

Carbohydrates as Organic Raw Materials

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1. Introduction

Because our fossil raw materials, derived from prehistoric organic matter, are irrevocably decreasing and because the pressure on our environment is intensifying, the progressive changeover of the chemical industry to renewable feedstocks for its raw materials emerges as an inevitable necessity [1–3]; i.e. it will have to proceed increasingly to utilize raw materials that prevailed before natural gas and oil outpaced all other resources.

Historically, such raw materials were substantially renewable, as depicted in Figure 1, with the utilization of biomass and coal being almost equal a century ago [4]. In the 1920s, however, coal tar-based materials had taken the lead reaching a maximum around 1930, but

thereafter fossil gas and oil irresistibly took over, nearly eliminating coal completely and reducing renewable feedstocks to very modest levels.

This over-reliance of the chemical industry on fossil resources has its foreseeable limits as they are depleting and are irreplaceable, the only question being: When will affordable fossil fuels be exhausted? Or, stated more appropriately: When will fossil-based raw materials have become so expensive that biofeedstocks are an economically competitive alternative?

Fossil oil will be around for a long time, even if it has to be isolated eventually from oiliferous rocks or shale. So the prevailing issue is: When will be the end of cheap oil? Experts realistically predict this to occur within the next two to three decades [5–7]. Accordingly, the curve for the

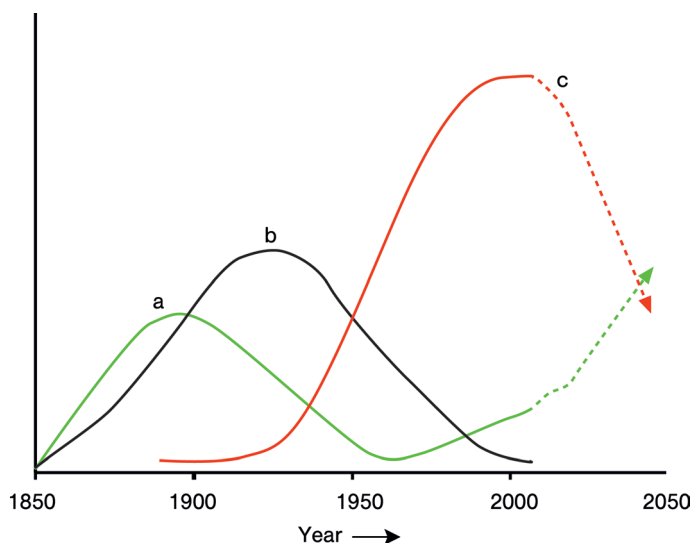


Figure 1. Raw materials used by the chemical industry in historical perspective a) renewable feedstocks; b) coal; c) natural gas, oil

utilization of biofeedstocks in Figure 1 will have to rise such that it meets that of fossil raw materials somewhere around 2030–2040.

The terrestrial biomass to be utilized for the transition from fossil to renewable raw materials, however, is — compared to fossil resources — an exceedingly complex array of low and high molecular mass products, exemplified by sugars, hydroxy and amino acids, lipids, and biopolymers such as cellulose, hemicelluloses, chitin, starch, lignin, and proteins. By far the most important class of organic compounds in terms of volume produced are *carbohydrates* as they represent roughly 75% of the annually renewable biomass of about 180×10^9 t (Fig. 2).

Of these, only a minor fraction (ca. 4%) is used by man, the rest decays and recycles along natural pathways.

Thus, carbohydrates, a single class of natural products — aside from their traditional uses for

food, lumber, paper, and heat — are the major biofeedstocks from which to develop industrially and economically viable organic chemicals that are to replace those derived from petrochemical sources.

2. Availability of Carbohydrates

The bulk of the annually renewable carbohydrate biomass is made up of polysaccharides, yet their nonfood utilization is confined to the textile, paper, and coating industries, either as such or in the form of simple esters and ethers. Organic commodity chemicals, however, are usually of low molecular mass, so they are more expediently obtained from low molecular mass carbohydrates than from polysaccharides. Accordingly, the constituent repeating units of these polysaccharides — *glucose* (cellulose,

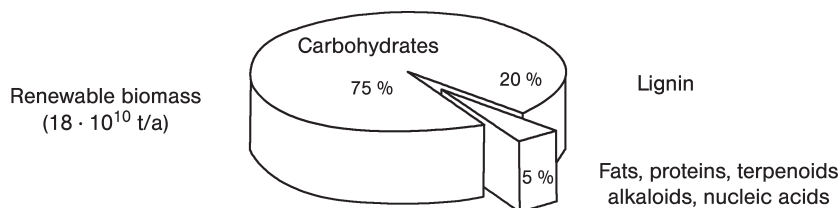


Figure 2. Distribution of types of natural products in biomass

starch), *fructose* (inulin), *xylose* (hemicelluloses), etc., or disaccharide versions thereof — are the actual carbohydrate raw materials for organic chemicals with tailor-made industrial applications. They are inexpensive, ton-scale accessible, and provide an ensuing chemistry better worked out and more variable than that of their polymers.

Table 1 lists the availability and bulk-quantity prices of the eight least expensive

Table 1. Annual production volume and prices of simple sugars, sugar-derived alcohols and acids as compared to some petrochemically derived basic chemicals and solvents

		World production ^a , t/a	Price ^b , €/kg
Sugars	Sucrose	169 000 000	0.20
	D-Glucose	30 000 000	0.30
	Lactose	295 000	0.60
	D-Fructose	60 000	1.00
	Isomaltulose	70 000	2.00
	Maltose	3000	3.00
	D-Xylose	25 000	4.50
	L-Sorbose	60 000	7.50
	Sugar alcohols	D-Sorbitol	650 000
Erythritol		30 000	2.25
Xylitol		30 000	5.00
D-Mannitol		30 000	8.00
Sugar-derived acids	Citric acid	1 500 000	1.00
	D-Gluconic acid	60 000	1.40
	L-Lactic acid	150 000	1.75
	L-Tartaric acid	35 000	6.00
	L-Ascorbic acid	80 000	8.00
	L-Glutamic acid	1 500 000	1.20
	L-Lysine	740 000	2.00
Petrochemicals	Ethylene	90 000 000	0.40
	Propylene	45 000 000	0.35
	Benzene	23 000 000	0.40
	Terephthalic acid	12 000 000	0.70
	Aniline	1 300 000	0.95
	Acetaldehyde	900 000	1.10
	Adipic acid	1 500 000	1.70
	Solvents	Methanol	25 000 000
Toluene		6 500 000	0.25
Acetone		3 200 000	0.55

^aReliable data are available for the world production of sucrose only, the figure given referring to the crop cycle 2007/2008 [9]. All other data are average values based on estimates from producers and/or suppliers as the production volume of many products are not publicly available.

^bPrices given are those attainable in early 2005 for bulk delivery of crystalline material (where applicable) based on pricing information from sugar industry (sugars) and the Chemical Market Reporter 2009 (acids, basic chemicals, and solvents). The listings are intended as a benchmark rather than as a basis for negotiations between producers and customers. Quotations for less pure products are, in part, markedly lower, e.g. the commercial sweetener “high fructose syrup”, which contains up to 95% fructose, may readily be used for large-scale preparative purposes.

sugars, some sugar alcohols and sugar-derived acids — all well below € 10/kg — compared with some basic chemicals from petrochemical sources. The result is stunning, since the five cheapest sugars, their alcohols, and some important sugar-derived acids are within the same price range as basic organic bulk chemicals such as naphtha, ethylene, acetaldehyde, or aniline. Actually, the first three of these sugars, sucrose, glucose, and lactose, are in the price range of some of the standard organic solvents.

The uniqueness of this situation becomes even more imposing when looking at the availability of these sugars. *Sucrose*, “the royal carbohydrate” [8], has for centuries been the world’s most abundantly produced organic compound, annual production being an impressive 169×10^6 t in 2007/08 [9]. Similarly bulk scale-accessible are its component sugars *D-glucose*, produced by hydrolysis of starch (\rightarrow Glucose and Glucose-Containing Syrups), and *D-fructose*, generated either from glucose by base-induced isomerization or from inulin or sucrose by hydrolysis (\rightarrow Fructose). *Isomaltulose*, an $\alpha(1\rightarrow6)$ -isomer of sucrose, has become accessible on an industrial scale through enzymatic transglucosylation (\rightarrow Sugar Alcohols, Chap. 5), *lactose* and *maltose* are available in large quantities from whey (\rightarrow Lactose and Derivatives) and starch, *D-xylose*, the cheapest pentose, from wood- or straw-derived xylans. *L-Sorbose* is the cheapest, large-scale accessible L-sugar, because of its production from D-sorbitol (= D-gluconitol) in the Vitamin C fabrication process (\rightarrow Vitamins, Chap. 10). The sugar alcohols *D-sorbitol*, *erythritol* [10], *D-xylitol*, and *D-mannitol* (\rightarrow Sugar Alcohols, Chaps. 2–4), each of comparatively high yearly production via hydrogenation of their parent aldoses, are mainly used as food ingredients because of their sweetening properties, yet also have potential as inexpensive raw materials for broad-scale preparative purposes. The same holds for D-gluconic acid (\rightarrow Gluconic Acid) and the other sugar-derived acids listed.

Despite their large-scale accessibility at comparatively low cost, it seems surprising that the chemical industry currently utilizes these mono- and disaccharides to a minor extent as feedstock for organic chemicals, despite intense efforts within the last decade [11–20] to boost

the acquisition of organic chemicals from sugars in Table 1.

There are a variety of reasons for this. Current use of fossil raw materials is more economic and, as important, the process technology for the conversion of petrochemical raw materials into organic chemicals is exceedingly well developed and basically different from that required for transforming carbohydrates into products with industrial application profiles. This situation originates from the inherently different chemical structures of the two types of raw material, the essence of which is manifested in their structure-based names (Fig. 3). Our fossil resources are hydrocarbons, distinctly hydrophobic, oxygen-free and devoid of functionality, thus, organic functional groups such as hydroxyl, amino, aldehyde, acid, ester or halo functionalities have to be introduced — usually into olefinic hydrocarbons such as ethylene, propylene and butane — to obtain the industrially important intermediate chemicals. By contrast *carbohydrates* are overfunctionalized with hydroxyl groups and markedly hydrophilic in nature. Needless to say, that the methods required for converting carbohydrates into viable industrial chemicals — reduction of oxygen content with introduction of C=C and C=O unsaturation — are diametrically opposed to those prevalent in the petrochemical industry.

