take into account the enzyme specificity issue, such as, e.g., that β-glucosidase accepted glucose, galactose, fructose, and mannose as donors, moreover the fact that this enzyme was able to catalyze the formation of α- and also β-linkages is highly improbable, if not impossible).

3.3.3 Thiamin

Thiamin (vitamin B_1, **22**) (Fig. 14) – an important cofactor of decarboxylases, transketolases, carboxy-lyases, and some other enzymes – was successfully glycosylated by enzymatic transglycosylation using β-galactosidase [59] and β-*N*-acetylhexosaminidase [60] from *A. oryzae*.

4 Glycoside Bioprocessing in Food and Flavor Chemistry

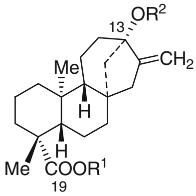
4.1 Steviol Glycosides

The leaves of *Stevia rebaudiana* (Compositae) are a source of several sweet glycosides of steviol (**26**) (Fig. 15) [1, 61]. The major glycoside, stevioside (**27**), is used in oriental countries as a food sweetener and the second major glycoside named rebaudioside (**28**), which is sweeter and more delicious than stevioside, is utilized in beverages.

Stevioside (**27**) and rubusoside (**29**) (Fig. 15) taste somewhat bitter, and have an unpleasant aftertaste. To improve the sweetness and the taste, modifications of the sugar moieties of both the glycosides were performed by enzymatic glycosylations and/or enzymatic trimming. Cyclomaltodextrin-glucanotransferase (CGTase) efficiently catalyzes the transfer of (one or more) α-glucosyl moieties from starch onto the 4-OH of a glucosyl moiety.

Stevioside was treated with this system and this resulted in a complex mixture of mono-, di-, tri-, and polyglucosylated derivatives on both existing glucose moieties of the original compound. Significant improvement to the quality of their taste was observed for most of the glucosylated products, especially for **30** and **31**, which were mono- and diglucosylated at the 13-sophorosyl moiety of stevioside [62]. A remarkable enhancement of the intensity of sweetness was also observed for both these products, while glucosylation at the 19-*O*-glucosyl moiety (ester bound) resulted in a decrease in the intensity of sweetness (Table 1).

Rubusoside was also transglucosylated using the same enzyme system and a large number of products were obtained. Strong enhancement of the sweetness intensity was observed for the products, which were di- or triglucosylated at the 13-*O*-glucosyl moiety. Tetraglucosylation at the 13-*O*-glucosyl moiety as well as glucosylation at the 19-*O*-glucosyl moiety led to a decrease in sweetness [63]. Therefore, after transglucosylation the products are "trimmed" enzymatically using β-amylase that releases maltose from the nonreducing end of the α-glucoside. Using this treatment, tri- and more α1-4-glucosyl chains are converted into mono- and



26 Steviol R^1 = H, R^2 = H
27 Stevioside R^1 = β-D-Glc*p*, R^2 = Glc(β1→2)Glcβ
28 Rebaudioside-A R^1 = β-D-Glc*p*, R^2 = Glc(β1→2)Glc3
↑
Glcβ1
29 Rubusoside R^1 = β-D-Glc*p*, R^2 = β-D-Glc*p*

Fig. 15 Structures of steviol glycosides – for their relative sweetness see Table 1

Table 1 Relative sweetness intensity of various glucosyl derivatives **26**–**29** of stevioside [62] (Fig. 15)

Compound	19-*O*-Glycosyl (R^1)	13-*O*-Glycosyl (R^2)	RS	QT
Stevioside (**27**)	–Glc	–Glc–Glc	160	0
Rebaudioside (**28**)	–Glc	–Glc–Glc \ Glc	210	+2
Rubusoside (**29**)	–Glc	–Glc	134	−2
30	–Glc	–Glc–Glc–**α–Glc**	180	+4
31	–Glc	–Glc–Glc–**α–Glc–α–Glc**	205	+4
32	–Glc	–Glc–Glc–**α–Glc–α–Glc–α–Glc**	117	+3
33	–Glc–**α–Glc**	–Glc–Glc	133	+2
34	–Glc–**α–Glc**	–Glc–Glc–**α–Glc**	136	+1
35	–Glc–**α–Glc**	–Glc–Glc–**α–Glc–α–Glc**	146	0
36	–Glc–**α–Glc–α–Glc**	–Glc–Glc	136	0
37	–Glc–**α–Glc–α–Glc**	–Glc–Glc–**α–Glc**	150	+1
38	–Glc–**α–Glc–α–Glc–α–Glc**	–Glc–Glc	121	+3

RS Relative sweetness to sucrose

QT Quality of taste, stevioside: 0, + better, − worse

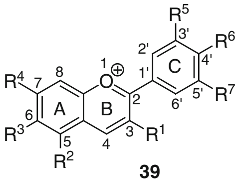
diglucosides, which results in a further improvement of their sweetness. The commercial product of transglucosylated stevioside always undergoes this treatment [64].

Replacement of the 19-*O*-glucosyl group with a β-galactosyl group led to a worsening of the taste [65]. A significant improvement in the taste quality was achieved by enzymatic transfructosylation at the 19-*O*-Glc moiety of both stevioside and rubusoside [66]. The β-fructofuranosyl moiety is, however, unstable and prone to hydrolysis. This is a practical demonstration of the advantage of glycosidic moiety modification in optimizing the physiological properties of the compound(s).

Further experiments dealing with the prolongation of sugar chains were done by Shibata and coworkers [67]. Glucosyltransferases isolated from *Stevia rebaudiana* were successfully used to glycosylate steviol, steviolmonoside, steviolbioside, stevioside, and other flavonol aglycones (e.g., quercetin and kaempferol). On the other hand, the selective hydrolysis of stevioside using glycosidases from other sources has also been described [68, 69].

4.2 Anthocyanins

The anthocyanidins (aglycons **39**) that are found in their glycoside form are known as anthocyanins (Fig. 16). Anthocyanins are members of the flavonoid group of phytochemicals (predominant in wines, fruits, and vegetables), utilized as vegetable colorants in the food industry. Their stability is affected by several factors such as pH, storage temperature, chemical structure, concentration, light, solvents, and the presence of enzymes, proteins, and metallic ions. Another significant property of anthocyanins is their free radical scavenging and antioxidant activity, which plays a vital role in the prevention of cardiovascular diseases, cancer, and diabetes. To date



39

Fig. 16 General anthocyanin structure

more than 900 different anthocyanins have been reported [70–72]. The glycoside derivatives most widespread in nature are 3-monosides, 3-biosides, and 3,5- and 3,7-diglucosides. The most common anthocyanin is the cyanidin-3-glucoside (R^1=R^2=R^4=R^5=R^6=OH; R^3=H).

4.3 Glycosides as Aroma Precursors

In a large number of fruits, including grapes, a significant number of important flavor compounds are accumulated as nonvolatile and flavorless glycoconjugates, which are denoted as glycosidic aroma precursors. The glycoside parts are mainly *O*-β-D-glucosides or *O*-glycobiosides. In a few cases, trisaccharides glycoconjugates were observed [73]. The aglycone moiety is always linked to β-D-glucopyranose, following α-L-arabinofuranose, α-L-arabinopyranose, α-L-rhamnopyranose, β-D-glucopyranose, β-D-apiofuranose, and β-D-xylopyranose (Fig. 17).

The aglycon part of glycoside is often represented by monoterpenes, C13-norisoprenoids, benzene derivatives, and long-chain aliphatic alcohols (Fig. 18) [74, 75].

Glycosidic aroma precursors are relatively stable and their acidic hydrolysis occurs slowly under wine storage conditions. Therefore, the use of an enzyme may significantly improve flavor. Most exogenous enzymes with mono- or diglycosidase activity [76–78], including commercial enzymes, glycosidase from yeast [79, 80], filamentous fungi in solution, or immobilized forms [81–84], have been applied in juice processing and winemaking to enhance the qualities of their aroma. The enzyme's activity could be confined to alcohol and glycoside (feedback) inhibition, although the concentration such of compounds is usually below their inhibition limit.

5 Glycosylation of Antibiotics and Cancerostatics

5.1 Vancomycin Group

Vancomycin (**40**) [85] is a glycopeptide antibiotic that is widely used in the treatment of Gram-positive bacterial infections (Fig. 19). It was discovered in a soil sample from the jungles of Borneo during a research program carried out by the pharmaceutical company Eli Lilly in the mid-1950s. *Streptomyces orientalis* (later

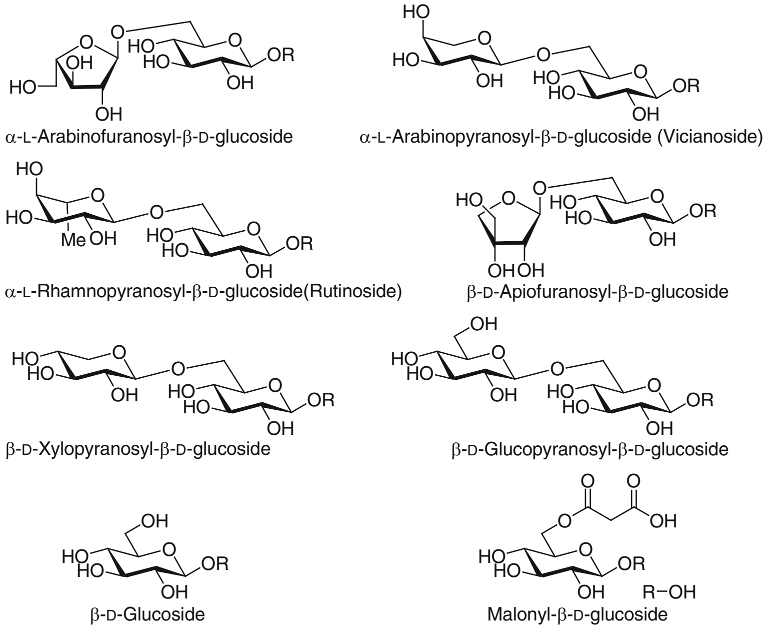


Fig. 17 Typical glycosidic structures in the aroma precursor glycosides

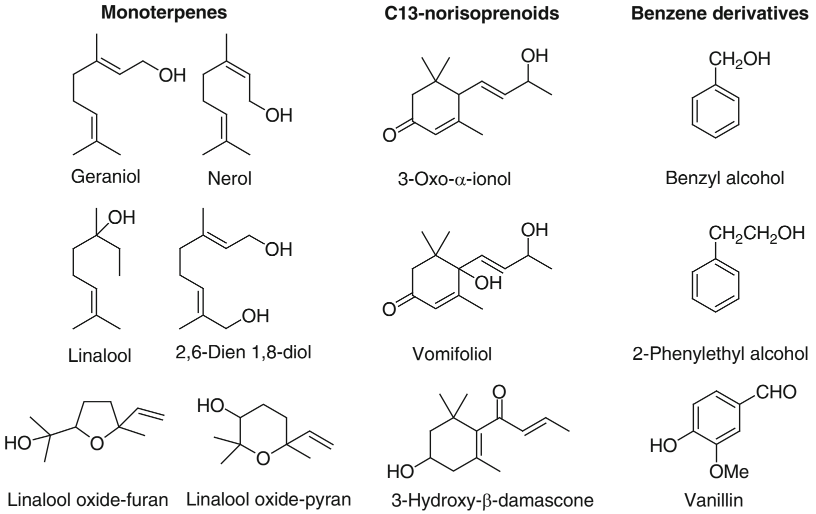
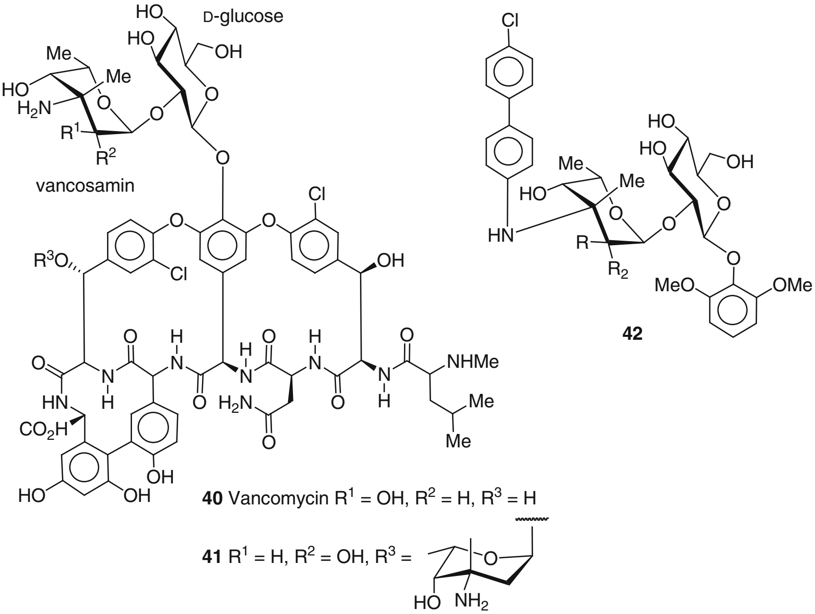


Fig. 18 Aromatic compounds occurring as glycosides

reclassified as *Nocardia orientalis* and finally *Amycolatopsis orientalis*) was used to produce this antibiotic, which was first used in clinics in 1959. Its importance has recently increased considerably, as it is one of the few antibiotics effective against



40 Vancomycin $R^1 = OH$, $R^2 = H$, $R^3 = H$

41 $R^1 = H$, $R^2 = OH$, $R^3 =$

Fig. 19 Vancomycin and its glycosides

nosocomial infections, e.g., multiple-resistant bacteria – an atypical example is methicilline-resistant *Staphylococcus aureus* (MRSA), and, together with gentamycin, it is a last resort antibiotic. Unfortunately, resistance has also developed against vancomycin and teicoplanin [86, 87] and, therefore, its further modification including glycorandomization is of the utmost importance.

Vancomycin consists of a core heptapeptide with attached saccharide moieties, one of which is the deoxyaminosugar vancosamine. Vancomycin exhibits its antibacterial activity by binding bacterial cell wall mucopeptide precursors terminating in the sequence L-Lys-D-Ala-D-Ala [88], thereby impeding further processing of these intermediates into peptidoglycans. Five hydrogen bonds account for this binding specificity, and the disruption of one of these hydrogen bonds by replacing the terminal alanine with lactate (D-Ala-D-Lac) in the mucopeptide precursor is the molecular basis for resistance to **40**. Bacterial cell-wall biosynthesis proceeds in two steps at the exterior of the cell starting with the disaccharide moiety attached to the peptide being transported from the cytoplasm out of the cell. Here, they are linked together by transglycosidase.

Because of the ultimate importance of vancomycin in the treatment of often fatal infections caused by multiple-resistant bacteria, extensive efforts have been directed toward the discovery of vancomycin derivatives with activity against these drug-resistant bacteria [89]. As a result of these efforts, several derivatives such as **41** (LY264826) have been found to be up to 500 times more effective than vancomycin itself. The most notable difference is the presence of another aminosugar (R^3) attached to amino acid (Fig. 19). This extra sugar possibly facilitates the dimerization of the antibiotic and/or anchors the antibiotic to the cell membrane, both of which have been shown to be important for vancomycin activity [85]. It was also demonstrated that the conformations of vancomycin and its aglycone differ in their alignment of the amide protons that participate in the hydrogen-bonding network with cell-wall precursors [90]. Alkylation of the 3-amino group on the disaccharide at amino acid residue further enhances its activity, probably by serving as a hydrophobic anchor to the cell membrane [91] (Fig. 19).

Another target for modification of vancomycin is the vancosamine moiety. Recently it was found that *N*-alkylation with *n*-decyl or 4-chlorobiphenyl groups results in an antibiotic acting via a different mechanism than vancomycin itself [92] and, therefore, exhibits activity against vancomycin-resistant microorganisms. Sugar-altered vancomycin interferes with the polymerization of a glycopeptide monomer to form cell wall material in the first place. Thus, altered vancomycin may disrupt cell wall formation at multiple targets of the glycopeptide monomer, straight-chain polymer, and cross-link reinforcement.

In fact, the altered disaccharide derivative itself (**42**) has strong antibacterial activity, even if not attached to the rest of the large vancomycin molecule [92]. This compound, however, acts via a different mechanism than vancomycin. It inhibits the transglycosylation step that precedes the transpeptidase step blocked by vancomycin itself. This finding explains the complex mechanism of action of derivative **41**.

Vancomycin can also serve as an excellent example of glycorandomization (see below) that has been accomplished by Fu et al. [93] (Fig. 20).

6 Glycorandomization

The isolation of several sugar biosynthesis gene clusters and glycosyltransferases from different antibiotic-producing organisms, and increasing knowledge on these biosynthetic pathways opened up the possibility of generating novel bioactive compounds through combinatorial biosynthesis. Recent advances in this area indicate that antibiotic glycosyltransferases show some substrate flexibility that can allow the types of sugar transferred to the different aglycones to be altered or, less frequently, to change the position of its attachment [94, 95]. Recently, two complementary glycorandomization strategies have been described, namely, neoglycorandomization, a chemical approach based on a one-step sugar ligation reaction that does not require any prior sugar protection or activation, and chemoenzymatic glycorandomization, a biocatalytic approach that relies on the substrate promiscuity of enzymes to activate and attach sugars to natural products.

These “glycorandomization” approaches (occasionally referred to as “glycodiversification”) are expected to foster our understanding of the role of sugars in a variety of glycoconjungates and the exploitation of these critical attachments. Two types of glycorandomization strategies have been described: (1) *neoglycorandomization*, a recently disclosed chemical approach based upon a one-step sugar ligation reaction that does not require prior sugar protection or activation, and (2) *chemoenzymatic glycorandomization*, a biocatalytic approach that relies on the substrate promiscuity of enzymes to activate and attach sugars to natural products.