As higher oil prices, environmental issues, and regulations begin to adversely affect the manufacture of chemicals from fossil raw materials, the inevitable transition to a biobased

production system urgently necessitates the systematic elaboration of appropriate chemical and microbial process methods to convert carbohydrates into industrially viable products, be it bulk, intermediate and fine chemicals, pharmaceuticals, agrochemicals, high-value-added speciality chemicals, or simply enantiomerically pure building blocks for organic synthesis.

3. Current Nonfood Industrial Products from Sugars

Current utilization of carbohydrates as a feedstock for the chemical industry — whether for bulk, commodity, intermediate, fine or high-value-added specialty chemicals — is modest when considering their ready availability at low cost and the huge as yet unexploited potential. These examples are outlined briefly that are presently realized on an industrial scale.

3.1. Ethanol

With a production of about 52×10^6 t in 2008 (17335×10^6 gallons [21]), fermentation ethanol (“bioethanol”) is the largest volume biobased chemical utilized today. The principal organism for fermentation is *Saccharomyces cerevisiae*, an ascomycetous yeast that can grow on a wide variety of carbohydrate feedstocks — sugar crops, and sugar-containing byproducts such as sugar cane, sugar beet, sorghum, molasses, and (after hydrolysis to glucose) starchy crops such as corn, potatoes and grains, or cellulosic materials; e.g. wood pulping sludges from pulp and paper mills [22]. Developments starting in 2000 [23] replace the conventional yeast by bacteria (*Zymomonas mobilis*) and/or genetically engineered organisms, which seem to improve productivity significantly.

The enormous growth in production of industrial-grade fermentation ethanol in the early 2000s is less due to its use as a solvent or as a starting material for follow-up chemicals, such as acetaldehyde, ethyl esters (e.g. EtOAc) and ethers (Et₂O) as these mostly result from ethylene-based processing lines; rather it is its use as fuel additive, directly mixed to standard gasoline at a level of 5–10%. There is considerable debate [24] about how useful bioethanol is

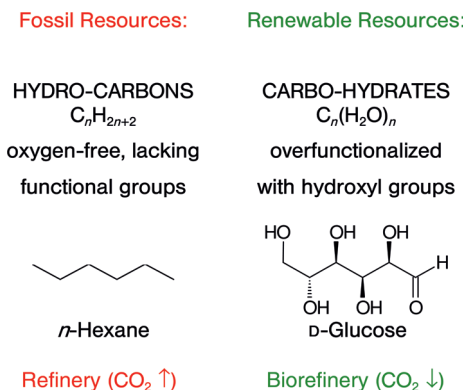


Figure 3. Hydrocarbons versus carbohydrates: more than a play on words, as their names, taken literally, reveal the basic differences in their utilization as organic raw materials

in replacing fossil fuels, arguments going as far as considering this a giant misguided effort to reduce oil insecurity. First of all, present production predominantly relies on grain (wheat, corn) thereby diverting large areas of land for nonfood purposes, which indubitably will result in food price inflation. Furthermore, the production process is not CO₂ neutral as fermentation yields as much CO₂ as ethanol:

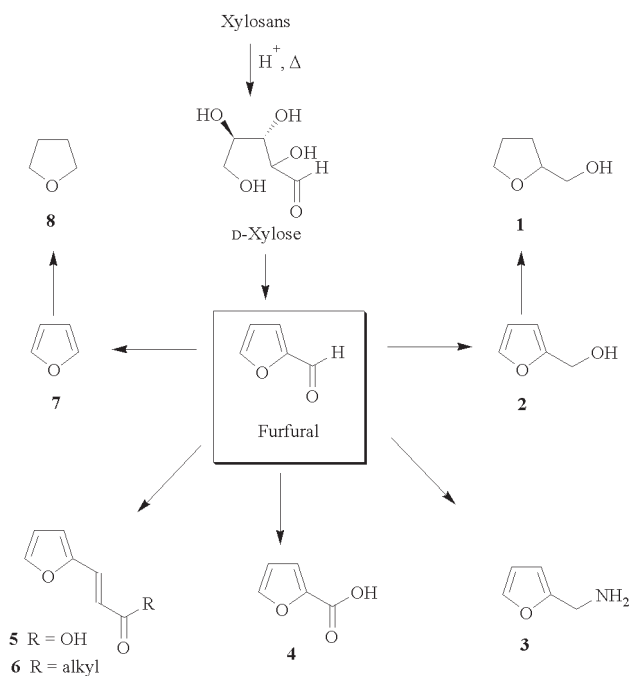


Ethanol is economically only viable, at least in Europe, with hefty government subsidies (exemption of gasoline tax) and — a further disadvantage — it cannot be used in diesel engines due to its comparatively low boiling point. Although developments with cellulosic ethanol production [23] and commercialization may allay some of these flaws, the transition to more sustainable and considerably more effective second-generation biofuels such as 2,5-dimethylfuran (see Section 4.1.2) or 1-butanol [24], generated from cellulosic biomass in agricultural and forestry wastes and the like, are imperative.

3.2. Furfural

With an annual production of approximately 25×10^4 t, furfural (2-furfuraldehyde) seems to be the only unsaturated large-volume organic chemical prepared from carbohydrate sources. The technical process involves exposure of agricultural or forestry wastes — hemicellulose up to 25% D-xylose polysaccharides (xylosans) — to aqueous acid and fairly high temperatures; the xylosans are first hydrolyzed, and then undergo acid-induced cyclodehydration (\rightarrow Furfural and Derivatives) [26b, 26c].

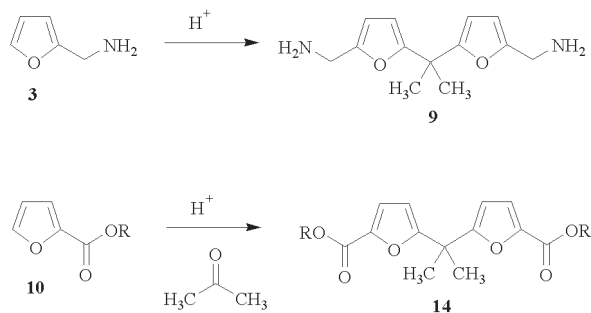
The chemistry of furfural is well developed, providing a host of versatile industrial chemicals by simple straightforward operations (Scheme 1): furfuryl alcohol (**2**) and its tetrahydro derivative **1** (hydrogenation), furfurylamine (**3**) (reductive amination), furoic acid (**4**) (oxidation) and furanacrylic acid (**5**) (via a Perkin reaction), or furylidene ketones **6** (aldol condensations). Furfural is also the key chemical for the commercial production of furan (through catalytic decarbonylation) and tetrahydrofuran (**8**) (hydrogenation), thereby



Scheme 1. Furanic commodity chemicals derived from pentosans in agricultural wastes (corn cobs, oat hulls, bagasse, wood chips)

providing a biomass-based alternative to its petrochemical production by dehydration of 1,4-butanediol (\rightarrow Furfural and Derivatives) [26b, 26c]. Further importance of these furan chemicals stems from their ring-cleavage chemistry [27], which has led to a variety of other established chemicals, for example fumaric, maleic and levulinic acid, the last a byproduct of the production of furfural (\rightarrow Oxocarboxylic Acids).

The susceptibility of the furan ring in these compounds for electrophilic substitution at C-5 has been widely exploited. Mineral acid-promoted condensations with aldehydes or ketones convert **3** into the difurfural diamine **9** [28], whereas esters of 2-furoic acid afford the respective difurfuryl dicarboxylates (**10** \rightarrow **11**). Both — the latter on saponification — are relevant monomer components for the generation of polyesters and polyamides [29].



Most of the furfural currently produced is used as a selective solvent in the refining of lubricating oil, and, together with furfuryl alcohol in condensations with formaldehyde, phenol, acetone or urea to yield resins of complex, ill-defined structures, yet excellent thermosetting properties, most notably exhibiting high corrosion resistance, low fire hazard and extreme physical strength (\rightarrow Furfural and Derivatives, \rightarrow Resins, Synthetic, Section 3.1) [26a, 26b]; they are extensively used in the foundry industry as cores for high-quality castings.

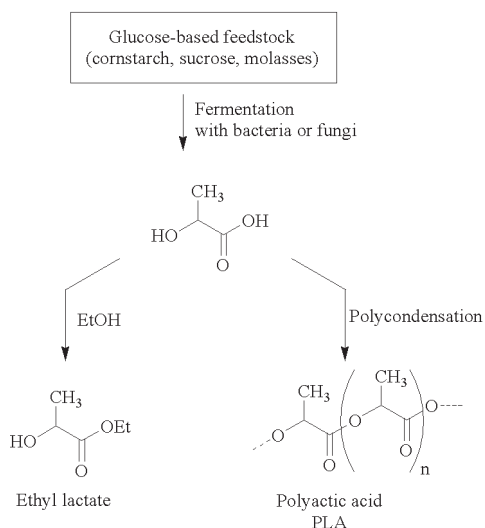
3.3. D-Sorbitol (\equiv D-Glucitol)

Although D-sorbitol has a sizable annual production (Table 1), the main consumer is the food industry, primarily as a noncaloric sweetening

agent and as a key intermediate in the production of ascorbic acid (vitamin C). However, D-sorbitol has important nonfood applications because of its moisture conditioning, softening and plastifying properties (\rightarrow Sugar Alcohols, Chap. 3). These result in its use in adhesives, paper, printing, textiles, cellulose-based films and pharmaceutical formulations. Other nonfood applications of D-sorbitol result from etherification and polycondensation reactions which provide biodegradable polyetherpolyols used for soft polyurethane foams and melamine-formaldehyde or phenolic resins [28]. Sizable amounts of D-sorbitol are also used for production of the sorbitan ester surfactants (cf. Section 3.5.1).

3.4. Lactic Acid and Polylactic Acid (PLA)

Large amounts of D-glucose — in the crude form obtainable from corn, potatoes or molasses by acid hydrolysis — enter into industrial fermentation processes towards the production of lactic acid (see Scheme 2), citric acid and different amino acids; for example, L-lysine or L-glutamic acid. Although the major use of these products is in food and related industries, nonfood exploitation of lactic acid has made it a large scale, organic commodity chemical. Most of it is



Scheme 2. Production and uses of lactic acid

subsequently polymerized via its cyclic dimer (lactide) to polylactic acid [30], a high-molecular mass polyester.

Because of its high strength, PLA can be fabricated into fibers, films, and rods that are fully biodegradable (formation of lactic acid, CO₂) and compostable, degrading within 45–60 days. Accordingly, PLA and copolymers of lactic and glycolic acid are of particular significance for food packaging and in agricultural or gardening applications, but they are also highly suitable materials for surgical implants and sutures, as they are bioresorbable [31].

Since 1989 Cargill has invested some \$ 750×10⁶ to develop and commercialize polylactic acid (tradename INGENEO by NatureWorks), its Nebraska plant with an annual capacity of 14×10⁴ t opened in 2002 [32]. Thus, polylactides, because they combine favorable economics with green sustainability, are poised to compete in large-volume markets that are now the domain of thermoplastic polymers derived from petrochemical sources.

Another green development based on lactic acid is its ethyl ester which has been marketed as ELSOL by Vertec Biosolvents for applications in specialty coatings, inks, and directly for cleaning because of its high performance and versatility [33]. As a most benign solvent—green, readily biodegradable, and with excellent low toxicology—this chemical has the potential to displace a variety of petrochemically-based solvents such as acetone, DMF, toluene or *N*-methylpyrrolidone in industrial processes.

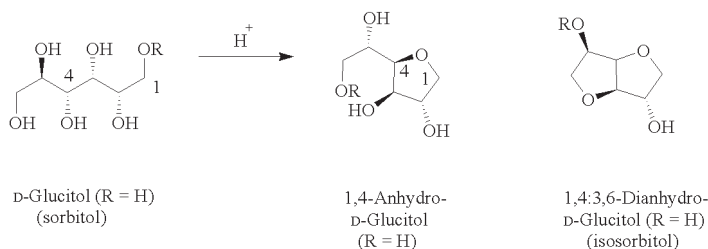
3.5. Sugar-Based Surfactants

Utilization of cheap, bulk-scale accessible sugars as the hydrophilic component and fatty acids or fatty alcohol as the lipophilic part provides nonionic surfactants which are non-toxic, nonskin-irritating and fully biodegradable. Typical examples of such industrially relevant surfactants are fatty acid esters of sorbitol (sorbitan esters) and of sucrose, fatty acid amides of 1-methylamino-1-deoxy-D-glucitol (NMGA) and, most pronounced in terms of volume produced, fatty alcohol glucosides, the so-called alkyl polyglucosides (APGs) [34, 35].

3.5.1. ‘Sorbitan’ Esters

Bulk-scale accessible D-sorbitol (cf. Table 1) readily undergoes dehydration on exposure to mineral acid at fairly high temperatures to give anhydrosorbitol or sorbitan, de facto a mixture of sorbitol and its 1,4-anhydro and 1,4:3,6-dianhydro derivatives, the exact composition depending on the conditions employed [35] (Scheme 3). Esterification of this mixture with C₁₆/C₁₈ fatty acid chlorides/base or transesterification with their methyl esters leads to either sorbitan monoesters (SMS for sorbitan mono-stearate), or di- and triesters (“SMS”).

Because of their favorable hydrophilic/hydrophobic balance (HLB) values, sorbitan esters find use as nonionic surfactants and as solubilizers and emulsifiers in cosmetics, pharmaceuticals, textile processing, and a variety of other formulations [40]. Having been commercially



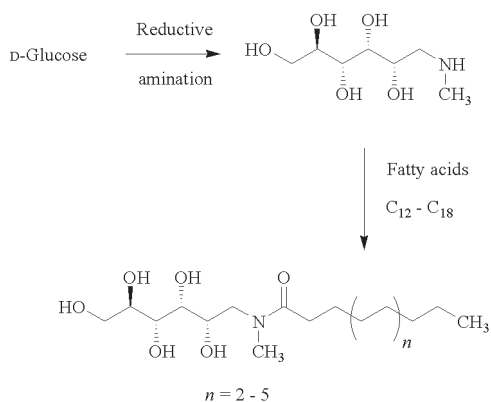
"Sorbitol monoester" (SMS) : R = C₁₆ - C₁₈-acyl

Scheme 3. Dehydration of D-sorbitol to “sorbitan”, giving the ‘sorbitan monoester’ surfactant on esterification with C₁₆/C₁₈-fatty acids

available since the 1940s, de facto they constitute one of the first fully green synthetic surfactants, presently produced at an estimated 2×10^4 t/a.

3.5.2. *N*-Methyl-*N*-acyl-glucamides (NMGA)

Reductive amination of D-glucose with methylamine smoothly generates an aminoalditol, 1-methylamino-1-deoxy-D-glucitol, which, on amidation with fatty acids gives the corresponding fatty acid amides, carrying a methyl group and a pentahydroxylated six-carbon chain at the amido nitrogen.



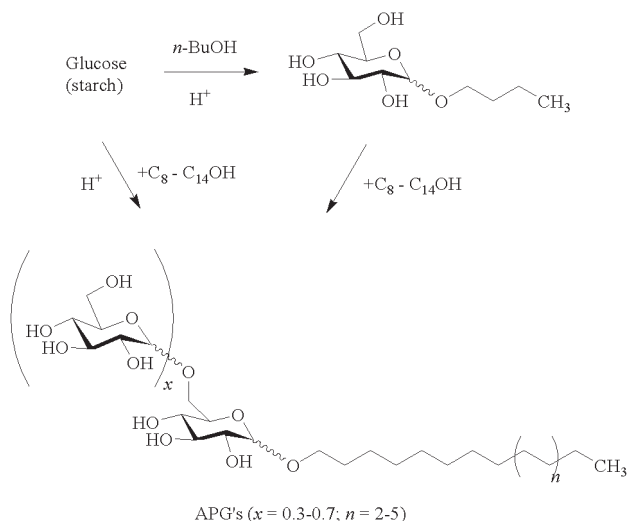
The NMGA's have highly advantageous ecological and toxicological properties which

allow their use as surfactants and cleansing agents, and also in cosmetic applications [35, 36].

3.5.3. Alkylpolyglucosides (APG)

APGs are commercially produced by several companies — most notably Cognis, with a capacity in the 50×10^3 t/a range — Kao, Seppic, and ICI. They are by far the most important nonionic surfactants and comprise fatty alcohol glucosides with an alcohol chain length normally between C_8 and C_{14} . Their industrial synthesis entails either direct acid-catalyzed Fischer glycosidation of glucose (in the form of a syrupy starch hydrolysate) or starch itself. The alternate process consists of two stages, the first being Fischer glycosidation with *n*-butanol to butyl glycosides which are subsequently subjected to acid-promoted transacetalization [34].

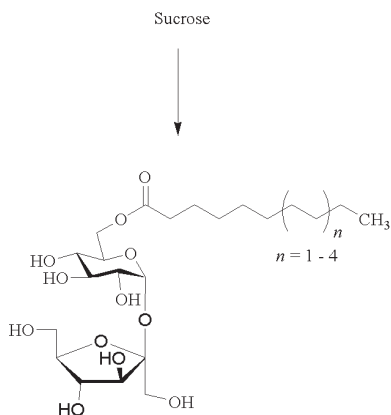
The resulting product mixtures predominantly contain the α -D-glucosides, as designated in the general formula (Scheme 4) and are marketed as such. APGs are not skin-irritating, have good foaming properties, and are completely biodegradable; hence they are widely used in manual dishwashing detergents and in the formulation of shampoos, hair conditioners and other personal care products [34].



Scheme 4. Synthesis of alkyl polyglucosides (APG's)

3.5.4. Sucrose Fatty Acid Monoesters

These compounds are currently produced at an approximate 4×10^3 t/a only, and are mostly used in cosmetic and personal care formulations because of their attractive dermatological properties. Produced by transesterification of fatty acid methyl esters or with fats, the resulting sucrose monoesters (if 1:1 molar ratios have been used in the process) are not defined products, acylated exclusively at the primary glucose-6-OH as indicated in the formula, but also at the other primary and some of the secondary OH groups [37].



3.6. Pharmaceuticals and Vitamins

Alongside the enormous amount of sugars, mostly glucose and sucrose, that flows into the fermentative production of amino and hydroxy acids (see Table 1) (a substantial part of which is for food use), a significant volume of these sugars is used in fermentation processes furnishing high-value-added products — antibiotics and vitamins, much too complex in their structures as to be generated by chemical synthesis. Figure 4 lists several representative examples — penicillins and cephalosporins with an estimated world production in the 7×10^3 t/a range, the aminoglycoside antibiotics of the kanamycin and spectinomycin type, or the optimized bioprocesses for the bulk-scale production of vitamins C and B₆.

Some sugar-derived drugs obtained by chemical means have also reached some importance, e.g. ranitidine (Zantac), an inhibitor of gastric acid secretion — one of the top 30 drugs

based on sales (→ Pharmaceuticals, General Survey) — isosorbide dinitrate, a coronary vasodilator (→ Cardiovascular Drugs, Chap. 15) [38], or topiramate, a fructose-derived anticonvulsant drug with high antiepileptic efficacy [39].

4. Toward Further Sugar-based Chemicals: Potential Development Lines

Considering the large-scale, low-cost availability of the basic biomass-sugars listed in Table 1, most notably sucrose, glucose and fructose, their present nonfood utilization by chemical industry is modest indeed; i.e. the huge potential as the raw material for further viable industrial chemicals and materials is largely untapped. In view of the need for the chemical industry to somehow bring about the changeover from fossil raw materials to biofeedstocks, most notably carbohydrates from agricultural crops and waste materials, their further exploitation to produce industrially viable products is one of the major “green” challenges. The attempt to trace those sugar-based development lines along which the further use of the key sugars of biomass is likely to proceed, implies an assessment of many imponderables, particularly with regard to current dynamics in exploiting genetically engineered enzymes and the products resulting from them. Nevertheless, an “inventory” based on the present status may be expedient for focusing efforts on those areas where useful methods leading to promising products already exist yet await further development.

4.1. Furan Compounds

In addition to furfural, an established sugar-based five-carbon commodity with versatile industrial applications (see Section 3.2), several other furan compounds, readily prepared from sugars, hold high promise as industrial intermediate chemicals, albeit — for purely economic reasons — they are not (yet) produced on an industrial scale.