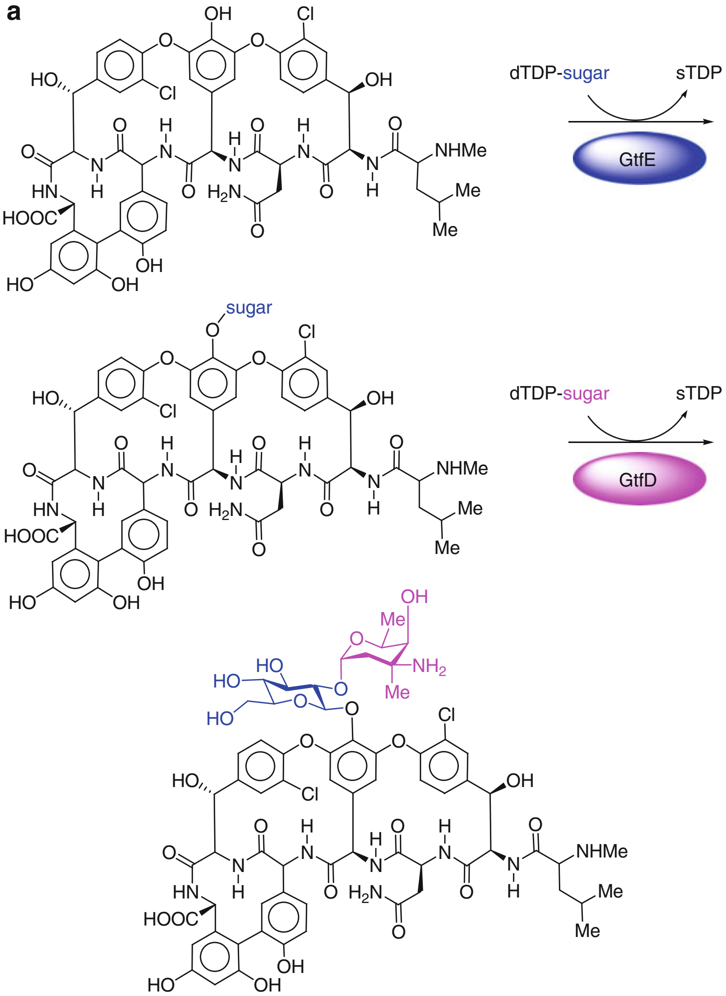


Fig. 20 Vancomycin neoglycorandomization: the culminating steps of vancomycin biosynthesis and a phase I vancomycin IVG library. (**a**) The final stages of vancomycin biosynthesis catalyzed by GtfE (glucosyltransferase; *blue*) and GtfD (vancosaminyltransferase; *magenta*). (**b**) Variants from stage I IVG of the vancomycin aglycone. Changes from the GtfE wild-type substrate (glucose) are highlighted in *red* [93]. Adapted by permission from Macmillan publishers Ltd. © 2003 [93]

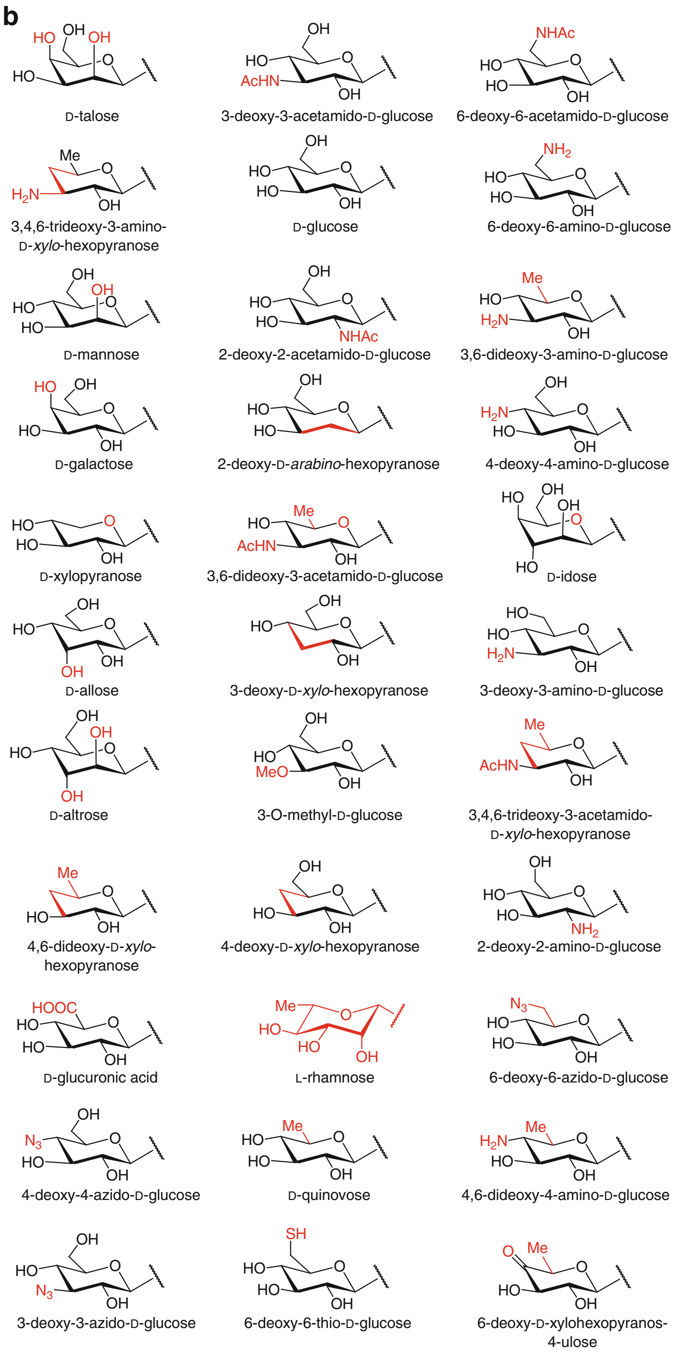


Fig. 20 (Continued)

Neoglycorandomization, which was developed by J.S. Thorson and coworkers, relies on a broad variety of reducing monosaccharides without a protection/deprotection methodology [96]. Neoglycorandomization is based on the selective formation of glycosidic bonds between reducing sugars and secondary alkoxyamine-containing aglycones to form a library of "neoglycosides" [96].

Sugars and acceptors containing secondary alkoxyamines are reacted with reducing sugars to generate oligosaccharide and glycopeptide mimics. Unlike primary alkoxyamines, which yield open-chain oxime isomers, secondary alkoxyamines react to form closed-ring neoglycosides. Such secondary alkoxyamines presumably react with reducing sugars to form an intermediate oxy-ammonium species, which then undergoes ring closure [97].

Chemoenzymatic glycorandomization [98, 99] employs the inherent or engineered substrate promiscuity of anomeric kinases and nucleotidyltransferases, chemoenzymatic glycorandomization attempts to provide activation pathways for the synthesis of nucleotide diphosphosugar donor libraries. In chemoenzymatic glycorandomization, these activated sugar libraries in turn serve as substrates for inherently promiscuous natural product glycosyltransferases, thereby providing a rapid chemoenzymatic means to glycodiversity. Such multienzyme, one-pot reactions offer an attractive alternative to the extensive synthetic manipulation typically required for chemical glycosylation strategies.

In the last 3 years, a variety of examples have appeared supporting this robust methodology: four glycosyltransferases from two distinct natural product biosynthetic pathways – calicheamicin and vancomycin – readily catalyzed reversible reactions, allowing sugars and aglycones to be exchanged. More than 70 differentially glycosylated calicheamicin and vancomycin variants were prepared. This study [100] suggests that the reversibility of glycosyltransferase-catalyzed reactions may be general and useful for generating exotic nucleotide sugars and establishing in vitro glycosyltransferase activity in complex systems. A monoglycosylated vancomycin library was prepared using flexible glycosyltransferases with a nucleotide diphosphosugar library [93].

High-level expression of three macrolide glycosyltransferases created a synthetic "tool kit" with such plasticity that 12 modified macrolide antibiotics (oleandromycin and erythromycin) have been readily created [101].

Another, more advanced methodology uses a combination of chemoenzymatic synthesis (substrate modifications) together with in vivo pathway engineering, as demonstrated in the recent excellent review by Thibodeaux and Liu [102] on macrolide glycodiversification.

Successful implementation of these sugar-engineering studies relies on our understanding of the substrate flexibilities of the enzymes involved in the sugar synthesis. Studies elucidating the mechanisms and biochemical properties of sugar biosynthetic enzymes are of paramount significance.

On the other hand, mostly synthetic methodologies have been developed so far and this will definitely be furthered by better understanding the activity mechanisms via specific SAR studies, enabling antibiotic optimization of existing antibiotics and the construction of new ones. In this way our fundamental knowledge of the role of carbohydrates in the biological activity of glycosides can be capitalized upon.

7 Trends and Perspectives

Obviously, applications of enzymes in food and pharma biotechnology have already proven their viability. Glycosidases, glycosyltransferases, and other carbohydrate-processing enzymes are being used more and more in these processes, mostly due to their better availability and accessibility thanks to advanced biochemical and biomolecular procedures. Glycosylation, typically the introduction of α-glucopyranosyl units in numerous natural products, is used mostly for solubility and bioavailability improvement by some companies in Japan and elsewhere. Glycoside trimming and selective glycosylation with engineered glyco-enzymes are another useful technological methods, as was nicely demonstrated by Whithers [103] in developing the concept of glycosynthases. Therefore, completely altered enzyme specificity can now be employed. This type of enzyme still awaits its major application in biotechnology.

A very important application of glyco-enzymes in natural product modification is the glycorandomization of antibiotics and other complex compounds. This methodology pioneered by the Thorson group [93] can bring revolutionary results by creating new antibiotics that are now desperately needed. Another, more advanced methodology uses a combination of chemoenzymatic synthesis (substrate modifications) together with in vivo pathway engineering as demonstrated in the recent excellent review by Thibodeaux and Liu [102] on macrolide glycodiversification.

Successful implementation of these sugar engineering studies relies on our understanding of the substrate flexibilities of the enzymes involved in the sugar synthesis. Studies elucidating the mechanisms and biochemical properties of sugar biosynthetic enzymes are of paramount significance. On the other hand, mostly synthetic methodologies have been developed so far and this will definitely be furthered by better understanding the activity mechanisms via specific SAR studies, enabling antibiotic optimization of existing antibiotics and construction of new ones. In this way, our fundamental knowledge of the role of carbohydrates in the biological activity of glycosides can be capitalized upon.

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Synthetic Polymers from Readily Available Monosaccharides

J.A. Galbis and M.G. García-Martín

Abstract The low degradability of petroleum-based polymers and the massive use of these materials constitute a serious problem because of the environmental pollution that they can cause. Thus, sustained efforts have been extensively devoted to produce new polymers based on natural renewing resources and with higher degradability. Of the different natural sources, carbohydrates stand out as highly convenient raw materials because they are inexpensive, readily available, and provide great stereochemical diversity. New polymers, analogous to the more accredited technical polymers, but based on chiral monomers, have been synthesized from natural and available sugars. This chapter describes the potential of sugar-based monomers as precursors to a wide variety of macromolecular materials.

Keywords α,ω-Alkanediamines, 1,4:3,6-Dianhydrohexitols, Aldaric acids, Aldonolactones, Aminoalditols, D-Glucitol, Diaminoalditols, D-Mannitol, D-Xylitol application, Erythritols, Isoidide, Isomannide, Isosorbide, L-Arabinitol, Lipase-catalysis, Polyamides, Polycarbonates, Polyesteramides, Polyesters, Polyethers, Polyureas, Polyurethanes, Super-acid, Tartaric acids

Contents

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1 Introduction

The exhaustible nature of the oil reserves and the pollution that oil-based technological polymers can have on the environment has rekindled an interest in polymers of natural origin, in particular the biotechnological polymers. Until now, however, the polyhydroxyalkanoates are the only biotechnological polymers that have been developed industrially, occupying a notable position as biodegradable and biocompatible biomaterials for temporary use [1, 2].

Another approach is the development of new polymers with characteristics similar to those of the industrial polymers, but synthesized from monomers derived from renewable raw materials. These synthetic polymers mimic the structure and function of biological polymers, increasingly blurring the borders between natural and artificial materials [3]. The incorporation of sugar-derived units into traditional condensation polymers such as polyamides, polyesters, and polyurethanes is seen as an interesting method for the preparation of new biodegradable and biocompatible materials for use in biomedical applications and in other sectors of greater consumption, such as the packing of foodstuffs [4, 5].

Synthetic polymers obtained from sugar-based monomers are innocuous for human health. Their hydrophilic nature ensures a greater hydrolytic degradability [6], and reduces their environmental impact compared to classic polymers [3].

The main problem in the synthesis of this type of polymers comes from their multiple functionalities. Although syntheses have been carried out using sugar-derived monomers with free hydroxyl groups [7–9], most of the syntheses of high-molecular-weight linear polymers are carried out with derivatives in which the hydroxyl groups have been appropriately blocked [10].

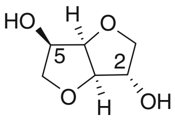
Some reviews have been published on the synthetic carbohydrate-based polymers and glycopolymers [11–15]. However, they refer mainly to poly(vinylsaccharide)s and other conventional functionalized polymers having sugars as groups pendant from the main chain of the polymer. In this chapter we shall describe those sugar-based monomers which lead to polymers having the sugar units incorporated into the main chain. The topic has also been reviewed [10, 16–20], but as the interest in this kind of carbohydrate-based polymer has been steadily increasing, a considerable number of papers have been published on the subject during the last few years. The following sections report on the synthesis and polymerization of this type of sugar-derived monomers that have been produced mainly during the past decade.

2 Sugars as Monomers

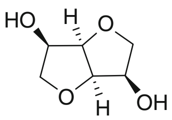
Carbohydrates are an important natural source of building blocks for the synthesis of biodegradable polymers, especially for biomedical applications, because of their inherent properties of biocompatibility and biodegradability, and for the design of optically active polymers containing stereocenters in the repeating unit. In order to obtain regio- and stereoregular polymers, strict control of the stereochemical course of the polymerization is required. Otherwise, random orientation of the chiral unit will lead to atactic polymers.

2.1 Alditols

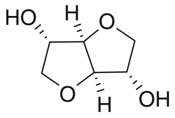
Alditols occur extensively in Nature. Aldoses and ketoses can be reduced to alditols. Thus, D-glucose gives D-glucitol, trivially referred to as “sorbitol”. The reduction of ketoses generates a new stereogenic center, and gives two epimeric alditols; for example, D-fructose produces D-mannitol and D-glucitol. The thermally stable 1,4:3,6-dianhydrohexitols are the carbohydrate-based monomers most widely employed in the synthesis of chiral polymers because they are easily available. The three stereoisomeric dianhydroalditol monomers having 1,4:3,6-dianhydro-D-gluco (**1**), -D-manno (**2**), and -L-ido (**3**) configurations have attracted increasing interest as building blocks for the synthesis of polycondensates, as reported by Kricheldorf [17]. These dianhydroalditols are referred to as isosorbide, isomannide, and isoidide, respectively.



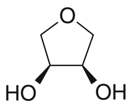
1 D-*Gluco*



2 D-*Manno*



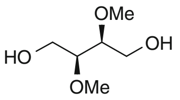
3 L-*Ido*



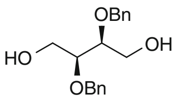
4 D-*Erythro*

Thiem et al. [21–23] studied the ring-opening polymerization of 1,4-anhydro-2,3-di-*O*-alkyl-D-erythritols (**4**) using super-acids.

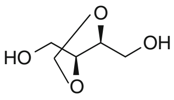
Within the framework of systematic research to explore the potential of sugar-based polymers, Muñoz-Guerra and Galbis et al. [24–31] have employed various acyclic *O*-methyl alditol derivatives **5–15** to prepare novel polymers, as well as chemical modification of other well-known materials.



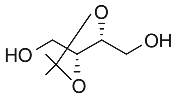
5 L-*Threo*



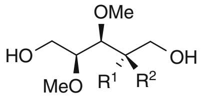
6 L-*Threo*



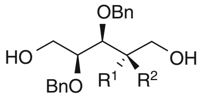
7 L-*Threo*



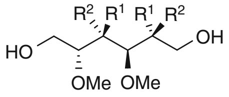
8 D-*Threo*



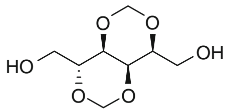
9 L-*Arabino* R^1= OMe, R^2= H
10 *Xylo* R^1= H, R^2= OMe



11 L-*Arabino* R^1= OBn, R^2= H
12 *Xylo* R^1= H, R^2= OBn



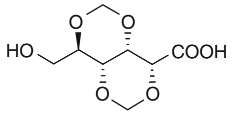
13 D-*Manno* R^1= OMe, R^2= H
14 D-*Galacto* R^1= H, R^2= OMe



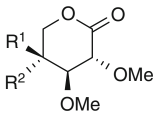
15 **D-***Gluco*

2.2 Aldonic Acids and Lactones

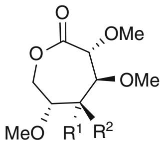
Several *O*-protected aldonic acids and aldonolactones such as **16–21** have been used as monomers in polycondensation and ring opening polymerization reactions [32–34].



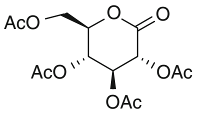
16 D-*Gluco*



17 L-*Arabino* R^1= OMe, R^2= H
18 *Xylo* R^1= H, R^2= OMe



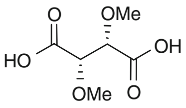
19 *Gluco* R^1= OMe, R^2= H
20 *Galacto* R^1= H, R^2= OMe



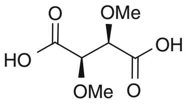
21 D-*Gluco*

2.3 Aldaric Acids

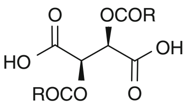
Unprotected and *O*-protected aldaric acids such as **22–36** have been extensively used in polycondensation reactions, mainly in the preparation of polyamides and polyesters. A review has been published on potentially important aldaric acids as monomers for the preparation of polyamides [35].



22 D-*Threo*

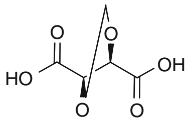


23 L-*Threo*

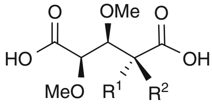


24 L-*Threo*

R= Me, ^{i}Pr, Ph, 3,5-C_6H_4

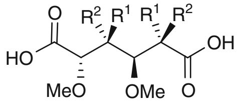


25 L-*Threo*



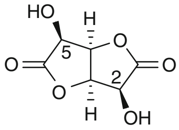
26 L-*Arabino* R^1= OMe, R^2= H

27 *Xylo* R^1= H, R^2= OMe

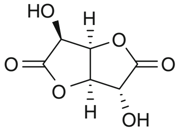


28 D-*Manno* R^1= OMe, R^2= H

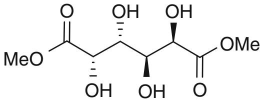
29 *Galacto* R^1= H, R^2= OMe



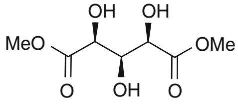
30 D-*Manno*



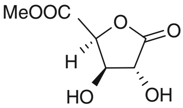
31 D-*Gluco*



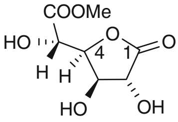
32 *Galacto*



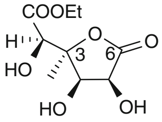
33 *Xylo*



34 *Xylo*



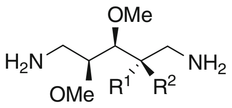
35 D-*Gluco*



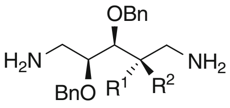
36 D-*Gluco*

2.4 Aminosugars

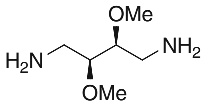
Amino- (**48**, **50**, **51**) and diaminoalditols (**37**–**44**), aminoaldonic acids (**45**–**47**, **49**), diaminoanhydroalditols, and some others amino-derivative of sugars (**52**–**58**) have been extensively used in the preparation of polyamides, polyurethanes and polyureas.



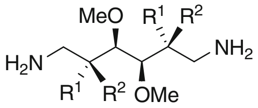
37 L-*Arabino* R^1= OMe, R^2= H
38 *Xylo* R^1= H, R^2= OMe



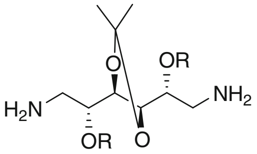
39 L-*Arabino* R^1= OBn, R^2= H
40 *Xylo* R^1= H, R^2= OBn



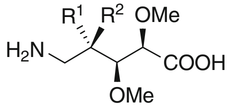
41 L-*Threo*



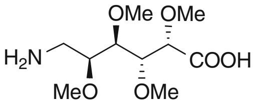
42 D-*Manno* R^1= OMe, R^2= H
43 L-*Ido* R^1= H, R^2= OMe



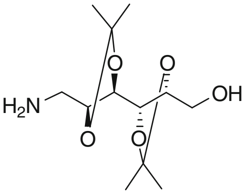
44 D-*Manno* R= H, Me



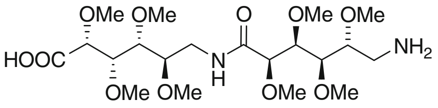
45 L-*Arabino* R^1= OMe, R^2= H
46 *Xylo* R^1= H, R^2= OMe



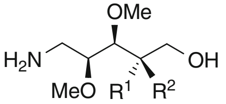
47 *Galacto*



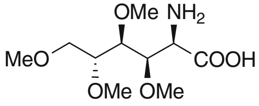
48 *Galacto*



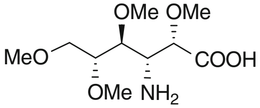
49 D-*Gluco*



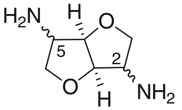
50 L-*Arabino* R^1= OMe, R^2= H
51 *Xylo* R^1= H, R^2= OMe



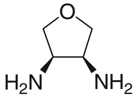
52 D-*gluco*



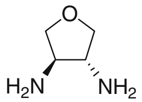
53 D-*altro*



54 D-*Gluco* (2-exo/5-endo)
55 D-*Manno* (2-endo/5-endo)
56 L-*Ido* (2-exo/5-exo)



57 *Erythro*



58 *Threo*

3 Polyesters

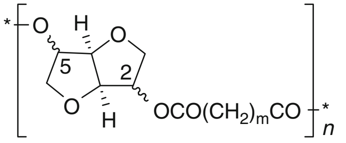
Aliphatic polyesters are the most economically competitive of the biodegradable polymers; moreover, synthetic polyesters are expected to be degraded nonspecifically by lipases. Although these polyesters are biodegradable, they often lack good thermal and mechanical properties. On the other hand, aromatic polyesters – such as

PET [(poly(ethylene terephthalate)] – have excellent mechanical properties, but are resistant to degradation by chemical or biological agents.

3.1 From Aliphatic Dicarboxylic Acids

Aliphatic polyesters may be classified into two groups, depending on the bond constitution of the monomers: poly(hydroxy acid)s [i.e., polyhydroxyalkanoates (PHAs)] and poly(alkylene dicarboxylate)s. The former are polymers of hydroxy acids (α, β,...ω-hydroxy acids), obtained by ring-opening polymerization or polycondensation reactions. The latter are synthesized by the polycondensation reaction of diols with dicarboxylic acids. Depending on the mechanism of biodegradation, polyesters can also be classified broadly into two groups: those degraded by enzymatic hydrolysis, and those not degraded by enzymes, although both group-sare generally susceptible, to some degree, to both kinds of hydrolysis. It is well known that polymers having hydrophilic moieties in their repeating units show an enhanced biodegradability. Thus synthetic carbohydrate-based polymers having hydrophilic groups would be excellent candidates for biomedical applications because of their inherent properties of biodegradability and biocompatibility.

Carbohydrate-based monomers as aldonic and aldaric acids, along with linear and dianhydroalditols, have been used to prepare aliphatic polyesters. Pioneering work of Braun and Bergmann used dianhydroalditols **1** (isosorbide) and **2** (isomannide) for the syntheses of polyesters, polyethers, polyurethanes, and polycarbonates [36]. They reported that the thermal and mechanical properties of the polymers obtained were similar to those of the respective polymers obtained from usual petrochemical raw materials. Okada et al. have worked extensively on biodegradable polymers based on the dianhydroalditols **1**–**3** (**3**: isoidide) as carbohydrate renewable resources [37, 38]. A series of polyesters **59** were synthesized by the bulk polycondensation of the respective three stereoisomeric dianhydroalditols (**1**–**3**) with aliphatic dicarboxylic acid dichlorides of 2–10 methylene groups. It was found that the biodegradability of the polyesters varied significantly depending on their molecular structures.



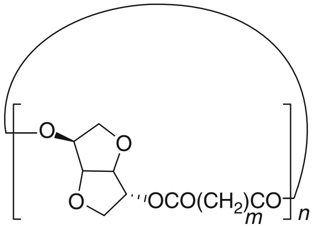
59 m= 2-10

5-*endo*/2-*exo*, D-*gluco*
5-*endo*/2-*endo*, D-*manno*
5-*exo*/2-*exo*, L-*ido*

Monomers **1** and **2** were also used as comonomers with dimethyl dialkanoates and monomers containing furan rings, for the synthesis of copolyesters by bulk polycondensations, in the presence of titanium isopropoxide or tetra-butyl-1,3-dichloro-distannoxane. In general, the biodegradability of the copolyesters of **1** decreased with increasing difuran dicarboxylate content, and copolymers containing sebacic acid units showed higher biodegradability. The enzymatic degradability of the polyesters based on isomeric 1,4:3,6-dianhydrohexitols and sebacic acid was found to decrease in the order **1** > **2** > **3**.

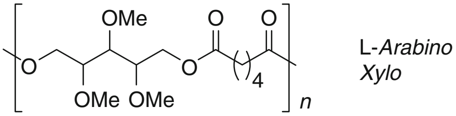
The 1,4:3,6-dianhydroalditols (mainly) and other saccharide derivatives were found to be useful chiral components of cholesteric materials with interesting optical properties, capable of forming Grandjean textures [17]. Chirality plays an important role in combination with the liquid crystalline (LC) character of low- or high-molecular-weight materials. A systematic study reported by Thiem on the twisting power of **1**–**3** derivatives contributed to increasing the interest in these monomers as building blocks of cholesteric polymers. Appropriate combinations of monomers should be sought that allow the incorporation of the sugar component without loss of the LC character, because the stereochemistry of the sugar diols is highly unfavorable for an LC character of their polymers. In fact, all homopolymers derived from sugar diols are isotropic.

Kricheldorf has studied extensively cholesteric polyesters **60** prepared from the mentioned dianhydroalditols; even cyclic polyesters from **1** were isolated by a selective extraction of the linear polymers [39].



60 *m*= 4, 6, 8, 10

Galbis et al. described a variety of carbohydrate-based linear polyesters **61** of the poly(alkylene dicarboxylate) type that were obtained by polycondensation reactions of the alditols 2,3,4-tri-*O*-methyl-L-arabinitol (**9**) and 2,3,4-tri-*O*-methyl-xylitol (**10**), and the aldaric acids 2,3,4-tri-*O*-methyl-L-arabinaric acid (**26**) and 2,3,4-tri-*O*-methyl-xylaric acid (**27**), butanediol, and adipic acid were also used as comonomers [28]. Copolyesters of the poly(alkylene-*co*-arylene dicarboxylate) type were obtained using bisphenols as comonomers (Scheme 1). Chemical polycondensation reactions were conducted in bulk or in solution. Enzymatic polycondensation reactions of adipic acid with the above-mentioned alditols were carried out successfully using Lipozyme® and Novozyme® 435. The hydrolytic degradations of some of these polyesters were also described.

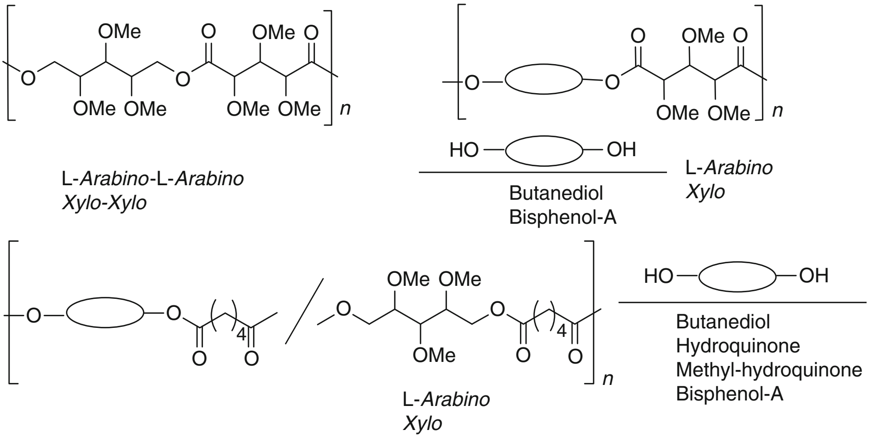


61

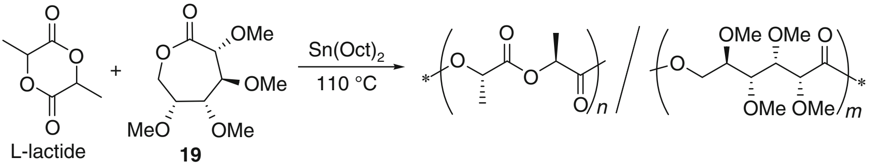
The polycondensation reaction of aldonic acids to generate polyesters has been less explored. Mehltretter and Mellies studied the polyesterification of the difunctional *O*-protected sugar 2,4;3,5-di-*O*-methylene-D-gluconic acid (**16**), obtaining low-molecular-weight polyesters. Drew and Haworth described the polycondensation of 2,3,4-tri-*O*-methyl-L-arabinono-1,5-lactone (**17**) to give an oligomeric material not completely characterized. Galbis et al. described an easy preparation of 2,3,4-tri-*O*-methyl-L-arabinose and 2,3,4-tri-*O*-methyl-D-xylose [31], which can be oxidized to give the corresponding lactones **17** and **18** [33]. The latter are susceptible to polymerization by ring-opening. However, attempts to polymerize these lactones were not met with success.

2,3,4,5-Tetra-*O*-methyl-D-glucono-1,6-lactone (**19**) was prepared from D-glucose by Galbis et al. as a crystalline compound in acceptable yield by two different routes [34]. Although the assays of homopolymerization of this lactone were also unsuccessful, copolymerization by bulk ring-opening polymerization of a mixture of L-lactide and lactone **19**, in a ratio of 5 to 1, using tin(II) 2-ethylhexanoate ($SnOct_2$) as initiator produced two copolymers (Scheme 2) containing 1.3% and 2.2% of the carbohydrate monomer, respectively, as determined by NMR studies.

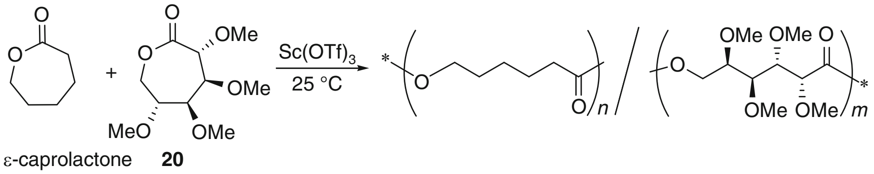
Varela et al. [40] obtained similar results from 2,3,4,5-tetra-*O*-methyl-D-galactono-1,6-lactone (**20**). The homopolymerization of this lactone, promoted by aluminum isopropoxide [$Al(O^iPr)_3$] or scandium triflate [$Sc(OTf)_3$], was attempted,



Scheme 1 Synthesis of copolyesters



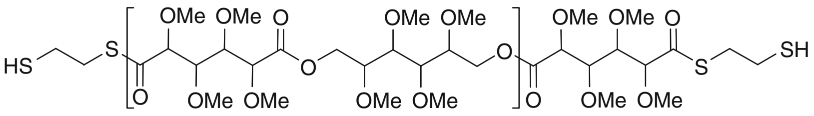
Scheme 2 Copolymerization of a sugar-lactone with L-lactide



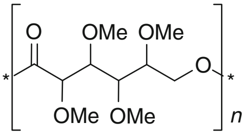
Scheme 3 Copolymerization of a sugar-lactone with ε-caprolactone

but failed in both cases. The copolymerization with ε-caprolactone, using scandium triflate as initiator, gave a low-molecular-weight copolymer (~3,000) with an incorporation of the sugar to the polymeric chain of about 10% (Scheme 3).

Guan et al. have recently published the preparation of galactitol and D-mannitol-derived permethylated polyesters **62** [41] and the living ring-opening polymerization of the galactonolactone **20** [42] giving polyester **63**. The latter exhibited protein resistance.



62 D-*manno*
Galacto

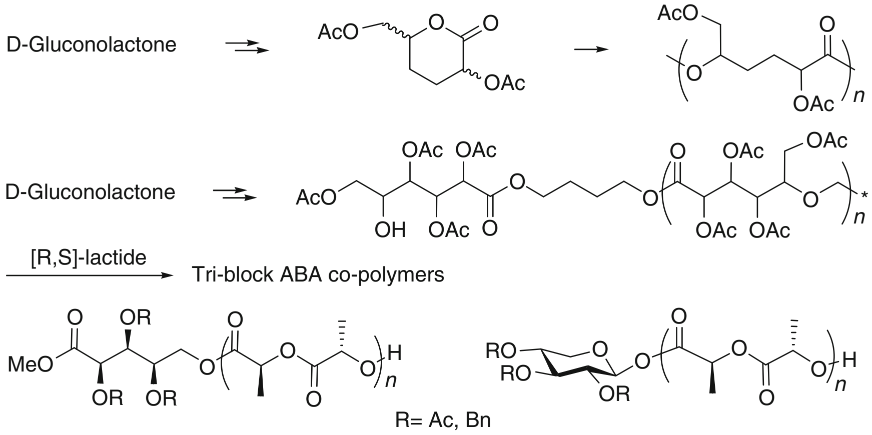


63 *Galacto*

Recently, Williams et al. have reported the ring-opening polymerization of carbohydrate lactones [43, 44] and the lactide polymerization coinitiated by carbohydrate esters and pyranoses [45] (Scheme 4).

Kobayashi and Gross, independently, have been working on the synthesis of alditol-based polyesters using lipases as catalysts for selective polyol polymerizations. Lipases and proteases provide regioselectivity during esterification reactions at mild temperatures. The first example of a sugar alcohol used as monomer in a "green" enzyme-catalyzed polymerization was reported by Kobayashi et al. in 2000 [46]. In this case, the activation of carboxylic acids with electron-withdrawing groups was thought to be necessary. They observed regioselective polymerization at positions C-1 and C-6 of D-glucitol (sorbitol) and divinyl sebacate in CH_3CN, applying a lipase catalyst derived from *Candida antarctica*.

Alditols are insoluble in nonpolar organic media but are soluble in polar solvents such as pyridine, dimethyl sulfoxide, 2-pyrrolidone, and acetone. Unfortunately, the latter solvents cause a large reduction in enzyme activity. A simple and versatile



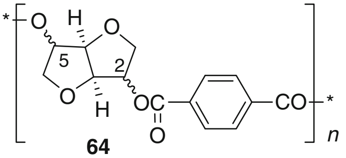
Scheme 4 Copolymerization of D-gluconolactone with lactide

strategy for performing selective lipase-catalyzed condensation polymerizations between dicarboxylic acids and polyols was explored by Gross. Instead of using organic solvents, the monomers adipic acid, glycerol, and sorbitol were solubilized within binary or ternary mixtures. Immobilized Lipase B from *C. antarctica* (Novozyme 435) catalyzed the bulk polycondensation of three monomers, forming a monophasic ternary mixture that resulted in hyperbranched polyesters with octanediol-adipate and glycerol-adipate repeating units [47]. The key to the success of this method was the use of a highly active and selective lipase-catalyst, as well as adjusting the reaction mixture so that it was monophasic. In this way, polyesters containing many hydroxyl functionalities, such as poly(sorbityl adipate), were prepared without the need to use protection–deprotection chemistry. Gross has also reported the use of various unprotected alditols, such as erythritol, xylitol, ribitol, D-mannitol, D-glucitol, and D-galactitol, in the preparation of polyesters applying lipase-catalyzed polycondensation with 1,8-octanediol and adipic acid [48].

Kobayashi et al. have worked extensively on enzymatic polymerization for the synthesis of both novel and natural oligo- and polysaccharides, and polyesters via polycondensation [49]. Lipase catalysis induced regioselective polymerization of divinyl ester with triols to give soluble polymers of relatively high molecular weight and for which the microstructure depended on the lipase origin. These authors also accomplished the enzymatic syntheses of a new class of cross-linkable polyesters by the polymerization of divinyl sebacate and glycerol, using *C. antarctica* lipase in the presence of unsaturated higher fatty acids. Thus, these polyesters had an unsaturated group in side chains. Biodegradable epoxide-containing polyesters derived from glycerol and unsaturated fatty acids were also obtained following a similar route.

3.2 From Aromatic Dicarboxylic Acids

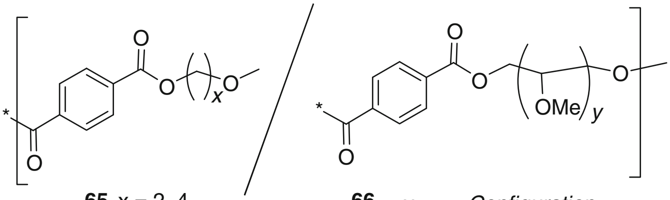
In 1984 Thiem et al. [50, 51] prepared polyterephthalates **64** of low molecular weight by melting condensation of terephthalic acid dichloride with 1,4:3,6-dianhydrohexitols. With labile isosorbide (**1**) polymers of cross-linked character were obtained. Later, Storbeck et al. [52] reinvestigated these polyterephthalates. The reaction conditions were optimized, and pyridine was found to be the most useful acceptor of hydrogen chloride.