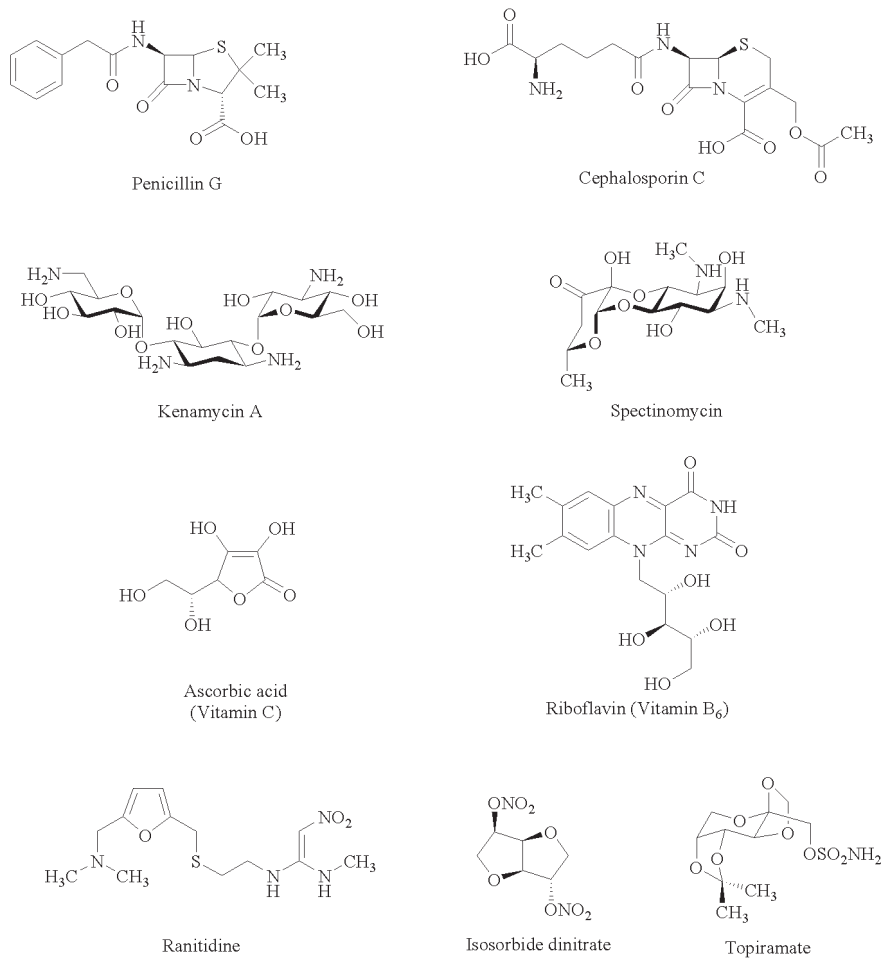
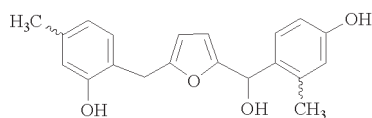


Figure 4. Sugar-derived high-value-added products — antibiotics, vitamins, and pharmaceuticals

4.1.1. 5-Hydroxymethylfurfural (HMF)

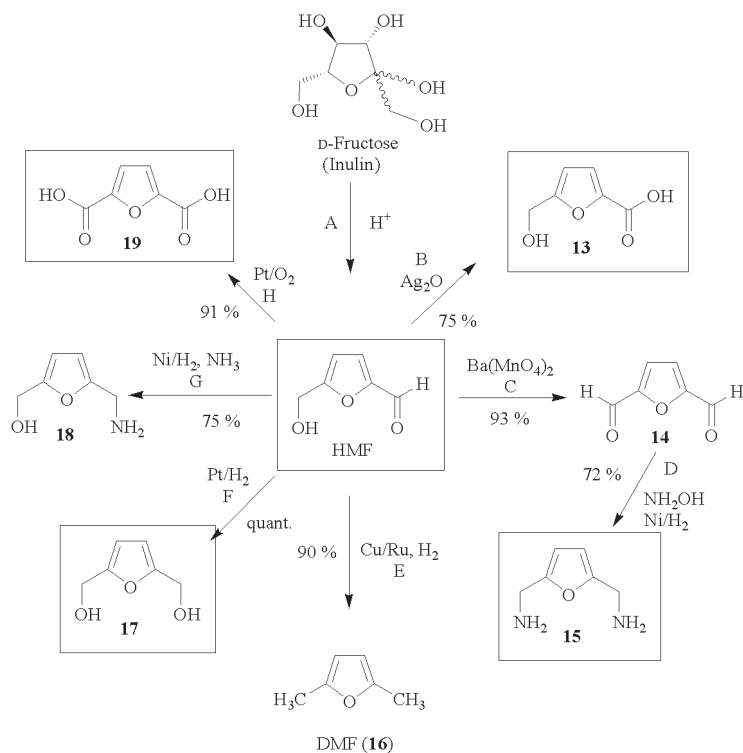
Like many petroleum-derived basic chemicals, e.g., adipic acid or hexamethylenediamine, HMF is a six-carbon compound with broad application potential, inasmuch as it is readily accessible from fructose or inulin hydrolysates by acid-induced elimination of three molecular equivalents of water [40]. Even a pilot-plant-size process has been elaborated [41].

HMF has been used for the manufacture of special phenolic resins of type **12**, because acid catalysis induces its aldehyde and hydroxymethyl group to react with phenol [42].



12

Of high industrial potential as key biomass-derived chemicals are various HMF-derived products for which well worked-out, large scale-adaptable production protocols are available (Scheme 5). Of these, 5-hydroxymethylfuroic acid (**13**), the 2,5-dicarboxylic acid **19**, the 1,6-diamine **15**, and the respective 1,6-diol



Scheme 5. Versatile intermediate chemicals from HMF.
A [40]; B [43]; C [43]; D [43]; E [44]; F [45]; G [46]; H [47]

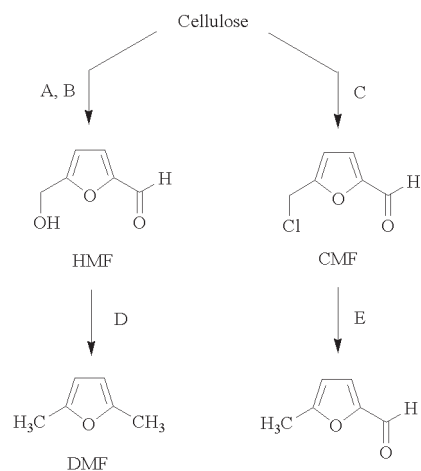
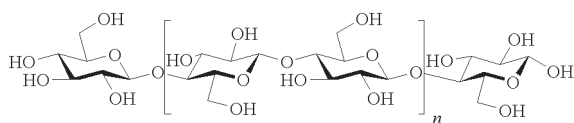
17 are most versatile intermediate chemicals of high industrial potential, because they are six-carbon analogues of adipic acid, of alkyldiols, or of hexamethylenediamine in the production of polyamides and polyesters. Indeed, an impressive series of furan polyesters and polyamides has been prepared [26, 28] in which the furandicarboxylic acid **19** replaces terephthalic and isophthalic acids in current industrial products (see Section 4.7.3). However, none has yet proved economically competitive with existing products.

4.1.2. 2,5-Dimethylfuran (DMF)

Hydrogenation of HMF over a copper-ruthenium catalyst affords DMF (**16**) in high yield [44]. DMF is considered to be a second-generation biofuel as it has vital advantages over ethanol such as full utilization of the six carbons of the sugar precursors; moreover, its energy content is similar to that of gasoline, it

has a higher boiling point (by 16 °C) and it is immiscible with water.

To become a bulk-scale industrial product, however, the raw materials basis for its generation will have to change from D-fructose (Scheme 5) or D-glucose (rearrangement by base to D-fructose) to nonfood raw materials, i.e. cellulosic biomass from agriculture and forestry waste or switch grass and the like. Indeed, there are some promising developments in this direction. Exposure of cellulose to treatment with dimethylacetamide containing lithium chloride in the presence of CrCl_2 at 140 °C affords HMF in 54% yield [48] (cf. Scheme 6), whilst untreated lignocellulosic biomass such as corn stover as the raw material, when subjected to these conditions except for using CrCl_3 as promoter, delivers HMF in 48% yield [48]. These promising results, upon further development along these veins, are likely to eventually turn HMF and its ensuing products into key biomass-derived chemicals; most notably DMF as a biofuel.



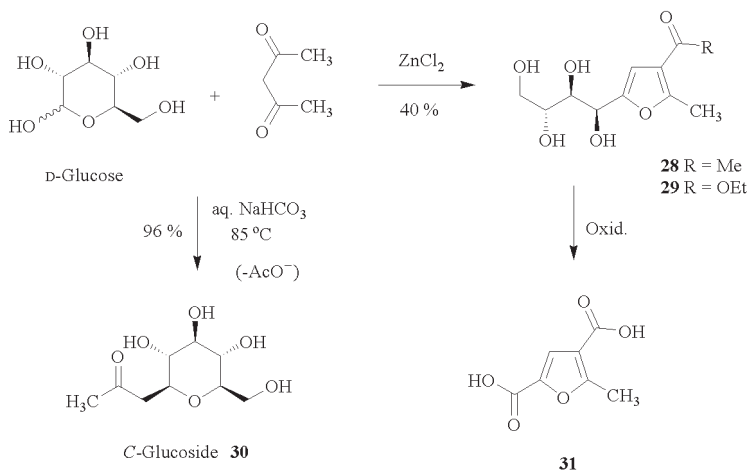
Scheme 6. Reactions and conditions

- A, dimethylacetamide/LiCl (10%), CrCl₂, [EMIM]Cl, 2 h, 140 °C, 54% from cellulose [48].
 B, dimethylacetamide/LiCl (10%), CrCl₃, [EMIM]Cl, 2 h, 140 °C, 48% from corn stover [48].
 C, LiCl/HCl in (CH₂Cl)₂, 65 °C, 71% [49].
 D, Cu/Ru/C, H₂ in *n*-butanol, 120 °C, 79% [44].
 E, PdCl₂/H₂ in *N,N*-dimethylformamide, 3 h, 40 °C, 88 [49]

4.1.3. Furans with a Tetrahydroxybutyl Side Chain

A very simple, one-step entry from hexoses to more highly substituted furans is their ZnCl₂-mediated reactions with 1,3-dicarbonyl compounds such as 2,4-pentenedione or ethyl acetoacetate. Because only the first two sugar carbons contribute to the formation of the furan, a distinctly hydrophilic tetrahydroxybutyl side-chain is produced. Thus, *D*-glucose smoothly provides furans **28** and **29** with the *D-arabino* configuration in the polyol fragment [50]; these can be shortened oxidatively to the dicarboxylic acid (**29** → **31**) or a variety of other furan building blocks (Scheme 7).