64

5-*endo*/2-*exo*, D-*gluco*
5-*endo*/2-*endo*, D-*manno*
5-*exo*/2-*exo*, L-*ido*

Muñoz-Guerra and Galbis et al. have employed several *O*-methyl alditol derivatives to prepare novel polymers **65**, **66**. Furthermore, poly(ethylene terephthalate) (PET), poly(ethylene isophthalate) (PEI), and poly(butylene terephthalate) (PBT) have been chemically modified by insertion of a series of *O*-methyl alditols. Among them, 2,3-di-*O*-methyl-L-threitol (**5**) was inserted into PET [24], and PET and PEI analogs were synthesized by total replacement of the ethylene glycol (EG) units with 2,3,4,5-tetra-*O*-methyl-hexitols having D-*manno* (**13**) and *galacto* (**14**) configurations [25]. They also prepared polyesters analogous to PET, PEI, and PBT by using 2,3,4-tri-*O*-methyl-L-arabinitol (**9**) and 2,3,4-tri-*O*-methyl-xylitol (**10**) [26, 27]. The 2,3,4-tri-*O*-benzyl ethers of L-arabinitol (**11**) and xylitol (**12**) were also used to prepare polyesters analogous to PET and PBT [29]. Butylene copolyesters based on per-*O*-methyl aldaric acids such as L-arabinaric (**26**) and galactaric (**29**) acids, and terephthalic acid were also prepared and characterized [30].



65 x = 2, 4

66

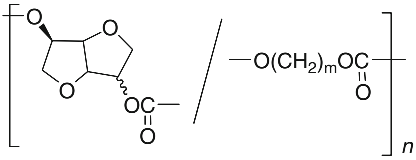
y	*Configuration*
2	L-*Threo*
3	L-*Arabino*
3	*Xylo*
4	D-*Manno*
4	*Galacto*

The hydrolytic degradation of a series of homo- and copolyesters analogous to PET and PEI based on the mentioned L-arabinitol, xylitol, D-mannitol, and galactitol were relatively fast at temperatures 10°C above their respective T_g [53].

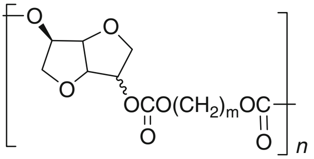
Degradability showed a clear dependence on the configuration of the sugar units present in the polymer chain, and the hydrolysis of copolyesters took place preferentially by cleavage of the ester groups of the sugar units.

3.3 Polycarbonates

Okada et al. prepared random (**67**) and alternating copolycarbonates (**68**) from 1,4:3,6-dianhydrohexitols and aliphatic diols in bulk or solution polycondensations [54]. Bulk polycondensations of 1,4:3,6-dianhydro-2,5-bis-*O*-(phenoxycarbonyl)-D-glucitol and -D-mannitol with α,ω-alkanediols of different numbers of methylene groups afforded random copolycarbonates. However, solution polycondensations of the corresponding *p*-(nitrophenoxycarbonyl) monomers in solution gave well-defined copolycarbonates having regular structures consisting of alternating sugar carbonate and aliphatic carbonate moieties. The environmental and enzymatic degradability of copolycarbonates consisting of **1** and **2** and alkylene diols or oligo(ethylene glycols) was also investigated [55].

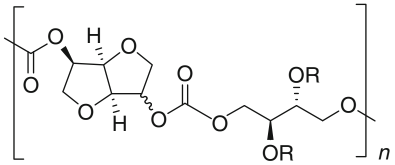


67 Random copolycarbonates



m= 4, 6, 8,10 **68** Alternating copolycarbonates

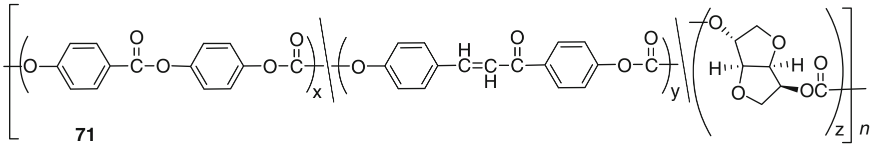
Tartaric acid has also attracted a great deal of interest as a substrate for synthesis of functional polymers based on carbohydrates. For example, L-tartaric acid is a natural product mainly obtained from a large variety of fruits. Okada studied polycarbonates with pendant functional groups, based on 1,4:3,6-dianhydrohexitols and L-tartaric acid derivatives [4]. Solution polycondensations of 1,4:3,6-dianhydro-bis-*O*-(*p*-nitrophenoxycarbonyl)hexitols and 2,3-di-*O*-methyl-erythritol or 2,3-*O*-isopropylidene-erythritol afforded polycarbonates **69** and **70** having pendant methoxy or isopropylidene groups, respectively. Subsequent acid-catalyzed deprotection of the isopropylidene groups gave well-defined polycarbonates having pendant hydroxyl groups regularly distributed along the polymer chain. Degradation of the polycarbonates with pendant hydroxyl groups was remarkably fast.



69 R= Me 2-*exo,* D-*gluco*
70 R,R= Isopropylidene 2-*endo* D-*manno*

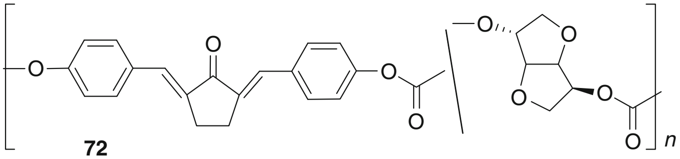
Homopolycarbonates based on **1** and **2** have been prepared by several groups. The interfacial polycondensation typical for the synthesis of aromatic polycarbonates is not useful with alditols, including **1**, because they are water-soluble and less acidic than diphenols. The **1**-based homopolycarbonate was prepared by phosgenation of the sugar diol, with phosgene or diphosgene in pyridine-containing solvent mixtures at low temperatures. The polycondensation of the isosorbide bischloroformate in pyridine is an alternative approach.

Kricheldorf et al. prepared cholesteric polycarbonates **71** derived from isosorbide bis(phenyl carbonate), methyl hydroquinone, and 4,4′-dihydrobiphenyl by polycondensation in pyridine-containing organic solvents [56]. Trichloromethylchloroformate (TCF) was successfully used for all these polycondensations. The use of solid TCF is advantageous over phosgene because it is easy to apply in stoichiometric amounts, easy to store, and commercially available. They also synthesized a series of ternary polycarbonates derived from isosorbide chloroformate, hydroquinone 4-hydroxybenzoate (HQHB) as mesogenic diphenol, and 4,4′-dihydroxychalcone in pyridine [57]. Particularly noteworthy is the finding that the alternating copolycarbonate of HQHB formed a broad cholesteric phase despite the unfavorable stereochemistry of **1**. The ternary copolycarbonates formed a cholesteric melt and a Grandjean texture upon shearing. It seems that the combination of **1** and carbonate groups is more favorable for the stabilization of a cholesteric molecular order than is the combination of **1** and ester groups.



71

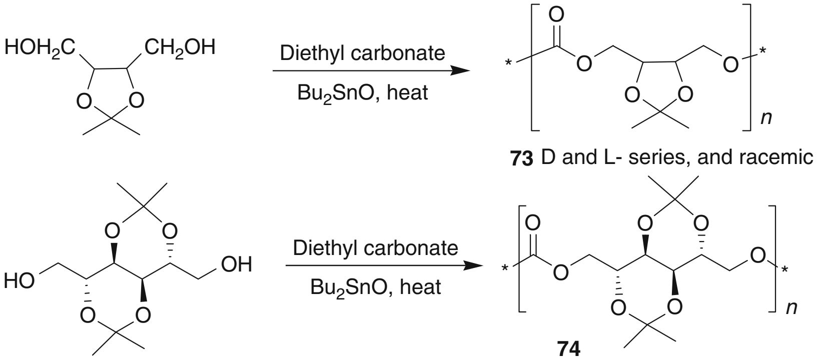
Cholesteric polycarbonates **72** derived from 1 and 2,5-bis(4′-hydroxybenzylidene)cyclopentanone were also described [58].



72

Isosorbide and equimolar amounts of various diols were polycondensed with diphosgene in pyridine. Different bisphenols, 1,3-bis(4-hydroxybenzyloxy)propane, and 1,4-cyclohexane diol were used as comonomers [59]. In some cases, large amounts of cyclic oligo- and polycarbonates were formed.

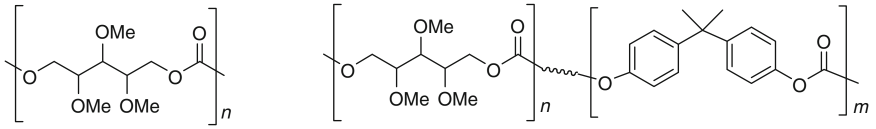
Bioerodible polymers having pendant functional groups are of particular interest, since they are capable of covalent pro-drug formation. Acemoglu [60] prepared biodegradable poly(hydroxyalkylene carbonate)s **73** and **74** from the optically active and racemic 2,3-*O*-isopropylidene-threitol and 2,4:3,5-di-*O*-isopropylidene-D-mannitol with diethyl carbonate in the presence of dibutyl tin oxide. The isopropylidene groups of the polycarbonates were hydrolyzed, and derivations were made on the hydroxy groups to obtain esters, orthoesters, and carbamates. The deprotected polycarbonates were water-soluble, and degraded in a few weeks by a mechanism in which hydroxy groups would participate.



73 D and L- series, and racemic

74

Galbis et al. also described the use of 2,3,4-tri-*O*-methyl-L-arabinitol (**9**) and 2,3,4-tri-*O*-methyl-xylitol (**10**) in the synthesis of polycarbonates. These pentitols were polycondensed using a commercial solution of phosgene in toluene, whereby homopolycarbonates (PsuC) and copolycarbonates with BPA, P(Su-co-BPAC) were obtained in high yields [5]. Both showed high resistance to chemical hydrolysis; however, they were enzymatically degraded to different degrees. The fastest degradation promoted by lipase B from *C. antarctica* was observed for the fully xylitol-based polycarbonate, followed by copolycarbonates also based on xylitol, which revealed a marked stereospecificity of the enzyme toward this sugar.



PSuC

L-*arabino*
Xylo

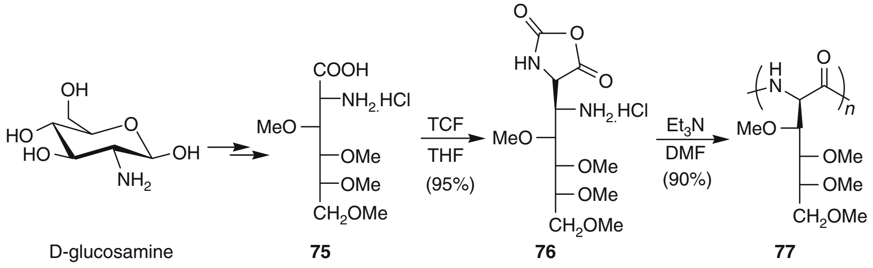
P(Su-*co*-BPAC)

4 Polyamides

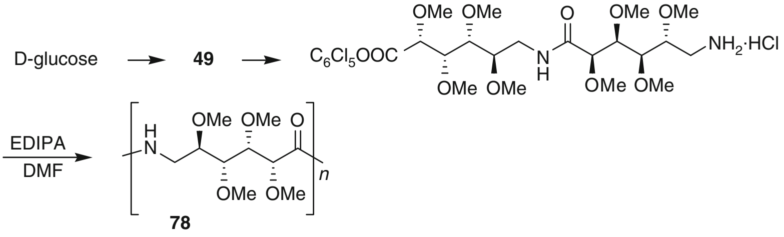
Polyamides and polyurethanes have been the carbohydrate-based polymers most widely studied. The preparation of hydrophilic nylon-type polyamides containing sugars was a great challenge, as reported in two reviews [16, 19]. In general, carbohydrate-based monomers present low thermal stability; thus, initial approaches to the synthesis of polyamides by melt polycondensation led only to brittle fibers of low molecular weights. The interfacial polycondensation technique made possible the synthesis of the first chiral nylon-type polyamide based on carbohydrates. The polymerizable sugar monomers required for the synthesis of polyamides should be diamino-sugars, aldaric acids, or aminoaldonic acids. As mentioned above, the multifunctionality of the sugars requires several protection and deprotection steps. The introduction of amino groups is generally accomplished by preparation of a sulfonyl ester, nucleophilic displacement by azide, and subsequent hydrogenation reaction. Alternative methods are also described [16].

4.1 AB-Type Polyamides

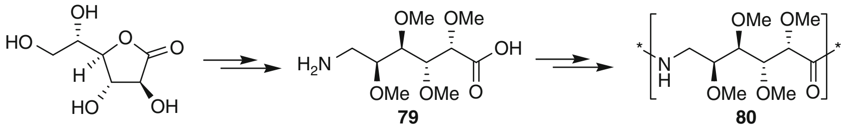
Galbis et al. synthesized two stereoregular polygluconamides starting from D-glucosamine and D-glucose [61]. The synthesis of the polyamide of the polypeptide type **77** [61, 62] was accomplished by ring-opening polymerization of the *N*-carboxyanhydride **76** obtained by treatment of 2-amino-2-deoxy-3,4,5,6-tetra-*O*-methyl-D-gluconic acid hydrochloride (**75**), obtained from D-glucosamine, with TCF in THF.



A methoxylated polyamide **78** analogous to Nylon 6 was obtained in several steps from D-glucose [61, 63] through the preparation of a dimeric active ester of 6-amino-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-gluconic acid (**49**). This polyamide was highly crystalline, and gave resistant films with a spherulitic texture.

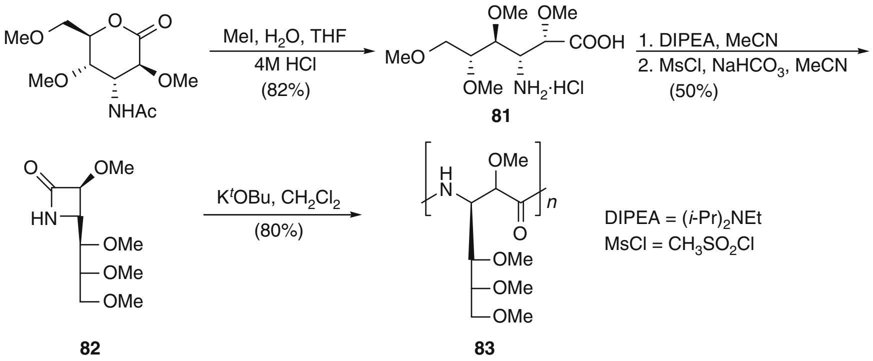


Varela et al. [64] prepared, from the D- and L-galactono-1,4-lactones, the corresponding 6-amino-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-(and L-) galactonic acids (**79**), which were polymerized by the procedure described by Galbis et al. [61] to give stereoregular sugar-based polyamides **80** analogous to Nylon 6 [65].



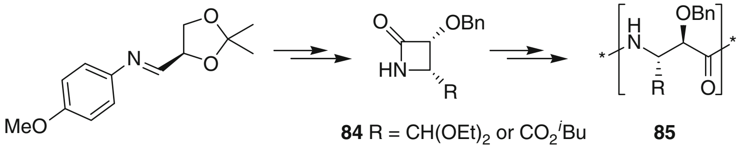
Fleet et al. have described some oligomers of *O*-protected-6-amino-6-deoxy-D-allonate [66] and D-galactonate [67], as intermediates in the preparation of polyhydroxylated Nylon 6 analogs.

A chiral β-polyamide **83** of the Nylon 3 type was also synthesized [68, 69] by Galbis et al. by ring-opening polymerization of the β-lactam derived from 3-amino-3-deoxy-2,4,5,6-tetra-*O*-methyl-D-altronic acid.



DIPEA = $(i\text{-Pr})_2$NEt
MsCl = CH_3SO_2Cl

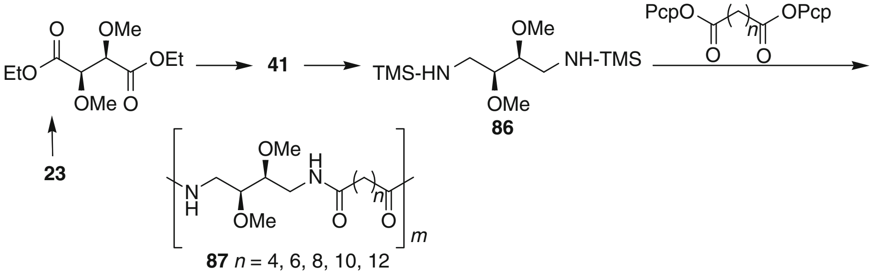
Some other chiral Nylon 3 analogs have also been prepared by the same authors applying ring-opening polymerization of chiral β-lactams **84** derived from D-glyceraldehyde [70, 71]. The enantiomerically pure (2*R*,3*R*) and the racemic (2*R*,3*R* and 2*S*,3*S*) β-polyamides were obtained, and their properties compared.



4.2 AABB-Type Polyamides

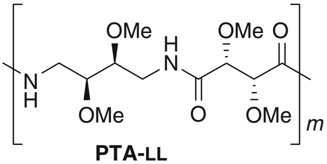
Muñoz-Guerra and Galbis et al. have initiated in the past decade a systematic study of a series of sugar-based AABB linear polyamides. These polyamides are derived from appropriately *O*-protected aldaric acids and 1,ω-diamino-dideoxyalditols. The diamino alditol monomers of L-threo, L-arabino, xylo, D-manno, and L-ido configurations (**37**–**43**) were obtained from the corresponding alditols, having the secondary hydroxyl groups protected as methyl ether.

Similarly, Muñoz-Guerra et al. [72] synthesized (2*S*,3*S*)-2,3-di-methoxy-1,4-butanediamine (**41**) from natural L-tartaric acid as raw material to prepare stereoregular polytartaramides **87** (Nylon 4,*n* analogs).

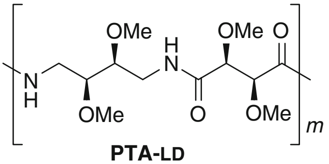


Since L-tartaric acid contains a C_2 symmetry axis, the resulting polyamides are regiochemically ordered. Polycondensation in a chloroform solution of diamine **41**, activated as the *N*,*N*′-bis(trimethylsilyl) derivative **86**, with activated pentachlorophenyl esters of aliphatic dicarboxylic acids, afforded stereoregular polyamides **87**. This method allows polycondensation under mild conditions, and the polyamides were obtained in good yields and with acceptable molecular weights. Because of their stereoregularity, these substituted polyamides present an interesting combination of properties – they are highly crystalline, have mechanical properties comparable to those of nylons, and may undergo hydrolytic degradation under physiological conditions.

Muñoz-Guerra also studied stereoregular polyamides fully based on D- and L-tartaric acid [73]. The bispentachlorophenyl esters of both 2,3-di-*O*-methyltartaric acids (**22** and **23**) were condensed with (2*S*,3*S*)-2,3-dimethoxy-1,4-butanediamine (**41**) to obtain optically active (PTA-LL) and racemic (PTA-LD) polytartaramides. Fiber-oriented and powder X-ray studies of these polyamides demonstrated that PTA-LL crystallized in an orthorhombic lattice, whereas PTA-LD seemed to adopt a triclinic structure. In both cases, the polymeric chain appears to be in a folded conformation more contracted than in the common γ form of conventional nylons.

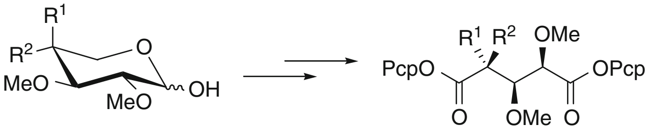


PTA-LL



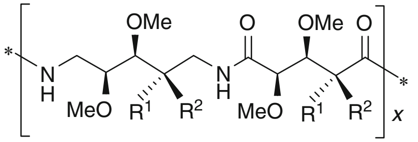
PTA-LD

Galbis et al. [31] described the preparation of the pentachlorophenyl esters of 2,3,4-tri-*O*-methyl-L-arabinaric and xylaric acids (**26** and **27**) as suitable bifunctional monomers for linear polycondensations.

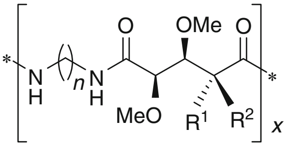


L-*arabino* R^1 = OMe, R^2 = H
D-*xylo* R^1 = H, R^2 = OMe

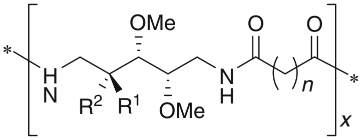
Three different types of polycondensate have been prepared: fully sugar-based polyamides (PA-ArAr and PA-XyXy), polyamides derived from pentaric acids (**26** and **27**) and aliphatic diamines (PA-*n*Ar and PA-*n*Xy, *n* = 6, 8, 12), and polyamides derived from the 1,5-diaminopentitols (**37** and **38**) and activated aliphatic dicarboxylic acids (PA-Ar*n* and PA-Xy*n*, *n* = 8, 10) [74]. In all these cases, *aregic* polymers were formed, since both sugar configurations lack the C_2 axis. Those polyamides entirely based on xylose were, as expected, not optically active. Their physical properties and crystal structures depended on their constitution and the configuration of the carbohydrate-based moiety. The feasibility of the hydrolytic processes of these polyamides was, in general, related to such structural properties [75]. Thus, the fully sugar-based (PA-ArAr and PA-XyXy) were amorphous, water-soluble materials, and were hydrolyzed in water at 70°C. PA-*n*Ar and PA-*n*Xy were crystalline and more resistant to hydrolysis – they were degraded at pH 2 and 70°C [T_g(s) 60–90°C]. PA-Ar*n* and PA-Xy*n* were amorphous and highly hygroscopic materials – they were hydrolyzed in water at 37°C [T_g(s) 25–40°C]. Similar polymers were derived from 2,3,4-tri-*O*-methyl-arabinaric acid (D) [76], the synthesis from 1,6-diamino-1,6-dideoxy-2,3,4,5-tetra-*O*-methyl-D-mannitol (**42**) and its L-iditol analog (**43**) [77–79].



PA-ArAr R^1 = OMe, R^2 = H
PA-XyXy R^1 = H, R^2 = OMe

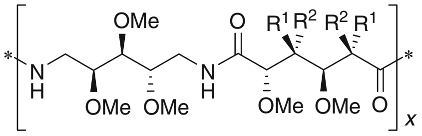


PA-*n*Ar R^1 = OMe, R^2 = H
PA-*n*Xy R^1 = H, R^2 = OMe

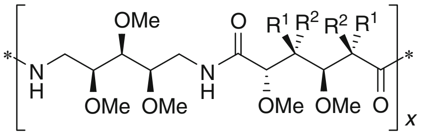


PA-Ar*n* R^1 = OMe, R^2 = H
PA-Xy*n* R^1 = H, R^2 = OMe

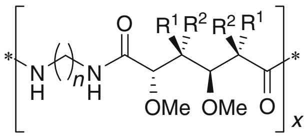
Some other water-soluble fully sugar-based polyamides have also been obtained from activated hexaric acids **28** and **29** and the 1,5-diamino-2,3,4-tri-*O*-methyl-pentitols (**37** and **38**) and a series of hydrophilic polyamides (PA-*n*Su) derived from these hexaric acids and noncarbohydrate alkylenediamines with even numbers of methylenes (*n* = 4, 6, 8, 10, 12) has also been prepared [80].



PA-ArMn R^1 = OMe, R^2 = H
PA-ArGa R^1 = H, R^2 = OMe



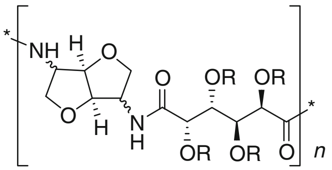
PA-XyMn R^1 = OMe, R^2 = H
PA-XyGa R^1 = H, R^2 = OMe



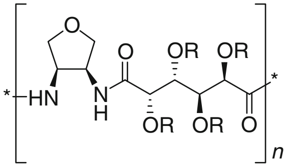
PA-*n*Mn R^1 = OMe, R^2 = H
PA-*n*Ga R^1 = H, R^2 = OMe

The thermal behavior of three series of sugar-derived polyamides (PA-*n*Su) made from the arabinaric, mannaric and galactaric acids, respectively, and α,ω-alkanediamines containing from 6 to 12 methylenes was investigated by DSC supported by polarizing optical microscopy. Crystallization from the melt under both isothermal and nonisothermal crystallization conditions were studied in detail. Melting temperatures of PA-*n*Su were found to decay steadily with the length of the polymethylene segment. Crystallization half-times indicated that "crystallizability" of PA-*n*Su increases with both the number of methylenes in the diamine unit and with the length of the carbohydrate-derived unit [81].

Hydrophilic polyamides **88** and **89** were prepared by the polycondensation reaction of 2,3,4,5-tetra-*O*-acetyl-galactaroyl dichloride with the diaminoanhydroalditols **54–57** [82].



88 D-*gluco,* D-*manno,* L-*ido* R= Ac, H

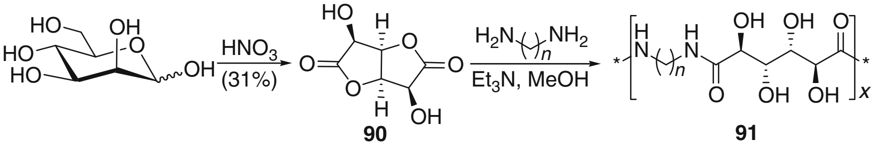


89 *Erythro*

Polyamides derived from D-glucose and D-glucosamine by interfacial and solution polycondensations of the sugar diamino derivatives with aromatic and aliphatic acyl chlorides have also been described [83].

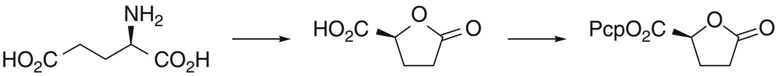
Aregic [84] and regioregular [85] polytartaramides made from di-*O*-methyl-L-tartaric acid and ethyl L-lysine have been reported by Muñoz-Guerra et al. The same authors [86] have prepared a series of polyamides from hexamethylenediamine and the pentachlorophenyl esters of 2,3-di-*O*-acyl-L-tartaric acid (**24**) by polycondensation in solution. Both *O*-alkanoyl and *O*-benzoyl esters were used as hydroxyl-protecting groups. Controlled hydrolysis of the protecting groups yielded poly(hexamethylene-L-tartaramide)s with different content of free hydroxyl groups.

Kiely et al. initiated the preparation of a novel type of stereoregular and nonstereoregular hydroxylated nylons (polyhydroxypolyamides) by direct polycondensation reaction of alkyl esters of unprotected aldaric acids (D-glucaric, galactaric, xylaric, D-mannaric) and their lactones with linear aliphatic and arylalkylenediamines [7–9, 87] and with aza- and oxa-alkylenediamines [88, 89]. They obtained high yields of solid polymers with low molecular weight, some of them being soluble in water. The mechanism of formation [90], conformational analysis [91], and adhesive properties [92] of these polyhydroxypolyamides have also been studied.



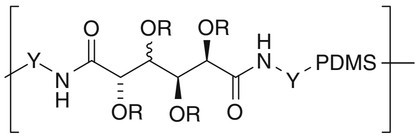
90 **91**

Varela et al. have described some stereoregular hydroxylated polymannaramides (**91**) [93] by reaction of D-mannaro-1,4:6,3-dilactone (**90**) with even-numbered alkylenediamines (n = 2, 6, 8, 10, 12). Hydroxylated stereoregular and nonstereoregular polyamides were also prepared by the same authors [94] from hexamethylene diamine and pentachlorophenyl (2*S*)-5-oxo-2-tetrahydrofurancarboxylate **93**, the latter being derived [95] from the chiral (2*S*)-2-hydroxypentanedioic acid 5,2-lactone (**92**), a compound obtained [96] by deamination of the easily available L-glutamic acid.



92 **93**

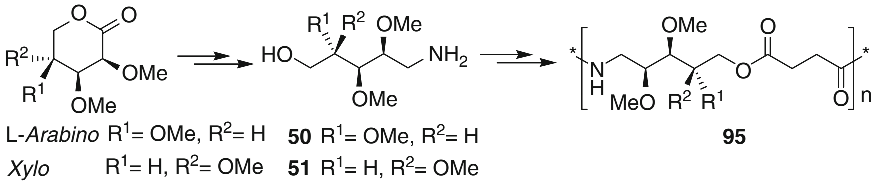
Thiem et al. have explored the synthesis and degradability of novel carbohydrate-segmented silicones polyamides **94**, obtained from activated glucaric and galactaric acid derivatives and different α,ω-diaminoalkyl polydimethylsiloxanes [97]. Galactaric acid segmented silicones display a higher T_g than their glucaric acid analogs. These materials can be partially degraded by enzymes, with the amide bond functioning as a predetermined breaking point.



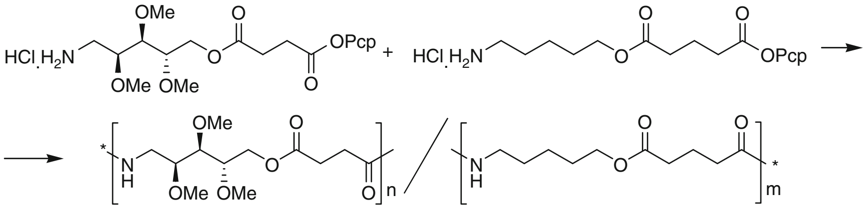
94 R = Ac or H
Y = $(CH_2)_2NH(CH_2)_3$ or $(CH_2)_3$
PDMS= $SiMe_2(SiMe_2O)_{70}$ or $SiMe_2(SiMe_2O)_{15}$

4.3 Polyesteramides

The high number of hydrogen bonds and the high crystallinity of the polyamide structure are possible reasons for the inertness of nylons to biodegradation. Their degradability may, however, be improved by inserting hydrolytically cleavable ester bonds into the chain, giving rise to poly(ester amides). The presence of hydrolytically cleavable ester bonds and the potential lowering of the crystallinity degree make the poly(ester amides) promising materials for their use in medicine. In our group, poly(ester amides) containing three methoxy groups stereoregularly attached to the main chain have been prepared by using naturally occurring L-arabinose and D-xylose as the starting materials. Thus, we have prepared 1-amino-1-deoxy-2,3,4-tri-*O*-methyl-L-arabinitol (**50**) and D-xylitol (**51**), which were transformed into a series of poly(ester amide)s **95** [98, 99]. The polymers were prepared by the active ester polycondensation method and characterized by elemental analysis, IR, and ^{1}H- and ^{13}C-NMR spectroscopies.



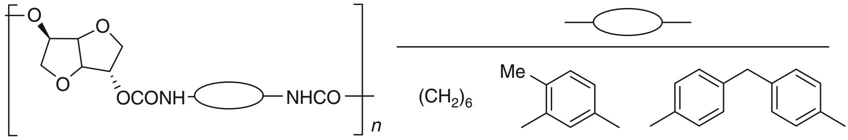
Copoly(ester amide)s (PVGAn), have also been prepared [100] by random copolymerization of 1-amino-1-deoxy-2,3,4-tri-*O*-methyl-5-*O*-[(pentachlorophenoxy) succinyl]-L-arabinitol hydrochloride and 5-amino-1-*O*-[(pentachlorophenoxy) glutaryl]pentanol hydrochloride by the active ester polycondensation method. The molar ratios of the two comonomers in the feed varied from 1/99 to 50/50. The two monomeric units are randomly distributed within the copolymers, as assessed by NMR analysis. Thermal properties depend on the copoly(ester amide) composition, since it was found that the melting and the decomposition temperatures decreased as the molar fraction of carbohydrate-based monomer unit increased, whereas the glass-transition temperature increased in parallel. Their hydrolytic degradation has been performed in phosphate buffer at 37°C and evaluated by weight loss and intrinsic viscosity. The degradation of the copoly(ester amide) was greatly enhanced with increasing amount of arabinose-succinyl monomer incorporated in the polymer chain. The presence of small amounts of this monomer was enough to produce a noticeable increase in polymer degradability. Spectroscopic investigations of the hydrolysis products provided evidence for succinimide ring formation, supporting the general mechanism proposed for the hydrolysis of poly(ester amide)s containing four carbon diacid units in their structure [101–103].



PVGAn

5 Polyurethanes and Polyureas

Polyurethanes **96** containing **1** have been prepared by several research groups, and complex polyurethanes with an elastomeric character and good mechanical properties were described in a few patents. These polymers were obtained from **1** and diisocyanates in the presence of suitable catalysts, e.g., Braun and Bergmann used triethylamine in dimethylsulfoxide [104].



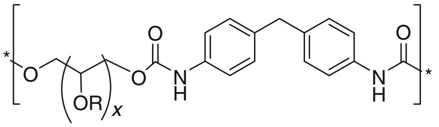
96

The 2,5-diamino-2,5-dideoxy-1:4,3:6-dianhydrohexitol dihydrochlorides with D-*gluco*, D-*manno*, and L-*ido* configurations (**54–56**) were prepared by Thiem et al. according to known procedures. They developed an initial approach to novel polyurethanes by interfacial polycondensation of these diamino monomers, as well as aliphatic diamines, with the bis(chloroformate) derived from 1,4:3,6-dianhydro-D-sorbitol [51, 105]. Catalytic polyaddition of the monomer 2-deoxy-1,4:3,6-dianhydro-2-isocyanato-L-iditol gave the corresponding AB-type polyurethane. A second route required the synthesis of the 2-azido-5-*O*-chloroformyl-1,2-dideoxy-1,4:3,6-dianhydro-L-iditol which underwent spontaneous polycondensation by catalytic hydrogenation through the 2-amino-5-*O*-chloroformyl derivative [106]. The 2,5-diamino-dianhydrohexitols **54–56** were also transformed into the corresponding diisocyanates by reaction with phosgene [107]. The dithiodiisocyanato derivative was prepared from the diamino-dianhydro-L-ido-hexitol and thiophosgene. Polyurethanes and polyureas were synthesized from the three monomers (**54–56**), and poly(thio)urethanes and poly(thio)ureas from the corresponding L-*ido* monomer (**56**) [107]. Several modified D-glycosylamine and D-glucosamine monomers were also synthesized by Thiem et al. to carry out catalytic polymerizations leading to polymers with urea and urethane linkages [108].

For polyurethane production, Donnelly [109] has carried out the synthesis of copolyurethanes based on mixtures of commercial poly(THF diol)s with glucose. Complex products resulted, which can be represented by mono- or bis(glucoside) structures. From a variety of polyol blends, solid polyurethanes were prepared which ranged from linear, soluble, weak elastomers to polymers of higher transition temperature and stiffness, low solubility, and low extension under tensile load [110].

Garcon et al. [111] have reported the synthesis of two new polyurethanes accomplished by reaction of 1,6-hexamethylene diisocyanate (HDI) with methyl 2,6-di-*O*-pivaloyl-α-D-glucopyranoside or methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, catalyzed by 1,4-diazabicyclo[2.2.2]octane.

Galbis and Muñoz-Guerra et al. used the secondary *O*-protected L-threitol, L-arabinitol and xylitol (**5–12**) as monomers for the preparation of a series of linear [*m*,*n*]-type polyurethanes **97** and **98** by polycondensation in solution with 1,6-hexamethylene diisocyanate (HDI) and 4,4′-methylene-bis(phenyl diisocyanate) (MDI) [112–115]. The polyurethanes derived from the *O*-methyl protected **5**, **9**, and **10** were amorphous with T_g being highly dependent on the aliphatic or aromatic nature of the diisocyanate used, but scarcely depending on the chemical structure of the alditol moiety. It was concluded that the alditol size, that is the number of methoxy side groups present in the repeating unit, seems to be of prime importance in determining the hydrodegradability of these polyurethanes [112].



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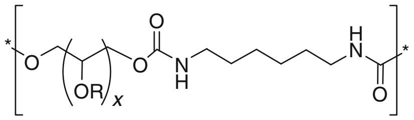


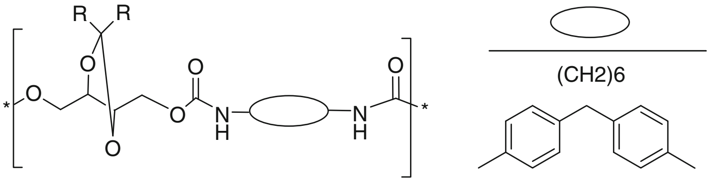
98

R= Me, Bn

x= 2, 3 (L-*Threo*, L-*Arabino*, *Xylo*)

The polyurethanes based on the *O*-benzyl protected **6**, **11**, and **12** yielded partially debenzylated products with T_g values ranging between 20 and 30°C. Fully benzylated polyurethanes showed high resistance to hydrolytic degradation, whereas polyurethanes with free hydroxyl side groups degraded significantly in saline buffer at pH 10 and 37°C [113, 114].