In contrast, under mildly basic conditions (aqueous bicarbonate at 85 °C), *D*-glucose reacts with pentane-2,4-dione in an entirely different manner, producing, via *C*-addition and subsequent retroaldo-type elimination of OAc⁻, the 2-*C*-glucosylpropanone **30** [51]. Because this conversion can be performed with the unprotected sugar and in aqueous solution with simple reagents, it may legitimately be referred to as a prototype of green and/or sustainable sugar transformations. The procedure is equally feasible with other aldohexoses and with *D*-fructose [52]; thus, it is one of the cleanest and most efficient preparative entries into the area of *C*-glycosides, which, as stable “mimics”



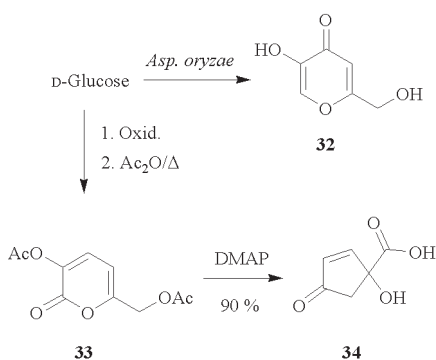
Scheme 7. One-pot conversions of *D*-glucose into hydrophilic furans [50] or, alternatively, into *C*-glucosides by reactions with acetylacetone [51]

of the usual *O*-glycosides, command major interest as glycosidase inhibitors [53].

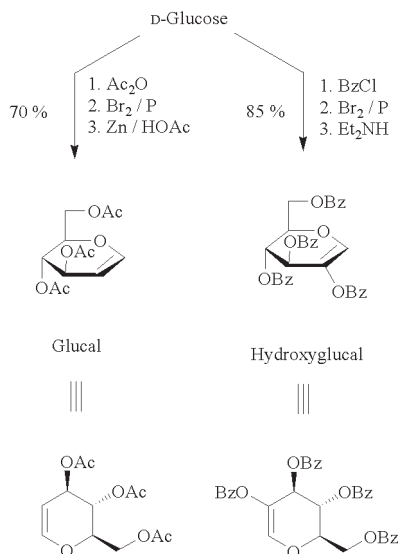
4.2. Pyrones and Dihydropyranones

The bulk-scale-accessible mono- and disaccharides of Table 1 invariably adopt pyran cyclohemiacetal forms, from which well-elaborated, efficient reaction channels lead to an unusually large variety of unsaturated pyran building blocks; for example, pyrones, dihydropyrans, and dihydropyranones, of which the last two have the additional advantage of being enantiomerically pure. They are treated only cursorily in this context, because their potential as ideally functionalized six-carbon building blocks, particularly for the preparation of pharmaceutical targets, has not been utilized comprehensively.

Pyrones of type **32** (kojic acid) are readily obtained from *D*-glucose, the former either enzymatically by growing *Aspergillus oryzae* on steamed rice [54] or chemically via pyran 3,2-enolones [55, 56], or the γ -pyrone **33** by oxidation to *D*-gluconic acid and acetylation [57]. Both compounds, at present, are of little significance as six-carbon building blocks, despite a surprisingly effective route from **33** to cyclopentanoid products of type **34** [58] which is surmised to have industrial potential.



Other highly useful derivatizations of the common sugars, particularly towards the generation of enantiopure six-carbon building blocks, comprise their three-step, one-pot conversion into glycol and hydroxyglycol esters, as depicted for *D*-glucose in Scheme 8. These



Scheme 8. Readily accessible pyran derivatives from *D*-glucose [59]

esters not only have the oxygen content of *D*-glucose reduced — a precondition for elaboration of industrially viable products — but carry olefinic unsaturation in the pyran ring.

Despite the ready accessibility of these glucal and hydroxyglucal esters, and their well-developed ensuing chemistry, their exploitation as industrial intermediates is exceedingly modest. Nevertheless, to emphasize their potential toward industrial intermediates, whether as enantiomerically pure building blocks for the synthesis of noncarbohydrate natural products [56, 60] or for agrochemicals and/or high-value-added pharmaceuticals, a particularly versatile array of *six-carbon dihydropyranones* is listed in Figure 5 all are accessible from *D*-glucose (via the glucal and hydroxyglucal esters) in no more than three to five straightforward steps.

A bicyclic dihydropyranone, levoglucosone, is accessible even more directly by vacuum pyrolysis of waste paper [70]. Although the yield achievable is relatively low — levoglucosan is also formed, the proportion depends on the exact conditions (Scheme 9), — relatively large amounts can be amassed quickly. Levoglucosone has been used for the synthesis of a diverse variety of natural products in enantiomerically pure forms [71].

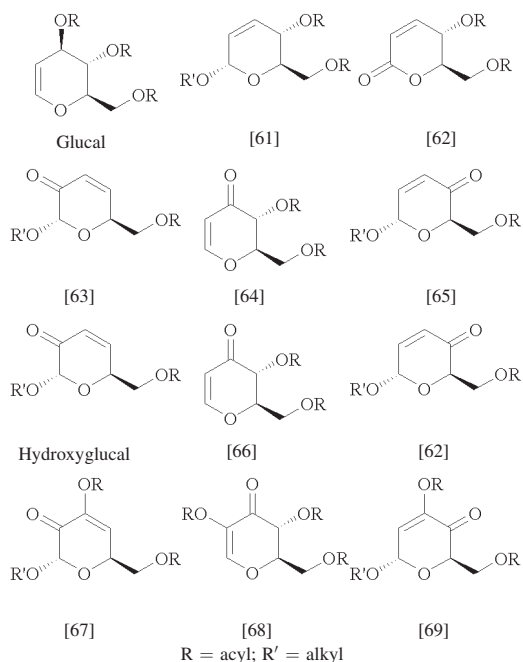
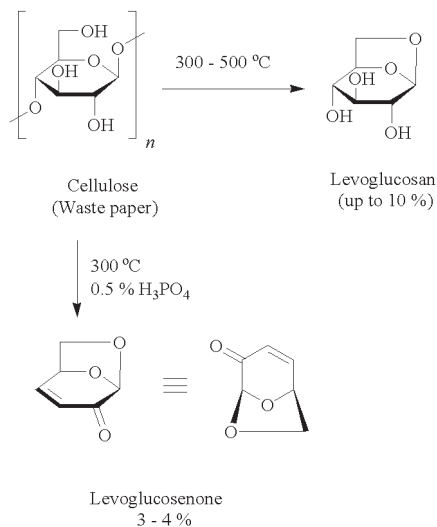


Figure 5. Pyranoid six-carbon building blocks accessible from D-glucose via glucal (upper half) or hydroxyglucal esters (lower entries). All products require no more than three to five straightforward steps from D-glucose [61–69].

4.3. Sugar-Derived Unsaturated Nitrogen Heterocycles

Although transformation of sugars into trace amounts of nitrogen heterocycles occurs extensively on exposure of foodstuffs to heat (Maillard reaction [72]), and although a variety of nitrogen heterocycles have been generated

from saccharide derivatives [73] procedures meeting preparative standards are exceedingly scarce. Improvements of existing procedures in the early 2000s and the development of new methods have led to the more ready acquisition of various nitrogen heterocycles from carbohydrates, e.g. imidazoles, pyrroles, pyrazoles, pyr-

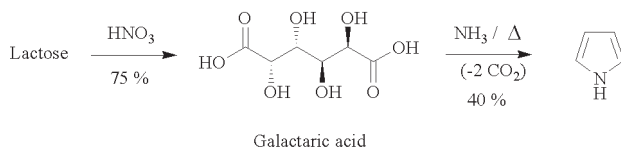


Scheme 9. High-vacuum pyrolysis of cellulose [70]

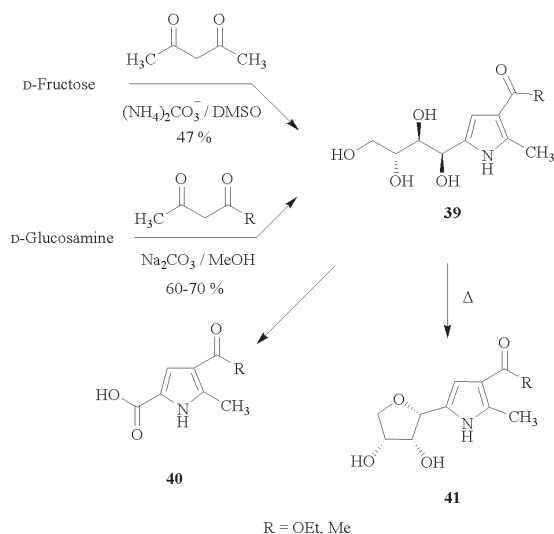
idines and quinoxalines which, because of their sugar derivation, have hydrophilic side chains — a favorable asset particularly in pharmaceutical applications [17].

4.3.1. Pyrroles

The generation of pyrroles by heating a glycerol solution of lactose-derived ammonium salt of galactaric acid over a free flame [74] seems to be the highest-yielding acquisition (40%) from a carbohydrate source — a process that, in this or modified form, does not seem to be utilized industrially.



Pyrroles with a hydrophilic tetrahydroxybutyl substituent, e.g. **39**, are available from D-glucosamine by exposure to acetylactone or ethyl acetoacetate under mildly basic conditions [75] or in a one-pot reaction from D-fructose by heating with acetylactone and ammonium carbonate in DMSO [76].

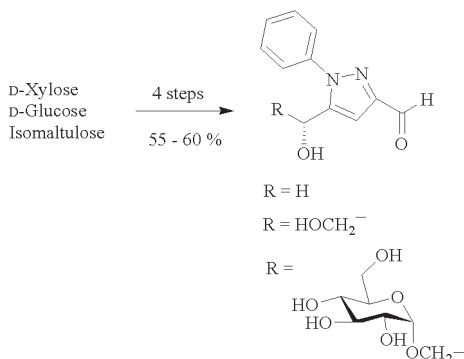


The hydroxylated side chain can, of course, be oxidatively shortened to give a variety of simple pyrrole building blocks, for example the carboxylic acid **40**, or cyclized to a furanoid ring (**39** \rightarrow **41**) [75], compounds that may be regarded as *C*-nucleosides.