Polyurethanes **99** derived from 2,3-*O*-methylene-L-threitol (**7**) or 2,3-*O*-isopopylidene-D-threitol (**8**) were amorphous and they displayed T_g higher than their unsubstituted analogs. The corresponding *O*-deprotected polyurethanes were semicrystalline materials. The highest degradation rates of such polyurethanes were obtained upon incubation at pH 10 at temperatures above T_g, the aliphatic hydroxylated polyurethanes being the fastest degrading compounds [115].

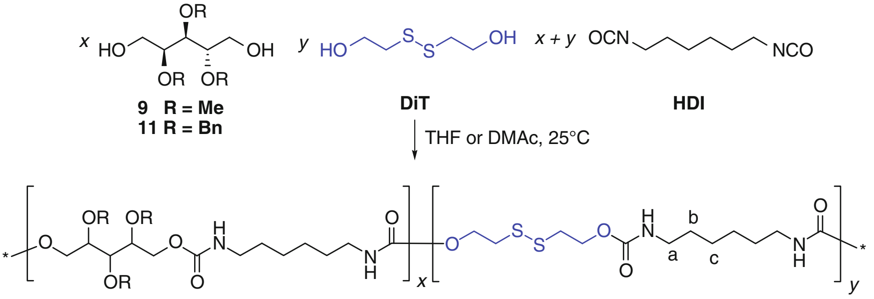


99 R= H (L-*Threo*)
R= Me (D-*Threo*)

Segmented poly(ester-urethane)s have been prepared from HDI, or MDI, and using 1,4-butanediol, isosorbide or 2,4:3,5-di-*O*-methylidene-D-glucitol (**15**) or mixtures of them as extenders. Hydroxyl end-capped polycaprolactone (Mw 3,000 g mol^{-1}) was used as soft segmented. Hydrodegradability increased with the presence of glucitol derived units, although degradation of the polymers took place essentially by hydrolysis of the polyester soft segment [116].

Linear [*n*]-polyurethane derived from 1-deoxy-1-isocyanate-2,3:4,5-di-*O*-isopropylidene-D-galactitol (prepared from **48**) in the presence of TEA or $Zr(acac)_4$, as well as its corresponding polyhydroxy derivative obtained by hydrolysis of the acetal protecting group, have been prepared [117]. They are semicrystalline materials that exhibit high melting temperatures and thermal stability up to 230°C.

Copolyurethanes based on L-arabinitol and 2,2′-dithiodiethanol have been obtained by polyaddition reaction of mixtures of 2,2′-dithiodiethanol (DiT) and 2,3,4-tri-*O*-methyl-L-arabinitol (**9**) or 2,3,4-tri-O-benzyl-L-arabinitol (**11**) to 1,6 hexamethylene diisocyanate (HDI) [118].

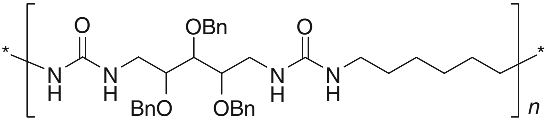


R = Bn: PU[(ArBnx-DiTy)-HDI]
R = Me: PU[(ArMex-DiTy)-HDI]
R = H: PU[(ArOHx-DiTy)-HDI]

x:y Diol Ratios, 80:20 or 50:50

The copolymer compositions were studied by elemental microanalyses and ^{1}H-NMR, revealing that the content of the copolymer units is in all cases very similar to that of their corresponding feed. The PU(DiT-HDI) homopolymer exhibited a high crystallinity, but the introduction of the arabinitol-based diols led to a reduction in the crystallinity of the copolymers. In their TGA curves, the copolymers exhibited a mixed trend of the related homopolymers, and all of them were thermally stable, with degradation temperatures above 220°C. The degradation properties of the macromolecules under physiological conditions in the presence of glutathione were tested. All the copolyurethanes proved to be biodegradable under the experimental conditions (pH 7.02 and 37°C).

Galbis and co-workers [113] also obtained a polyurea **100** by polyaddition reaction of the diaminopentitol **39** with 1,6 hexamethylene diisocyanate (HDI). This polymer was a semicrystalline material that showed high melting temperature and thermal stability up to 250°C.

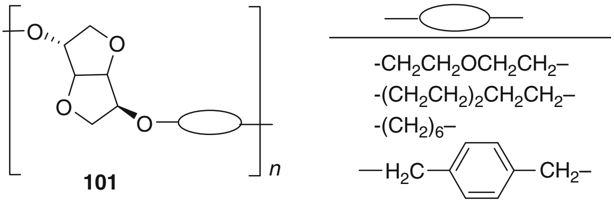


100 L-*arabino*

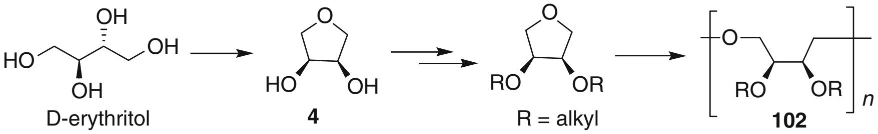
6 Other Sugar-Based Polymers

Kricheldorf [17] studied liquid-crystalline cholesteric copoly(ester-imide)s based on **1** or **2**. The comonomers to obtain these chiral thermotropic polymers were *N*-(4-carboxyphenyl)trimellitimide, 4-aminobenzoic trimellitimide, 4-aminocinnamic acid trimellitimide, adipic acid, 1,6-hexanediol, and 1,6-bis(4-carboxyphenoxyl) hexane. Apparently the poly(ester imide) chains are so stiff that the twisting power of the sugar diol has little effect.

Polyethers **101** derived from **1** were mentioned in a patent describing the synthesis and properties of epoxy resins, and linear polyethers were prepared from free **1**, which was reacted with α,ω-bischloroalkanes or 1,6-dibromohexane [17].



A series of polyphosphites, polyphosphates, polythiophosphates, and other polymers containing sulfone functions, based on **1**, have also been described [17, 119]. An efficient synthesis of polyethers from **1** and 1,8-dibromo or dimesyl octane by microwave-assisted phase transfer catalysis has been reported [120].



Poly(oxytetramethylene) is extensively used as a softening segment for polyurethane production. Thiem et al. studied, as an alternative, the ring-opening polymerization of 2,3-di-*O*-alkyl derivatives of 1,4-anhydro-D-erythritol (**4**) [21–23] using super-acids $HFSO_3$ and CF_3SO_3H, which led to novel functionalized poly(2,3-dialkoxytetramethylene)s **102**.

7 Conclusions and Perspectives

As fossil fuel resources dwindle, there is growing interest in developing new raw materials for future polymers [121]. As A. Gandini has stated "polymers from renewable resources are indeed the macromolecular materials of the future" [122]. Between the different renewable resources, carbohydrates stand out as highly convenient raw materials because they are inexpensive, readily available, and provide great stereochemical diversity.

From the results presented in this chapter we can conclude that it is feasible to prepare sugar-based polymers analogous to the more qualified technological polymers – polyamides, polyesters, polyurethanes – with an enhanced hydrophilicity and degradability. However, in most cases, the high costs associated with the preparation of the monomers restrict the application of these polymers to biomedical applications and other specialized fields. More readily available monomers and simpler polymerization processes have to be found if sugar-derived polymers should compete with petrochemical-based polymers that are used in domestic applications.

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Synthesis and Applications of Ionic Liquids Derived from Natural Sugars

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Abstract Aiming to develop environmentally compatible chemical syntheses, the replacement of traditional organic solvents with ionic liquids (ILs) has attracted considerable attention. ILs are special molten salts with melting points below 100°C that are typically constituted of organic cations (imidazolium, pyridinium, sulfonium, phosphonium, etc.) and inorganic anions. Due to their ionic nature, they are endowed with high chemical and thermal stability, good solvent properties, and non-measurable vapor pressure. Although the recovery of unaltered ILs and recycling partly compensate their rather high cost, it is important to develop new synthetic approaches to less expensive and environmentally sustainable ILs based on renewable raw materials. In fact, most of these alternative solvents are still prepared starting from fossil feedstocks. Until now, only a limited number of ILs have been prepared from renewable sources. Surprisingly, the most available and inexpensive raw material, i.e., carbohydrates, has been hardly exploited in the synthesis of ILs. In 2003 imidazolium-based ILs were prepared from D-fructose and used as solvents in Mizoroki–Heck and Diels–Alder reactions. Later on, the first chiral ILs derived from sugars were prepared from methyl D-glucopyranoside. In the same year, a family of new chiral ILs, obtained from commercial isosorbide (dianhydro-D-glucitol), was described. A closely related approach was followed by other researchers to synthesize mono- and bis-ammonium ILs from isomannide (dianhydro-D-mannitol). Finally, a few ILs bearing a pentofuranose unit as

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the chiral moiety were prepared using sugar phosphates as glycosyl donors and 1-methylimidazole as the acceptor.

Keywords Asymmetric synthesis, Chiral ionic liquids, Ion pairing, Local structure, Nuclear Overhauser effect, Task-specific ionic liquids

Contents

1 Introduction

One of the biggest problems posed to the chemical industry is to deal continuously with the fact that many chemical plants rely heavily on toxic, hazardous and flammable organic solvents. To evaluate the problem quantitatively it must be stated that world-wide chemical manufacturing industries spend annually over five billion dollars for the use of volatile organic solvents and over ten billions for controlling the pollution in the production and cleanup cycle [1]. However, the Montreal Protocol has resulted in a compelling need to re-evaluate many chemical processes that have otherwise proved satisfactory for much of the twentieth century. The design of environmentally benign solvents and solventless systems has therefore been one of the most active areas of green chemistry over the past 10 years. It is recognized that employing the use of “green solvents” as alternatives to the use of the environmentally unfriendly traditional solvents can drastically reduce waste solvent production and hence reduce environmental impact.

2 Structure and Properties of Ionic Liquids

Ionic liquids (ILs) are, together with water and supercritical fluids, one of the few alternative media for environmentally friendly processes, which seem to have more possibility of industrial application in the next 10 years. The range of demonstrated or proposed applications of ILs is extraordinary, going from their use as non-volatile, non-flammable solvents in organic synthesis to catalysts, materials for aiding separations and gas capture, advanced heat transfer fluids, lubricants, anti-statics, and so on [2–4]. Surpassing in magnitude the number of potential uses is the number of possible IL compositions, estimated to be in the billions [5]. The term “ionic liquids” includes all compounds composed exclusively by ions that are liquid at/or near room temperature, by definition below 100°C. The ionic nature induces in these compounds unique physico-chemical properties that make them suitable materials for industrially relevant processes [6]. ILs are generally characterized by the following properties: (l) they have no effective vapor pressure avoiding diffusion in atmosphere; (2) they have a wide liquid range (often more than 300°C), that allows tremendous kinetic control; (3) they are outstandingly good solvents for a wide range of inorganic, organic and polymeric materials, implying small reactor volumes; (4) they may have Brønsted, Lewis, and Franklin acidity, as well as Brønsted and Lewis basicity; (5) they range from hydrophobic to hydrophilic, from water-sensitive to air-stable; (6) they may be thermally stable up to 300°C; (7) they are relatively easy to prepare [7]. Moreover, other potential benefits of ionic liquids include: (8) they can be recycled. Excellent recovery and recycling of the catalyst is also possible using ionic liquids as reaction media. Solvent and catalysts recycle helps to keep waste production to a minimum. In addition: (9) existing equipment can be used with ionic liquids, helping to keep initial costs low. Last but not least: (10) their physical and chemical properties can be modified and finely modulated by structural modifications on anion and cation. Practically, it is always possible to design and synthesize the best ionic liquid for each application. However, some features of ILs require improvement. Ionic liquids are as yet relatively expensive. Furthermore, the recycling of ILs, which may help to justify the expenditure, generally reduces the purity of these compounds, reducing the applicability at least in some processes [8]. Finally, more research is necessary to establish the correlation between ionic liquids structure and toxicity. Recent data have shown that the ionic nature does not necessarily infer an absolute non-toxic or low toxic character. Several ionic compounds showed significant toxicity towards aquatic species [9–11]. However, it must be considered that the term IL defines an extremely large class of salts and the positive and negative properties characterizing a family of ILs cannot be extended to all low-melting salts. Often, problems and doubts arise from the unjustified attribution to all ionic liquids of properties observed for selected classes of ILs.

Structurally, the ILs that have been investigated to date are generally based on ammonium, sulfonium, phosphonium, imidazolium, pyridinium, picolinium, and pyrrolidinium cations, with the *N*,*N*-dialkylimidazolium salts representing the most studied and applied class of ionic compounds (Fig. 1). Inorganic and organic anions have been used to obtain low melting salts and historically ILs are classified into four groups based on anion nature: (1) systems based on $AlCl_3$ and organic salts, like 1-butyl-3-methylimidazolium chloride, [bmim][Cl]; (2) systems based on anions like PF_6^-, BF_4^-; (3) systems based on anions like $CF_3SO_3^-$, $(CF_3SO_2)_2N^-$ ($[NTf_2]$); (4) systems based on anions like alkylsulfates and alkylsulfonates (Fig. 1). However, many other anions have been used more recently to obtain suitable ILs; dicyanamide, lactate, saccharinates, boronates, and so on [12].

In addition, ILs bearing one or more functional groups on the cation or anion able to impart specific properties have also been synthesized and applied as designer media in catalysis and material sciences [13]. These salts, which are generally defined task-specific ionic liquids (TS-ILs), may show an increased

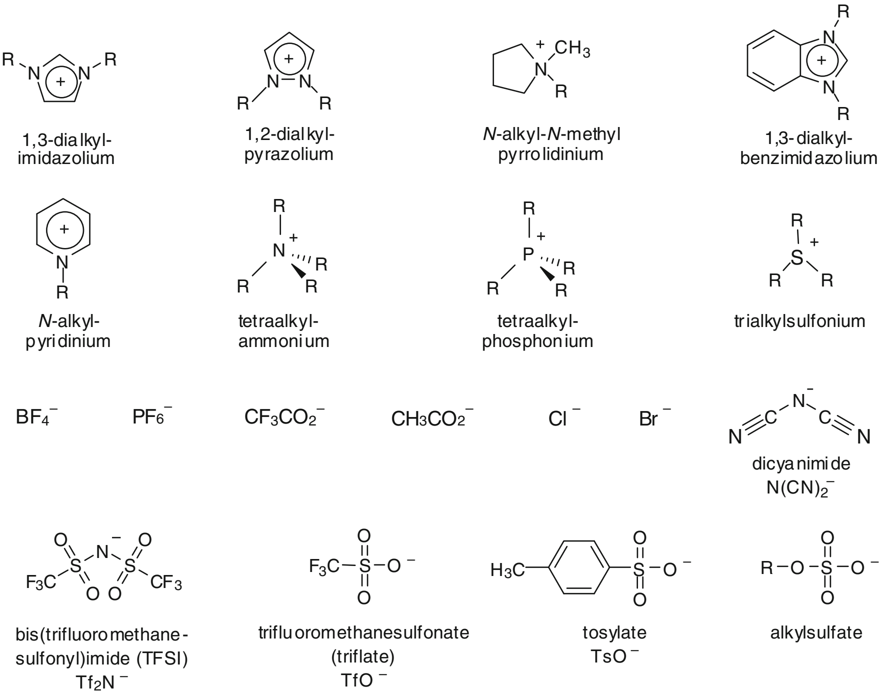


Fig. 1 Structures of cations and anions found in the most common ionic liquids

hydrogen bond ability, increased basicity or acidity, and the ability to bind metals or simple molecules. It is noteworthy that, although the solvent properties of many ILs are similar to those characterizing many molecular solvents [14], the combination of these properties is normally completely different from molecular solvents. In fact, some ionic liquids can dissolve, at least partially, species that are insoluble in common organic solvents, such as polysaccharides, polymers, or enzymes [15]. Enzymes often find here a more suitable environment than in molecular solvents [16] and show in ILs higher activity and stability. Design of new ILs, having selected physico-chemical properties, has become in the last few years one of the most active research areas [17, 18]. However, many other ILs can be designed and synthesized to improve not only solvent properties but also sustainability and biocompatibility.

3 Characterization of Ionic Liquids

ILs functionalization contributes to the development of new reaction media (TS-ILs) with improved properties with respect to molecular solvents and conventional ILs. Unfortunately, although in the last few years several experimental and theoretical studies have been performed to describe their liquid structure and their effect on various organic and inorganic solutes [19–23], generally these works are related to very common ionic liquids, mainly imidazolium-based ILs having as counteranion a chloride, tetrafluoroborate, hexafluorophosphate, or bis-(trifluoromethanesulfonyl)imide ion. Functionalization has been tested but the effect has been rarely quantitatively measured or calculated. The increase of the application fields and the rapid evolution of the ionic liquids favor the not always congruent development of this science; functionalized ILs are continuously developed but physical data are still collected on very simple, well-known ILs. In contrast, the most recent applications of ILs in emerging areas of chemistry and technology, e.g., catalysis and biocatalysis, underlined the need for a thorough understanding of the structure at molecular level of new, variously functionalized ionic liquids. The concept of "local structure" as a synonym of nanostructural organization was first introduced by Canongia Lopes and Pádua [24]. It is nowadays widely used in the field of IL chemistry, and indicates the fact that ILs show short-range aggregation motives resembling, in some cases, those found in the solid state by X-ray crystallography. The resultant mesoscopic ordering is one of the most peculiar and fascinating features of ILs, which is being investigated by a wide variety of physicochemical methods, ranging from highly sophisticated X-ray and neutron scattering methods [25] to more accessible but not less elegant NMR techniques [26]. In particular, NMR measurements on bulk ILs open the possibility to examine, at molecular level, the interactions among the components and related aggregation motives, if any. State-of-the-art studies by NMR relies upon the measurement of intermolecular nuclear Overhauser effect, either in the laboratory (NOE) or in the rotating frame (ROE). As NOE/ROE is based on the mutual relaxation of nuclei close in space (cross relaxation) mediated by dipolar interactions, it contains information on the spacial proximity of atoms within a molecule or among different molecules in an assembly [27]. In principle, all the repertoire of interaction within a given IL can be worked out: cation-cation, cation-anion, anion-anion. Moreover, if suitable amounts of a third component (solute) are added to bulk liquid, solute-cation and solute-anion contacts, if detectable, may provide unique information on the mechanism of solvation [28]. In the commonly encountered case of ILs containing perfluorinated anions (BF_4^-, PF_6^-, $(CF_3SO_2)_2N^-$, etc.) the presence of different NMR active nuclides on the components, e.g., ^1H on cation and ^{19}F on the anion, renders the separation of the intermolecular aggregations easier by the use of homo- and heteronuclear correlation experiments. Indeed, ^1H–^1H NOESY spots on the cation-cation interactions, ^{19}F–^{19}F NOESY provides information on the anion-anion contacts and heteronuclear ^1H–^{19}F NOE correlations (HOESY) allow for the assessment of cation-anion interactions [29]. Based on the same simple principle of separating the contribution of cation and anion interactions by observing different nuclei, the combined use of ^1H–^{19}F HOESY and pulsed field gradient spin-echo NMR spectroscopy (PGSE-NMR) [30] allowed for the direct observation of tight anion-cation association (ion pairing) in ILs containing perfluorinated anions [31]. PGSE-NMR is a powerful method for the measurement of the self-diffusion coefficients [32]. The applications of such an approach to the study of aggregation phenomena and nanostructuration of pure ILs and their solutions are continuously growing [33–35].