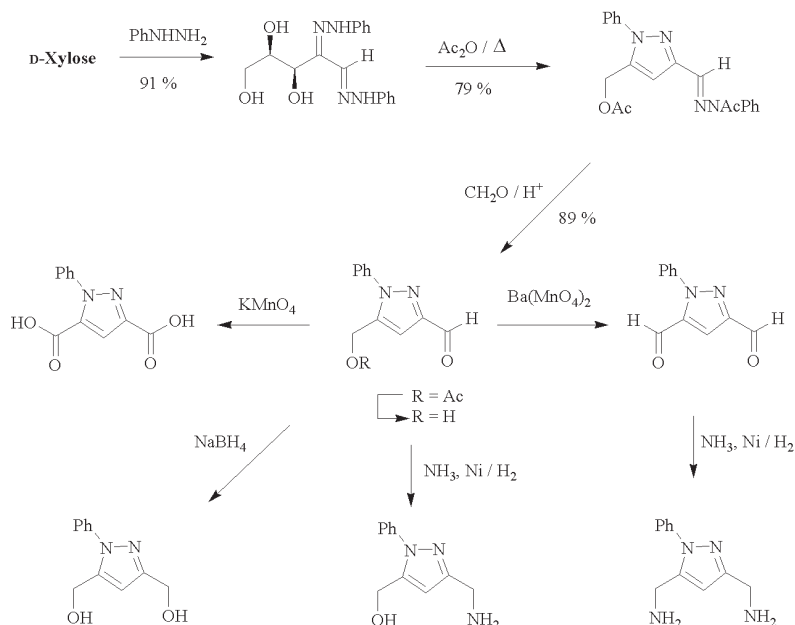
4.3.2. Pyrazoles

Expedient four-step approaches to 1-phenylpyrazole-3-carboxaldehydes with 5-

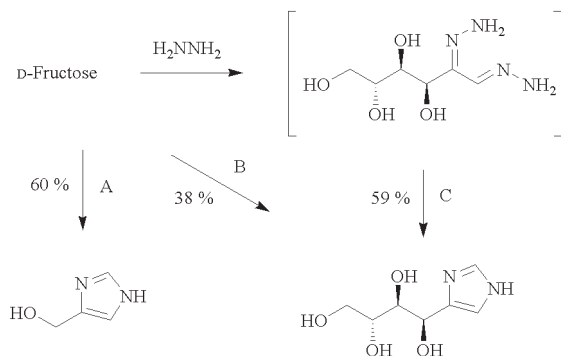
hydroxymethyl, 5-dihydroxyethyl, or 5-glucoxyloxymethyl substituents have been elaborated starting from *D*-xylose [77], *D*-glucose, and isomaltulose [78], respectively.



As illustrated for *D*-xylose, its osazone, formed almost quantitatively on reaction with phenylhydrazine, readily gives the pyrazole when added to acetic anhydride under reflux. Subsequent removal of the *N*-acetylphenylhydrazine residue with formaldehyde/acetic acid and de-*O*-acetylation provides a pyrazole aldehyde (57% overall yield from *D*-xylose), a versatile heterocyclic building block, useful for preparation of pharmaceuticals or monomers for the generation of polyamides and polyesters, e.g. the diamino and diol derivatives [77] (Scheme 10).



Scheme 10.



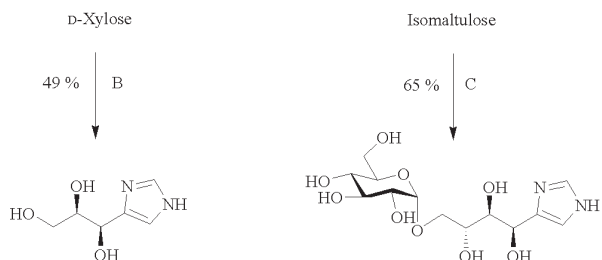
Scheme 11. Fructose-derived hydrophilic imidazoles
 A: CH_2O , aq. NH_3 , $\text{CuCO}_3/\text{Cu}(\text{OH})_2$, 2 h, 100°C [79]; B: formamidine ($\text{HOAc}/\text{liq. NH}_3$, 15 h, 75°C [80a]; C: $\text{N}_2\text{H}_4/\text{formamidine}$, HOAc , H_3BO_3 , 3 h reflux [80b]

4.3.3. Imidazoles

A variety of imidazoles carrying hydrophilic substituents in the 4-position are readily accessible in one-pot procedures from standard monosaccharides. Of those, the formation of 4-hydroxymethylimidazole by a Cu(II)-promoted reaction with formaldehyde and conc. Ammonia [79] is rather unique, because obviously retroaldolization to glyceraldehyde and dihydroxyacetone is involved (Scheme 11). The retroaldol fission can be partially suppressed, however, on heating D-fructose with formamidine acetate in liquid ammonia in a pressure vessel [80] or with

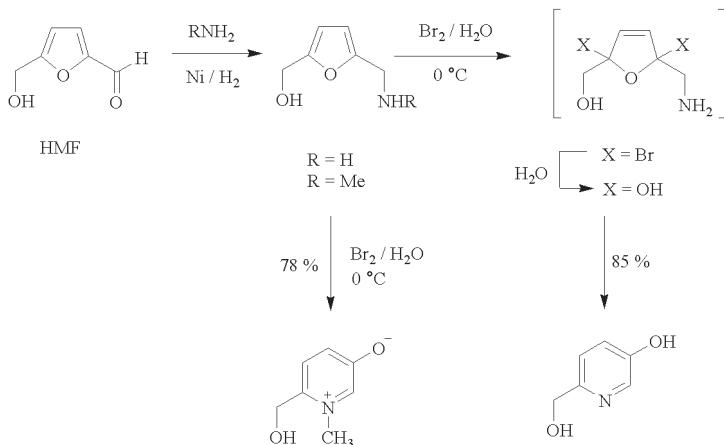
formamidine acetate in the presence of boric acid and hydrazine, obviously proceeding via a boric acid complex of the bis(hydrazone) of D-glucosone.

These conditions can be readily applied to pentoses or disaccharides with acceptable yields, as exemplified when using D-xylose [80a] and isomaltulose [80b] in one-pot procedures.



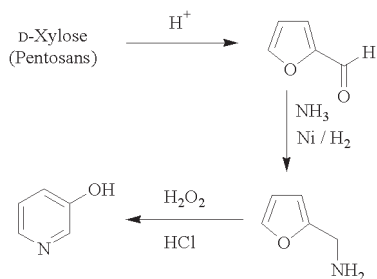
4.3.4. 3-Pyridinols

The conversion of pentosans or pentoses into 3-pyridinol can be effected in a practical three-step sequence, involving acid-induced dehydration to furfural, reductive amination to furfurylamine, and subsequent oxidation with hydrogen peroxide [81], the last step conceivably proceeding through the stage of a 2,5-dihydroxy-2,5-dihydrofurfurylamine, which



Scheme 12.

forms the pyridine nucleus by dehydration to a 5-aminopentenal intermediate and intramolecular aldimine formation. The pyridinol is a prominent intermediate chemical for the preparation of herbicides and insecticides [82], and cholinergic drugs of the pyridostigmine type.

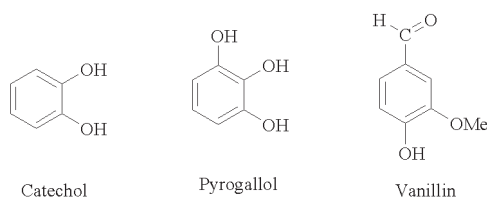


For the conversions of furfurylamines with readily oxidizable hydroxyl groups, e.g. those derived from fructose via HMF/bromine in water/methanol, the entire multistep process to the hydroxymethylpyridinol takes place in a one-pot procedure [83] (Scheme 12).

4.4. Toward Sugar-Based Aromatic Chemicals

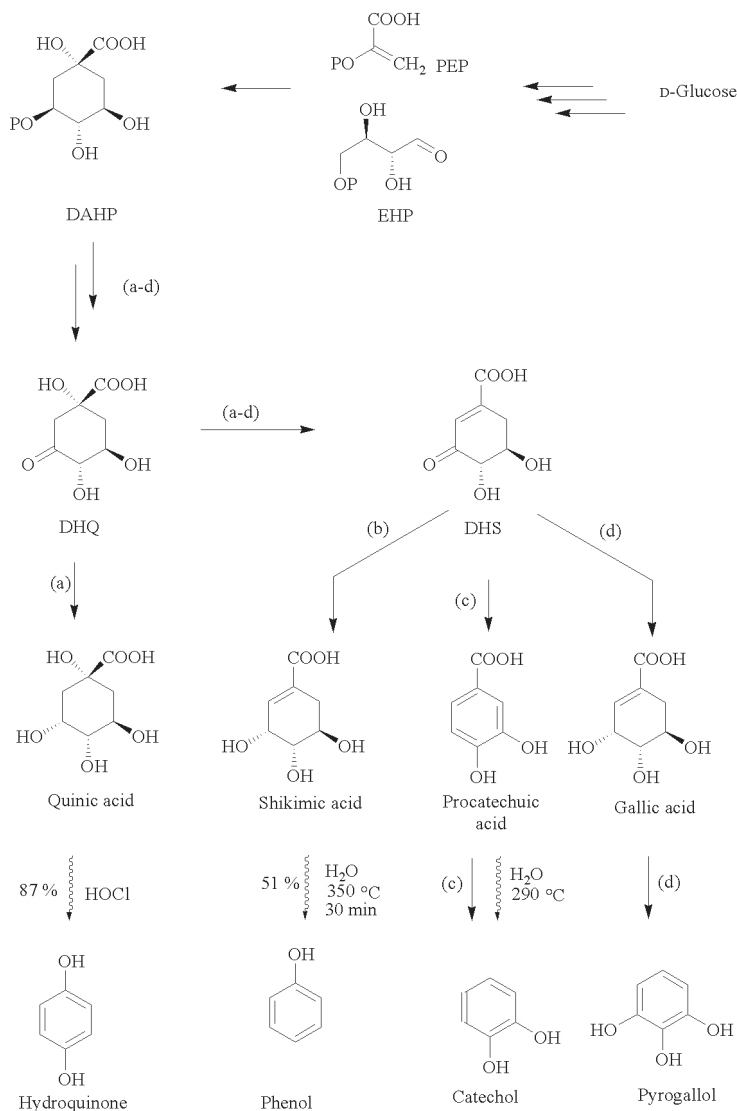
On the basis of a 1995 compilation [11], twenty of the 100 major organic chemicals in the US were aromatic compounds, invariably manufactured from fossil raw materials, mostly from the BTX (benzene–toluene–xylene) fraction derived from naphthas in the refineries. There are very few alternatives. The direct thermochemical conversion of biomass into an equivalent BTX product is not realistically feasible, because only small amounts of monocyclic aromatic hydrocarbons — phenols of the catechol and pyrogallol series — are formed on pyrolysis or thermal cracking of woody feedstocks. The same is true for exposure of simple sugars, for example D-xylose, D-glucose or D-fructose, to either basic or slightly acidic aqueous conditions at 100–160 °C [84]. Vanillin, however, is a byproduct of the manufacture of cellulose pulp by the action of alkali on calcium liginosulfonate and may be isolated in

yields of up to 25%.



An entirely different, highly-promising approach from sugars to industrially relevant aromatic compounds is based on microbial conversions along the shikimic acid pathway using genetically modified biocatalysts. By incorporation of the genomic portion encoding the synthesis of 3-dehydroquinic and 3-dehydroshikimic acid into *Escherichia coli* constructs, the carbon flow is channeled into the accumulation of large amounts of either quinic or shikimic acid [85] (Scheme 13); thus, rendering their availability independent of an often difficult isolation from plant sources. These improvements are likely to lead to pronounced expansion of the synthetic utilization of these enantiomerically pure carbocycles, not only in the pharmaceutical industry, where quinic acid already is already used as the starting material for the synthesis of the anti-influenza drug Tamiflu (oseltamir phosphate [86]), but for the production of bulk scale commodity chemicals such as hydroquinone [87] or phenol [88] by application of simple chemical transformations.

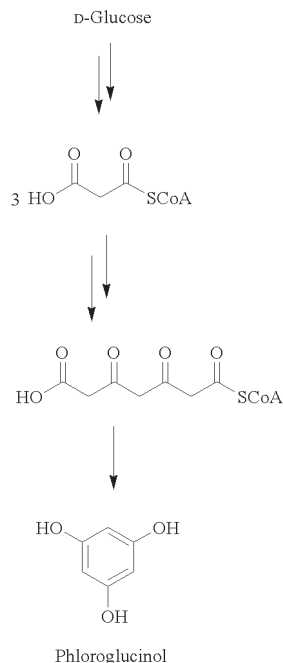
The powerful potential of metabolic engineering is similarly manifested in the *E. coli* biocatalyst-promoted conversion of D-glucose into protocatechuic acid, which can be readily decarboxylated to catechol [89]. This two-step process (see Scheme 13), feasible in a 24% overall yield, may replace the present process used to manufacture of this 25 000 t/a petrochemical commodity (→ Phenol Derivatives, Chap. 2). Of similar significance seems to be the genetically modified microbe-catalyzed conversion of D-glucose into gallic acid and pyrogallol [90]; the accessibility of these chemicals currently relies on their isolation from plant sources, despite a wide range of uses, particularly as starting materials for pharmaceuticals (→ Phenol Derivatives).



Scheme 13. Metabolic engineering of the shikimic acid pathway intermediates toward aromatic chemicals: → chemical transformations; → bioconversions with biocatalysts (a) *E. coli* QP1.1/pKD12.138 [85], (b) *E. coli* SP1.1PTS/pSC6.090B [85], (c) *E. coli* KL3/pWL2.46B [87], (d) *E. coli* KL7/pSK6.161 [88] Abbreviations: PEP = phosphoenolpyruvic acid, EHP = erythrose-4-phosphate, DAHP = 3-deoxy-D-arabinoheptulosonic acid 7-phosphate, DHQ = 3-dehydroquinic acid, DHS = 3-dehydroshikimic acid

The recent unraveling of the biosynthesis of phloroglucinol may also pave the way to its production from glucose. Thus, by expressing in *Escherichia coli* the *Pseudomonas fluorescens* enzyme (that assembles three molecules of malonyl coenzyme A into an activated

diketoheptanethioate) phloroglucinol can be generated from glucose in yields of up to 10 g/L. In this process the initially formed diketoheptanethioate subsequently undergoes cyclization and conceivably spontaneous aromatization into the trihydric phenol [91].



4.5. Microbial Conversion of Six-Carbon Sugars into Simple Carboxylic Acids and Alcohols

Major future development lines towards the economically viable generation of industrial chemicals from carbohydrates lie in the targeted

utilization of genetically engineered bioprocesses, most notably, those that involve the bioconversion of sugars into industrially relevant bioalcohols (other than ethanol) and into simple C₃–C₅-carboxylic acids other than those already exploited (i.e. lactic, citric and tartaric acids, and a variety of amino acids, see Table 1). Table 2 lists a variety of acids and alcohols that can be obtained by microbial production and substantial further activities in this field are to be expected.

However, which of these products are likely to enter industrial production will be determined by a variety of factors — demand, availability of a genetically engineered biocatalyst, and, not least, by economics, with rising oil prices increasingly providing more favorable conditions.

The products with significant industrial potential marked in bold in Table 2 are being briefly discussed below with respect to the current status of their microbial production and future prospects.

4.5.1. Carboxylic Acids

In 2004 the US Department of Energy (DOE) published a list of twelve sugar-derived chemicals worthy of industrial exploitation [93a–h],

Table 2. C₃–C₅ carboxylic acids and alcohols producible by microbial fermentation^a

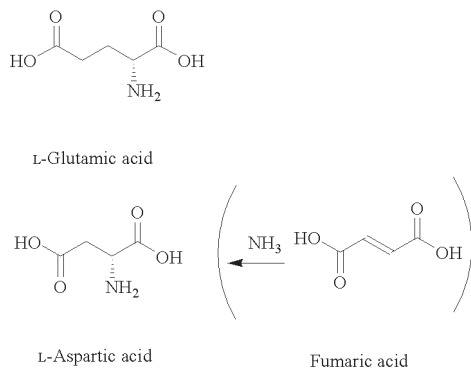
	Product ^b	Substrate	Microorganism
Acids	Propionic acid	various sugars	<i>Clostridium</i> sp. <i>Propionibacterium shermanii</i>
	Pyruvic acid	glucose	<i>Pseudomonas aeruginosa</i>
	3-Hydroxypropionic acid	glucose	<i>E. coli</i> constructs
	Butyric acid		<i>Clostridium butyricum</i>
	3-Hydroxybutyric acid	glucose	<i>Alcaligenes eutrophus</i>
	Succinic acid	various sugars	<i>Actinobacillus succinogenes</i> <i>Mannheimia succiniciproducens</i>
	Fumaric acid	various sugars	<i>Rhizopus nigricans</i> <i>Rhizopus arrhizus</i>
	L-Malic acid	various sugars	<i>Parcolobactrum</i> sp. <i>Brevibacterium</i> sp.
	Itaconic acid	various sugars	<i>Aspergillus terreus</i> <i>Aspergillus itaconicus</i>
2-Oxoglutaric acid	glucose	<i>Pseudomonas fluorescens</i>	
Alcohols	<i>n</i> -Propanol	glucose	<i>Clostridium fallax</i>
	Isopropanol	glucose	<i>Clostridium</i> sp.
	1,2-Propanediol	glucose	<i>E. coli</i> constructs
	1,3-Propanediol	glucose, glycerol	<i>Clostridium pasteurianum</i> <i>E. coli</i> mutants
	Glycerol	glucose	yeasts
	<i>n</i> -Butanol	various sugars	<i>Clostridium butylicum</i>
	2,3-Butanediol	glucose, xylose	<i>Klebsiella pneumoniae</i> <i>Bacillus polymyxa</i>
	1,2,4-Butanetriol	xylose (xylonic acid)	<i>E. coli</i> construct

^a Compiled from [92].

^b Acids already exploited industrially, i.e. lactic, tartaric and citric acid (cf. Table 1) are not listed here.

of which five are simple carboxylic acids accessible by biotransformations of sugars, mostly glucose:

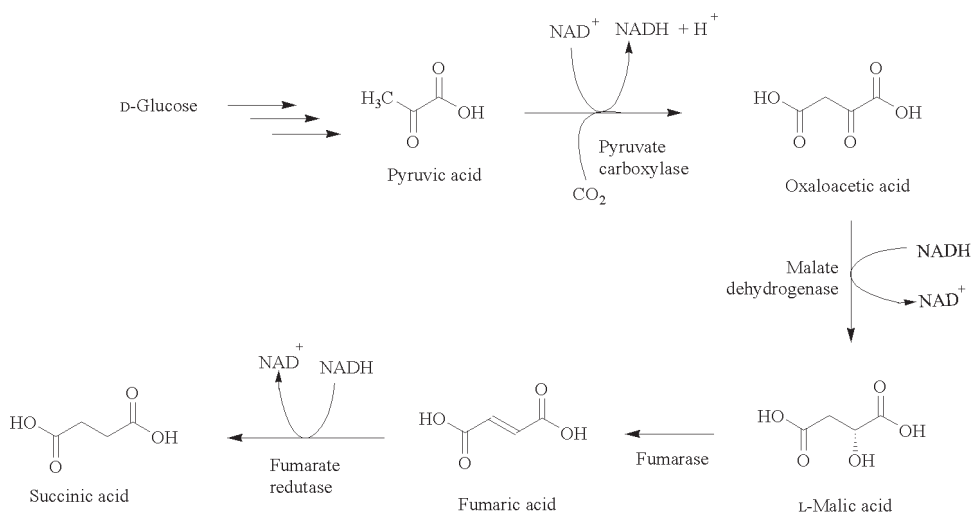
- 3-Hydroxypropionic acid (3-HPA)
- Four-carbon 1,4-diacids (malic, fumaric, succinic acids)
- Itaconic acid (IA)
- Aspartic acid (Asp)
- Glutamic acid (Glu)



Each of these are considered to have high “building block potential” either as monomers for the production of novel polyesters and polyamides [94] or as a starting material for a variety of commodity chemicals, currently produced

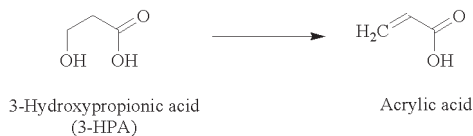
along petrochemical pathways. Accordingly, these five carboxylic acids are to become economically viable products if low-cost fermentation routes can be developed and implemented on an industrial level. Even for *glutamic acid* — for which several fermentation processes have been industrially realized to meet the need for its sodium salt as a flavor enhancer — the productivity of the organism and the final fermentation titer must be improved if it is to become an attractive candidate for chemical and microbial follow-up transformations [93a]. The same is true for *aspartic acid*, for which the tricarboxylic acid cycle of biocatalytic organisms can be engineered to overproduce oxaloacetate (cf. Scheme 14) to provide a product competitive with the (racemic) one obtained from petro-derived fumaric acid by amination [93b].