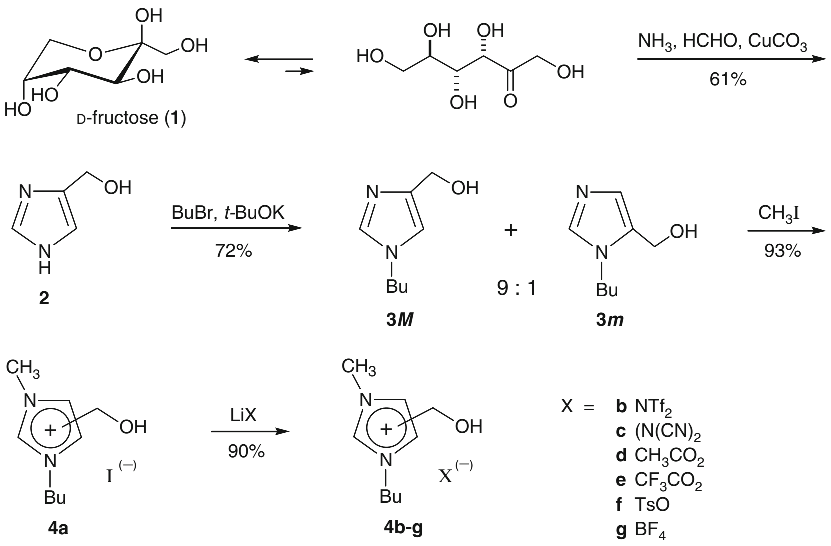
The first example of NMR studies based on intermolecular NOE reported on cation-cation ordering in pure ethyl-methyl-imidazolium chloride. It demonstrated the existence of local structure in bulk IL by observing dipolar contacts between neighboring cations [36]. The NOE approach has been extended to the study of the interaction of water with butyl-methyl-imidazolium tetrafluoroborate. By careful quantitation of intermolecular NOEs between selected protons as a function of the stoichiometric amounts of water added to the system, the type, number, and intensity of the intermolecular contacts were worked out. The data gave one of the first detailed picture of the aggregation motives and specific solute-solvent sites of interaction in archetypal system [37]. The quantitative interpretation of intermolecular NOE data and molecular dynamics simulations also gave a picture of the aggregation motives of imidazolium units [38]. Recent investigations based on intermolecular NOE dealt with larger systems, including micellar aggregates formed in ILs [39, 40]. Examples of the synergistic use of NOE and diffusion measurements [41, 42], as well as NOE and molecular dynamics simulation [43, 44], also provided significant structural achievements.

Concerning the theoretical calculations, it is noteworthy that, in order to obtain a realistic representation of solutes in ionic liquids, it is mandatory to involve a reliable description of the solvation environment [45]. This goal has been achieved using a QM/MM approach, with solute or reagents (described at QM level) inserted in a field of charges obtained through MD or Monte Carlo simulations [46]. Chiappe and coworkers have recently shown [47] the possibility to perform accurate ab initio calculations on species solvated in ILs, describing the solvent with a charge distribution using the KH closure to the integral equation, with a moderate amount of computing time.

Last but not least, for a comprehensive characterization of new ionic liquids an important aspect has to be considered, i.e., the toxicity as well as any other ecological factor concerning the ILs. Related to the problem of the lack of toxicity information, research in this field is growing up rapidly. Although some toxicological works have evidenced that the ionic nature not necessary gives to these compounds the feature of “absolutely non-toxic materials”, the data show that it is possible to design ILs having a low environmental impact [9–11, 48–54].

4 Synthesis of Ionic Liquids from Carbohydrates

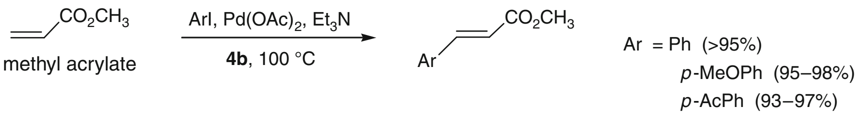
Until now, only a limited number of ionic liquids have been prepared from renewable sources. For instance, some anions were synthesized from naturally occurring hydroxy acids (lactic [55] and malic [56] acids) or proteinogenic amino acids [57], whereas cations were obtained from amino alcohols (choline [58] and ephedrine [59, 60]), hydroxy acids (lactic and tartaric acid [61]), amino acids [57], and terpenes [62–64].



Scheme 1 Synthesis of imidazolium-based ionic liquids from D-fructose

In 2003 Handy and coworkers [65] described the first synthesis of ionic liquids from naturally occurring sugars. They exploited the transformation of D-fructose (**1**) into monosubstituted imidazoles developed more than 50 years ago by Trotter and Darby [66], to prepare **2** in 61% yield (Scheme 1).

The authors made some modifications to the original procedure, such as the replacement of H_2S by thioacetamide to remove the copper salts as CuS and the use of column chromatography purification instead of the precipitation as perchlorate salt for the isolation of the hydroxymethylimidazole **2**. By this method, Handy and coworkers were able to convert 18.0 g of D-fructose into 5.6 g of the target heterocycle **2**. The latter compound was alkylated with butyl bromide in the presence of potassium *tert*-butoxide to give an inseparable 9:1 mixture of **3*M*** and **3*m***, which were methylated and then submitted to anion metathesis. Seven ILs (**4a**–**g**) were thus prepared and their physical properties were investigated. In particular, the authors found that the least viscous ILs of the collection, i.e., the triflimide (**4b**) and dicyanimide anion bearing ILs (**4c**), showed opposite solubility behaviors. In fact, **4b** was immiscible in water and well soluble in common organic solvents (CH_2Cl_2, AcOEt, CH_3CN, Et_2O), while **4c** was fully soluble in water and other polar solvents such as methanol, acetonitrile, acetone, and immiscible in Et_2O, toluene, and hexane. Then, the ionic liquid **4b** was employed as solvent for model Mizoroki–Heck reactions of methyl acrylate with simple aryl iodides in the presence of palladium acetate (Scheme 2). The coupling products were isolated in almost quantitative yields simply by extracting the crude mixtures with cyclohexane. Moreover, the solvent and catalyst were recycled 4–5 times without affecting the efficiency of the reaction. Finally, the kinetics of the reaction of methyl acrylate

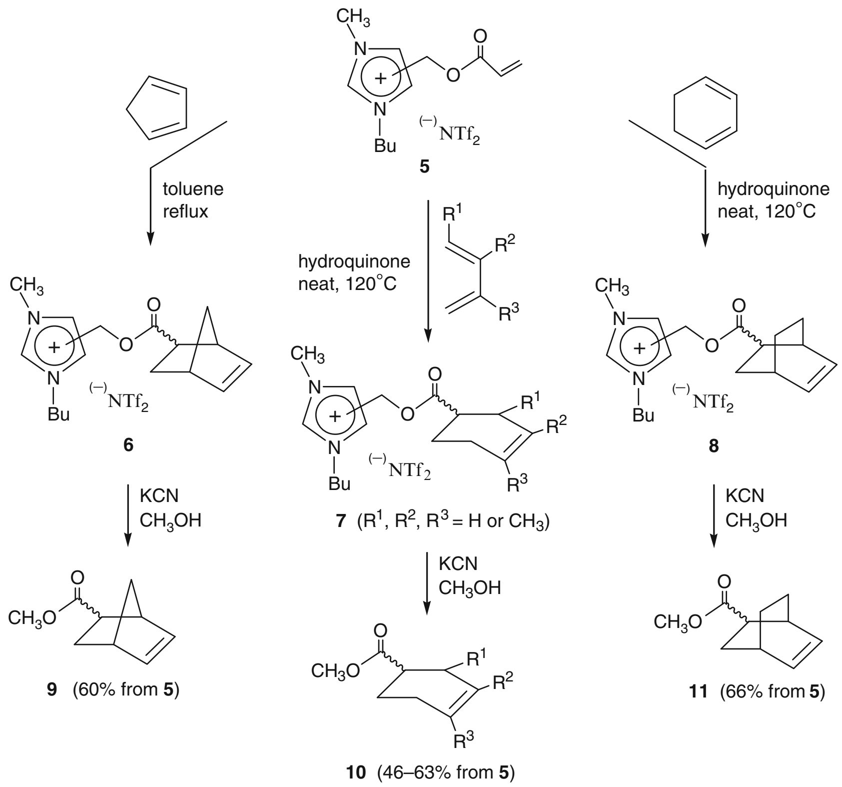


Scheme 2 Mizoroki–Heck reactions performed in the ionic liquid **4b**

with iodobenzene in **4b** and 1-butyl-3-methylimidazolium bistriflimide [bmim][NTf$_2$] and tetrafluoroborate [bmim][BF$_4$] were compared. The Mizoroki–Heck reaction carried out in **4b** was somewhat slower than those performed in the standard, non-protic [bmim] series of ionic liquids.

The same year, Handy and Okello [67] reported on another application of their fructose-derived ionic liquid **4b**. In fact, they exploited the hydroxymethyl group of **4b** to prepare a series of supported Diels–Alder adducts. The supported synthesis is a well-known methodology particularly useful for the preparation of libraries of biologically active compounds. Usually, the support is made of cross-linked polystyrene and is easily separated from the reaction medium by filtration. On the other hand, this kind of support can limit the reaction conditions and features a rather low loading (less than 2 mmol/g). Moreover, the recently developed polyethyleneglycol (PEG)-based supports, whose solubility can be modulated by an appropriate choice of solvent, display an even lower loading than that of the above-mentioned polystyrene supports (less than 1 mmol/g). In contrast, taking into account the low molecular weight of **4b**, it was anticipated that this ionic liquid would allow high loadings (>2 mmol/g). The latter behavior, together with the interesting solubility properties of **4b** (i.e., miscibility with H_2O and CH_3OH, immiscibility with apolar solvents), were the main reasons for its use as new soluble support. With this aim, the acrylate **5** (Scheme 3) was prepared in almost quantitative yield by reaction of **4b** with acryloyl chloride at −20°C in the presence of triethylamine. Optimized acylation conditions were required in order to avoid the formation of polymeric material derived by the deprotonation at the position 2 of the imidazolium moiety. Then, the ester **5** was submitted to standard thermal cycloaddition with cyclopentadiene, cyclohexadiene, and butadiene derivatives to afford the corresponding Diels–Alder adducts **6–8** in good yields (Scheme 3).

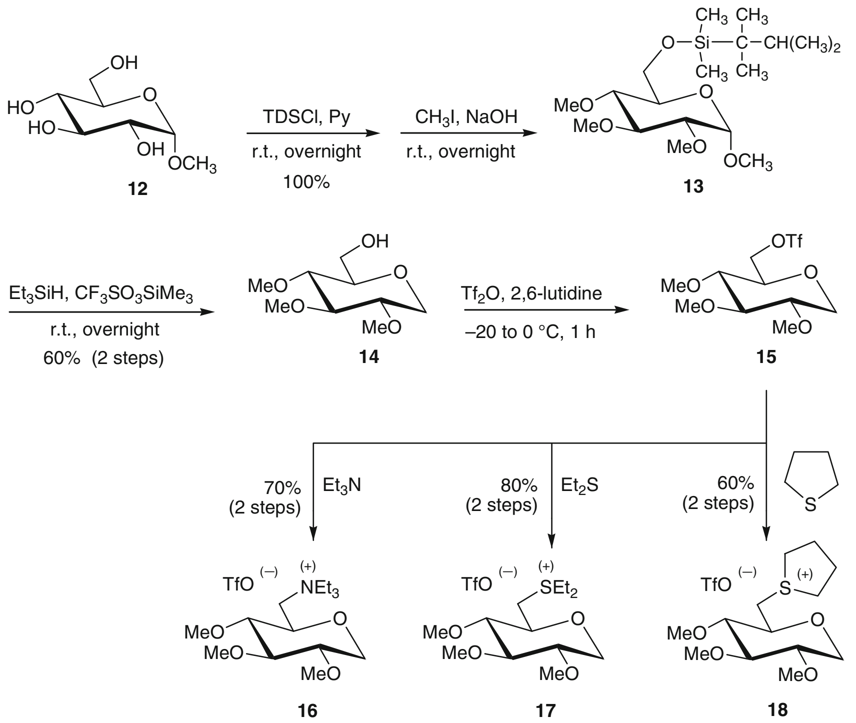
These supported cycloadducts were then treated with a base (LiOH, NaOH) in a mixture of water and alcohol to give the expected free acid derivatives. However, while the latter compounds were readily recovered, the same was not true for the ionic liquid **4b**, which was obtained as a dark brown liquid impure by NMR analysis. Very likely, the basic hydrolysis of the ester function caused the deprotonation of the imidazolium ring leading to a series of undesired side-reactions. Therefore, milder reaction conditions were explored to cleave the Diels–Alder product from the ionic liquid support. Handy and Okello found that the best method was the cyanide-mediated transesterification that gave the corresponding methyl esters **9–11** and allowed recover of **4b** in at least 90% yield. It was also demonstrated that the recovered **4b** could be used for further supported syntheses. In fact, in two subsequent runs the yields of the final ester compound were similar, indicating that the ionic liquid **4b** could be efficiently recycled.



Scheme 3 Synthesis of Diels–Alder cycloadducts using an ionic liquid as homogeneous support

In the synthetic approach described above [65], the chirality of the starting monosaccharide was not retained in the target ionic liquids and the latter products were isolated as mixtures of achiral regioisomers. The first chiral ILs derived from sugars were described by Poletti and coworkers [68]. They envisaged the preparation of such ionic liquids because these compounds can act as solvents for asymmetric syntheses, as chiral phases for gas chromatography, and as NMR shift reagents for the determination of the enantiomeric composition of pharmaceutically active products. Moreover, the use of carbohydrates as starting material leads to suitably protected polyoxygenated ionic liquids endowed with high coordination ability, particularly useful for the metal-catalyzed reactions.

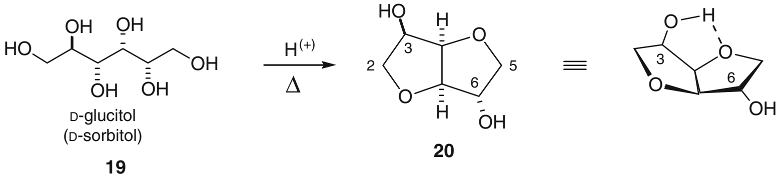
The key intermediate **14**, a stable tetrasubstituted tetrahydropyran derivative, was obtained from commercially available methyl D-glucopyranoside **12** via a three-step reaction sequence (Scheme 4). First the primary hydroxyl group was protected as thexyldimethylsilyl (TDS) ether, then the other OH groups were methylated under standard conditions to give **13**. The latter glycoside was deoxygenated at the anomeric position by treatment at room temperature with a Lewis acid (trimethylsilyl triflate) and a hydride donor (triethylsilane). This treatment also



Scheme 4 Synthesis of chiral ionic liquids from methyl α-D-glucopyranoside

cleaved the silyl ether protecting group affording the alcohol **14** in 60% overall yield. The latter compound was converted into the triflate **15**, which was submitted to the subsequent nucleophilic substitutions without intermediate purification. The reaction of **15** with triethylamine was carried out at −20°C in THF to give the tetraalkylammonium salt **16** in 70% yield, whereas the substitution of the triflate by diethylsulfide and tetrahydrothiophene required higher temperatures (60 and 40°C, respectively) to afford the corresponding salts **17** (80%) and **18** (60%).

Although these compounds are all well soluble in H_2O and scarcely soluble in Et_2O and CH_2Cl_2, their physico-chemical properties are quite different. First of all, **16** and **18** are solids at room temperature (mp 137.5 and 110°C, respectively) while **17** is a liquid that showed a glass-transition temperature of −53°C (DSC analysis). However, no solid-solid transition could be detected for the above-mentioned salts. Thermogravimetric analysis demonstrated that **16**, **17**, and **18** did not decompose at temperatures higher than 200°C, the most thermally stable being the tetraalkylammonium salt **16** that featured a decomposition temperature of 300°C. Finally, the three chiral ionic liquids were carefully analyzed by ESI mass spectrometry to assess their ion-pairing behaviors. This investigation revealed that **16** and **17** have a higher ion-pairing than that displayed by **18**, but much lower than that observed for a model imidazolium-based ionic liquid bearing the same anionic counterpart (i.e.,



Scheme 5 Synthesis and conformation of isosorbide

a triflate ion). Therefore, the cationic moiety of **16** and **17** should interact efficiently with all kind of dissolved catalyst.

In the same year, a family of new chiral ionic liquids was obtained by Nguyen Van Buu and Vo-Thanh [69] starting from commercially available isosorbide (1,4:3,6-dianhydro-D-glucitol, **20**) (Scheme 5). Isosorbide, a bicyclic compound obtained on large scale by dehydration of D-sorbitol (D-glucitol, **19**), is used as chiral auxiliary and chiral ligand in, amongst others, the Diels–Alder reaction [70] and asymmetric hydrogenation [71]. Isosorbide features two cis-fused tetrahydrofuran rings and shows a wedge-shaped tridimensional arrangement, which allows the intramolecular hydrogen bonding between the endo OH group at C-3 and the oxygen atom located into the neighboring ring.

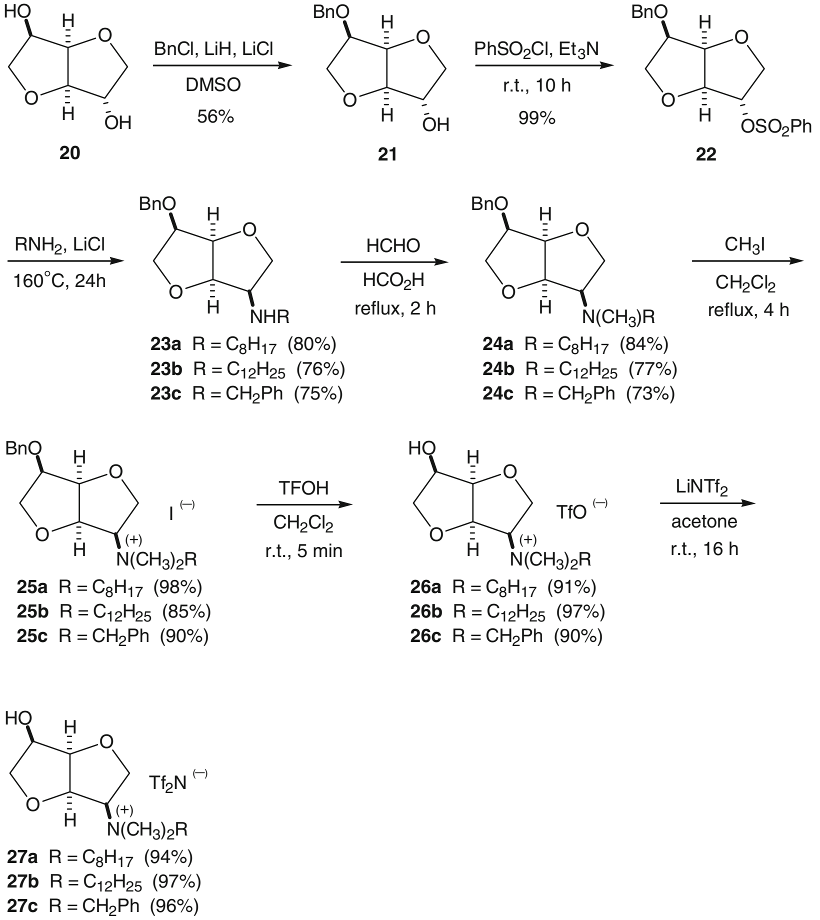
The first step of the synthesis of the new ionic liquids **26** involved the selective protection of the OH-3 to give the monobenzyl ether **21** in 56% yield (Scheme 6). Then the exo OH group at position 6 was quantitatively activated as benzenesulfonate and treated with an excess of three primary amines in a sealed tube at 160°C to afford the corresponding secondary amino derivatives **23a–c** in good yield. The latter compounds were transformed into the tertiary amines **24a–c** by reaction with formaldehyde in formic acid (Eschweiler–Clark reaction).

The quaternization of the nitrogen atom (CH_3I in refluxing CH_2Cl_2), followed by cleavage of the benzyl ether under strong acidic conditions (triflic acid, 20°C, 5 min), led to the ionic liquids **26a–c**. It should be noted that the treatment of **25a–c** with TfOH also caused the iodide to triflate anion exchange. Moreover, the bistriflimide derivatives **27a–c** were efficiently obtained by reaction of **26a–c** with $LiNTf_2$. All the salts shown in Scheme 6 were viscous liquids with the exception of **26a** that was a solid (mp 125°C).

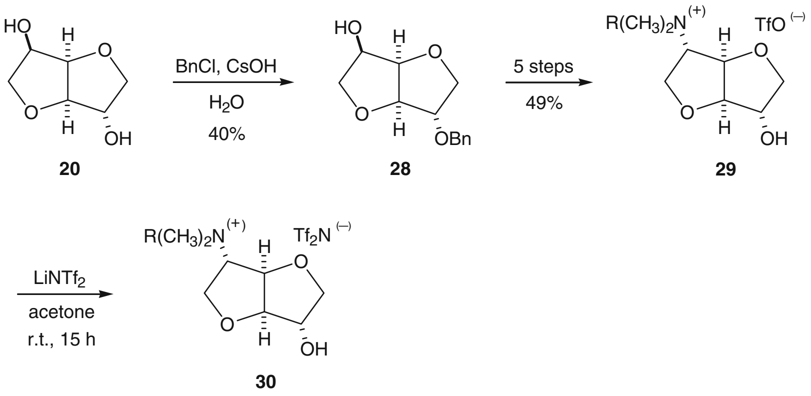
Exploiting the above-mentioned strategy, the two diastereomeric salts **29** and **30** were prepared from the 6-*O*-benzyl-isosorbide **28** (Scheme 7).

Then the potential for asymmetric induction of some of these chiral ionic liquids was investigated. The aza Diels–Alder cycloaddition between the enantiomerically pure (*R*)-imine **31** and the Danishefsky's diene **32** was chosen as model asymmetric reaction (Scheme 8). The reaction was performed at room temperature for 5 h using 0.5 equiv. of ionic liquid and 1.5 equiv. of diene. In the absence of chiral ILs, the same coupling required a Lewis acid catalyst (0.1 equiv. of $ZnCl_2$) and afforded the main product **33** in 60% yield and low diastereoselectivity (32% de).

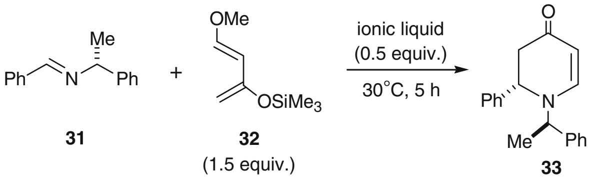
As already pointed out in previous studies [72–74], the presence of both an ammonium ion moiety and a free hydroxy function was crucial for the efficient



Scheme 6 Synthesis of chiral ionic liquids from isosorbide

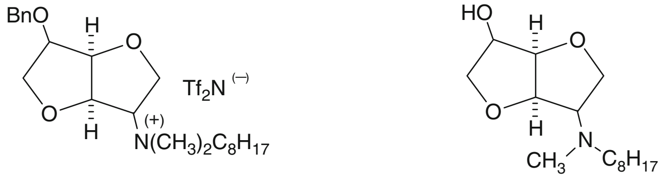


Scheme 7 Synthesis of a second series of chiral ionic liquids from isosorbide



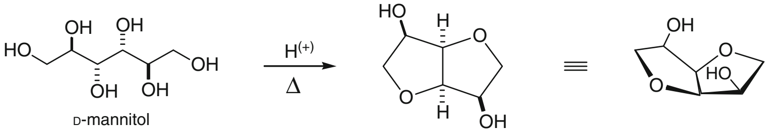
ionic liquid	yield of **33**	de
—	60%	32%
27a	73%	63%
30	56%	60%

Scheme 8 Model asymmetric aza Diels–Alder reaction in the presence of chiral ionic liquids



34 **35**

Fig. 2 Other chiral reaction media for the aza Diels–Alder cycloaddition shown in Scheme 8

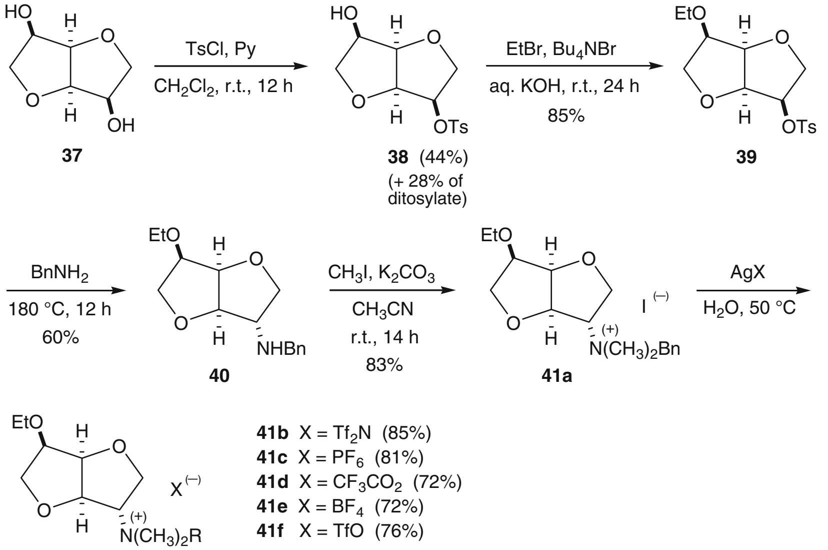


36 **37**

Scheme 9 Synthesis and conformation of isomannide

chirality transfer. In fact, when the aza Diels–Alder reaction was carried out in the presence of compounds **34** or **35** (Fig. 2) lacking the OH group or the ammonium ion, respectively, poor results were observed. On the other hand, the ionic liquids **27a** and **30** afforded **33** in moderate yields and diastereoselectivities (Scheme 8). Moreover, nearly the same results were obtained by recycling **27a** three times.

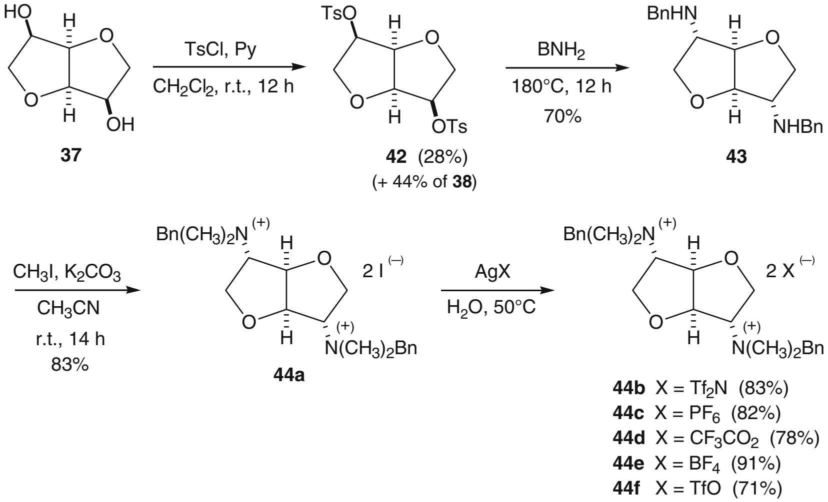
A closely related approach was followed by Parmar, Malhotra, and coworkers [75] to prepare a family of tetraalkylammonium-based chiral ionic liquids starting from isomannide (1,4:3,6-dianhydro-D-mannitol **37**). Commercial isomannide **37** is prepared on a large scale by acid-catalyzed double dehydration of D-mannitol **36**, which, like D-glucitol **19**, is a waste product formed during the processing of corn oil (Scheme 9). However, for synthetic purposes the isomannide presents an important advantage with respect to isosorbide as starting material. Since the former bicyclic diol is a molecule with C_2-axial symmetry, the protection of the OH groups gives a single monoprotected product together with small amounts of the sterically disfavored diprotected derivative. Under similar reaction conditions, the protection of the isosorbide OH functions is expected to afford a mixture of two mono- and one diprotected derivatives.



Scheme 10 Synthesis of mono-tetraalkylammonium chiral ionic liquids from isomannide

Isomannide **37** was monotosylated in moderate yield and then the other hydroxyl group was transformed into an ethyl ether function under phase-transfer conditions (Scheme 10). The bis-protected compound **39** was treated with an excess of benzylamine at high temperature to afford the corresponding amino derivative **40** showing a total inversion of configuration at the endocyclic carbon bearing the nitrogen atom (NMR analysis). Therefore, by means of the latter reaction the original isomannide unit was converted into an isosorbide moiety. The secondary amine **40** was then directly quaternized by treatment with iodomethane and potassium carbonate to give **41a** that was submitted to the anion metathesis using different silver salts in aqueous solutions. Thus, another five tetraalkylammonium salts **41b–f** were prepared and their physical properties were compared. Only two of these compounds (**41b**, **d**) were liquids at room temperature, the others were solids with melting points ranging from 80°C (**41f**) to 170°C (**41a**). This behavior was not unexpected since it is well known that salts bearing weakly coordinating anions, such as the bistriflimide, trifluoroacetate, and triflate ions, have low melting points. The main reason resides in the efficient charge delocalization allowed by these anions that leads to weak interactions with the counterions.

Then the chiral recognition ability of all the above-mentioned salts was investigated by NMR [75]. To a solution of the (enantiopure) iodide salt **41a** in CD_3CN was added the silver salt of racemic Mosher's acid. The formed AgI was removed by filtration and the solution analyzed by ^{19}F NMR spectroscopy (282.4 MHz). The spectrum of the diastereomeric salts mixture showed two close singlets for the trifluoromethyl group of the Mosher's acid anion. Since previous works suggested that achiral anions may affect the chiral recognition properties of chiral ILs [76, 77], further ^{19}F NMR spectra were registered using the above solution of diastereomeric



Scheme 11 Synthesis of bis-tetraalkylammonium chiral ionic liquids from isomannide

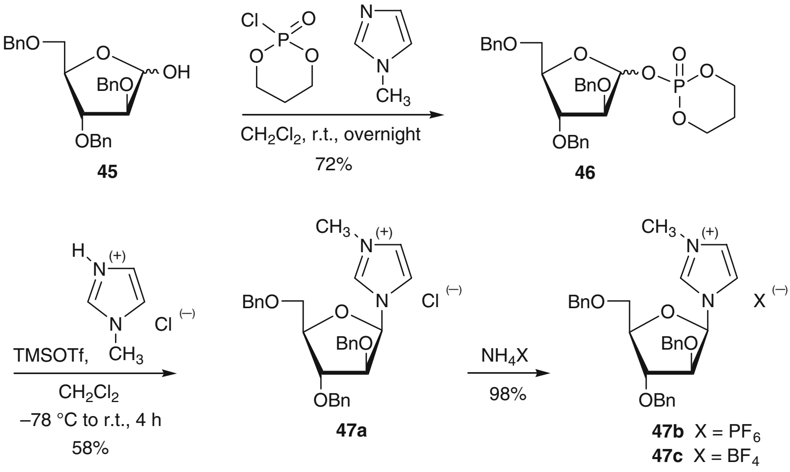
salts mixed with 3.5 equiv. of each product **41b–f**. Actually, enhancements of the chemical shift difference for the CF_3 group of the diastereomeric salts were observed ($\Delta\delta = 0.018$–0.032 ppm). Moreover, when the concentration of added chiral IL was increased, the $\Delta\delta$ value also increased.

Parmar and Malhotra and coworkers also described the preparation of bis-tetraalkylammonium ionic liquids starting from isomannide **37** (Scheme 11) [78]. The ditosylated compound **42** was obtained together with the monotosylated analog **38** (see Scheme 10) by treatment of **37** with tosyl chloride and pyridine. Then, double nucleophilic substitution ($BnNH_2$, 180°C) and subsequent exhaustive methylation (CH_3I, K_2CO_3) afforded the iodide salt **44a** in 58% overall yield from **42**. Usual anion metathesis gave five more salts (**44b–f**). All the bis-ammonium derivatives were solid at room temperature, although their melting points exhibited large variation (from 60°C for **44b** to 251°C for **44c**). As already described for the corresponding mono-ammonium salts (see Scheme 10), the anions allowing a better charge delocalization led to lower melting points.

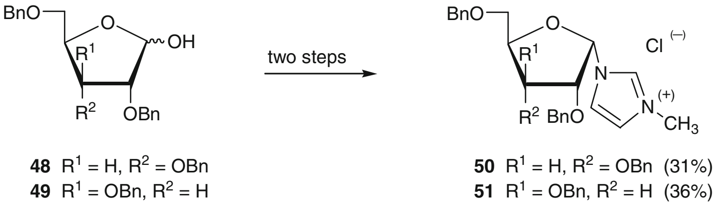
The new salts prepared were also submitted to ^{19}F NMR experiments under the same conditions described above. In this case, the authors found that the chemical shift differences for the CF_3 group of the two diastereomeric salts were larger ($\Delta\delta = 0.028$–0.081 ppm).

Moreover, one of the chiral bis-ammonium salts (i.e., **44b**) was used to determine the enantiomeric excess of three mixtures of Mosher's acids by ^{19}F NMR spectroscopy.

In 2008, the research group of Singh reported the synthesis of imidazolium-based ionic liquids in which the chiral moiety was constituted of a pentofuranoside unit [79]. The 2,3,5-tri-*O*-benzyl-D-arabinofuranose **45**, easily prepared from commercial D-arabinose in 75% yield following known procedures, was transformed



Scheme 12 Synthesis of chiral ionic liquids from 2,3,5-tri-*O*-benzyl D-arabinose



Scheme 13 Synthesis of chiral ionic liquids from 2,3,5-tri-*O*-benzyl D-ribose and D-xylose

into the phosphate **46** by reaction with propane-1,3-diyldioxyphosphoryl chloride in the presence of 1-methylimidazole (Scheme 12). The mixture of anomeric phosphates was then treated with 1-methylimidazolium chloride and catalytic amounts of trimethylsilyl triflate to give the ionic liquid **47a** as pure β-D anomer (^{1}H and ^{13}C NMR analyses). The latter compound was submitted to the anion metathesis to afford other chiral ionic liquids (**47b**, **c**) in nearly quantitative yields.

The same reaction sequence was repeated using commercially available L-arabinose as starting material in order to obtain the enantiomers of the ionic liquids shown in Scheme 12.

The use of 2,3,5-tri-*O*-benzyl-D-ribofuranose **48** or xylofuranose **49** instead of arabinofuranose **45** as starting material, allowed the straightforward synthesis of two diastereomeric methylimidazolium-based ionic liquids, **50** and **51**, respectively, although only as chloride salts (Scheme 13).

The new ILs, submitted to differential scanning calorimetry analysis, showed glass-transition temperatures ranging from −36°C (**47c**) to +18°C (**47a**). All the ionic liquids prepared were stable compounds that did not undergo hydrolysis of the anomeric C-N bond upon prolonged storage at room temperature. Moreover, their chemical stability was also supported by the recovery after the use as solvents in presence of organozinc and organomagnesium reagents. Unfortunately, when **47b** was employed as co-solvent for the addition of methylmagnesium chloride to various aromatic aldehydes, the formed chiral alcohols were recovered in almost quantitative yield as racemic mixtures.

5 Conclusion

It is worth pointing out that, besides D-sorbitol **19** and D-mannitol **36**, other low-molecular weight building blocks have been already obtained on the ton-scale from low cost or waste polymeric carbohydrates (starch, cellulose, hemicellulose, chitin) [80, 81]. Most of these compounds are densely functionalized enantiopure molecules that can be easily converted into high-value added products, including chiral ionic liquids. Therefore, further studies are required to develop other synthetic approaches to environmentally sustainable ionic liquids based on renewable raw materials.

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Index