3-Hydroxypropionic acid (3-HPA) represents a three-carbon building block with the potential to become a key intermediate for a variety of high-volume chemicals, most notably acrylic acid, presently produced on a 3×10^6 t/a level by oxidation of propylene or 1,3-propanediol [93c]. Cargill and Novozymes are jointly developing a low-cost fermentation route from sugars by metabolic engineering of the microbial biocatalyst that produces 3-HPA under anaerobic conditions, yet the hurdles still to be overcome are significant, delaying the



Scheme 14. Glycolytic pathway leading to L-malic, fumaric, and succinic acids [95]

immediate introduction of this technology [96].



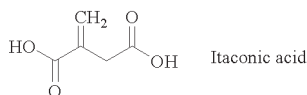
Fumaric acid is a metabolite of many fungi, lichens, mosses and some plants; it is mainly used as the diacid component in alkyd resins (\rightarrow Maleic and Fumaric Acids) and is produced commercially, to some extent, by the fermentation of glucose in *Rhizopus arrhizus* [97]. It seems, however, that improvements in productivity are essential before this approach can be considered an option for replacing the current petrochemical method that requires the catalytic isomerization of maleic acid.

Malic Acid. Most of the malic acid produced, approximately 10^3 t/a, is racemic, because it is derived from petrochemically produced fumaric acid. The L-form can also be produced from fumaric acid by hydration with immobilized cells of *Brevibacterium* or *Corynebacterium* species.

Succinic acid is used to produce food and pharmaceutical products, surfactants and detergents, biodegradable solvents and plastics, and ingredients to stimulate animal and plant growth. Although it is a common metabolite formed by plants, animals and microorganisms, its current commercial production of about 15×10^3 t/a is from petroleum; i.e. by hydrogenation of malic acid. The major technical hurdles for succinic acid as green, renewable bulk scale commodity chemical — 1,4-butanediol, THF, γ -butyrolactone or pyrrolidones are industrially relevant products — entail the development of very low-cost fermentation routes from sugar feedstocks. Currently available anaerobic fermentations of glucose include the use of an organism genetically cloned from *Aspergillus succinoproducens*, an engineered *E. coli* strain developed by DOE laboratories [93d], and several others [98]. The processes are currently under active development [99]. Production costs are to be at or below

\$ 0.25/lb to match those from fossil raw materials [93d].

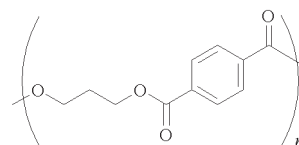
Itaconic acid (IA) is an α -substituted methacrylic acid; providing a C_5 building block with significant market opportunities. It is currently produced by fungal fermentation at approximately 10^3 t/a [100] and mainly used as a specialty comonomer in acrylic or methacrylic resins, as incorporation of small amounts of itaconic acid into polyacrylonitrile significantly improves its dyeability.



To become recognized as a commodity chemical, productivity improvements with the currently used fungi *Aspergillus terreus* and *Aspergillus itaconicus* are required. Progress seems to be encouraging [100]; however, to become competitive with analogous commodities the crucial production price of about \$ 0.25/lb has to be reached [93e] — a significant technical challenge yet to be solved.

4.5.2. Potential Sugar-Based Alcohol Commodities by Microbial Conversions

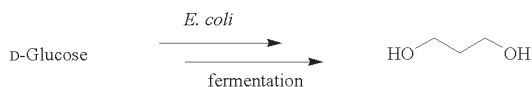
1,3-Propanediol and terephthalic acid, the dicarboxylic acid component of poly(trimethylene terephthalate)— a high performance polyester fiber with extensive applications in clothing textiles and carpeting — are currently manufactured from petrochemical raw materials by Shell (“Corterra”) and DuPont (“Sorona”) [101].



Poly(trimethylene terephthalate) (PTT)

For the diol portion of the polyester, 1,3-propanediol, however, biobased alternatives have been developed which rely on a microbial

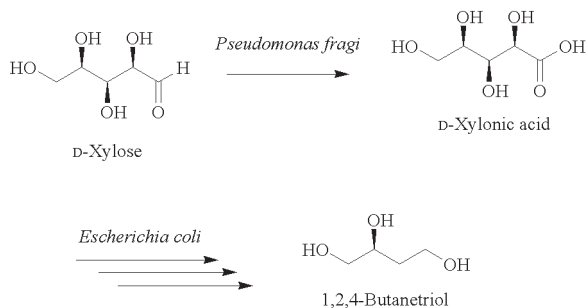
conversion of glycerol [102], a byproduct of biodiesel production, or of corn-derived glucose [103]. For the latter conversion, DuPont has developed a biocatalyst, engineered by incorporating genes from bakers' yeast and *Klebsiella pneumoniae* into *E. coli*, which efficiently converts corn-derived glucose into 1,3-propanediol [103]. The bioprocess is implemented on an industrial scale in a Tennessee manufacturing plant by a DuPont/Tate & Lyle joint venture ("BioPDO").



1,2-Propanediol, in its racemic form a petroleum-based high-volume-chemical with an annual production of over 5×10^5 t, is mostly used for the manufacture of unsaturated polyester resins, yet it also has excellent antifreeze properties. Enantiomerically pure (*R*)-1,2-propanediol accumulates along two different pathways via DAHP (cf. Scheme 13) or methylglyoxal, which is then reduced with either hydroxyacetone or lactaldehyde as the intermediates. Both routes have been examined for microbial production from glucose by means of genetically engineered biocatalysts, obtained either by expressing glycerol dehydrogenase genes or by overexpressing the methylglyoxal synthase gene in *E. coli* [104]. This work provides a basis for further strain and process improvements. Another approach entails inoculating silos containing chopped whole-crop maize with *Lactobacillus buchneri*. After storage for four months, yields of 50 g/kg were reported [105]; thus, prospects for elaborating an economically sound bioprocess look promising.

1,2,4-Butanetriol. Used as an intermediate chemical for alkyd resins and rocket fuels, 1,2,4-butanetriol is presently prepared commercially from malic acid by high-pressure hydrogenation or hydride reduction of its methyl ester. In a novel environmentally benign route to this chemical, wood-derived D-xylose is microbially oxidized to D-xylonic acid, followed

by a multistep conversion to the product by use of a biocatalyst specially engineered by inserting *Pseudomonas putida* plasmids into *E. coli* [106]. Although further metabolic engineering is required to increase product concentration and yields, microbial generation of 1,2,4-butanetriol is a clear alternative to its acquisition by chemical procedures.



4.6. Chemical Conversion of Sugars into Carboxylic Acids

The sugar-derived carboxylic acids listed in Table 1, i.e. gluconic, citric, lactic, tartaric, and ascorbic acids, are accessible in bulk by fermentation processes and may be considered (and used as) commodity chemicals despite being mostly used for food purposes. In addition to these compounds, however, there are several industrially attractive carboxylic acids obtainable from sugars by chemical means which have high potential as versatile building blocks.

In the 2004 DOE report [93], four of these sugar-derived carboxylic acids have already been singled out as suitable candidates for further development:

- Furan-2,5-dicarboxylic acid
- Glucaric acid
- Levulinic acid, and
- 3-Hydroxybutyrolactone

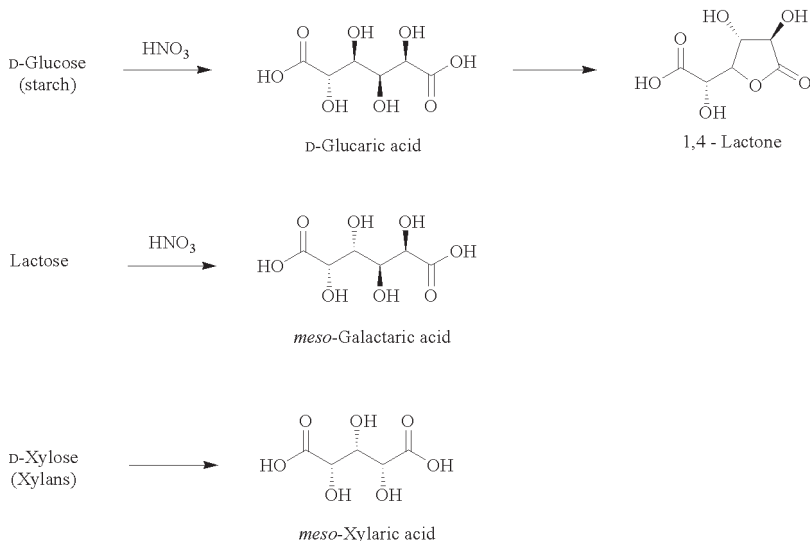
yet there are a many others that equally merit the development and implementation of low-cost preparative procedures to become competitive products. They are addressed briefly here.

Furan-2,5-Dicarboxylic Acid. The high industrial potential of furan-2,5-dicarboxylic acid (**19**) (cf. Scheme 5), has already been emphasized, because **19** could replace petroleum-derived diacids, such as adipic or terephthalic acid, in the production of polyesters and polyamides.

Aldaric Acids. The aldaric acids of the key hexoses and pentoses as highly hydrophilic diacids also have much potential in industrial use, similar to that of the sugar platform. The most important are D-glucaric acid, a direct nitric acid oxidation product of glucose or starch [107], usually isolated as its 1,4-lactone; galactaric and xylaric acid, accessible from lactose [108] and from D-xylose or hemicellulosic xylans. The technical barriers to their large-scale production are mainly development of efficient and selective oxidation technology for these sugars to eliminate the need for nitric acid as the oxidant. Investment in the Pt- or Au-catalyzed oxidation with oxygen appears to be a promising approach.

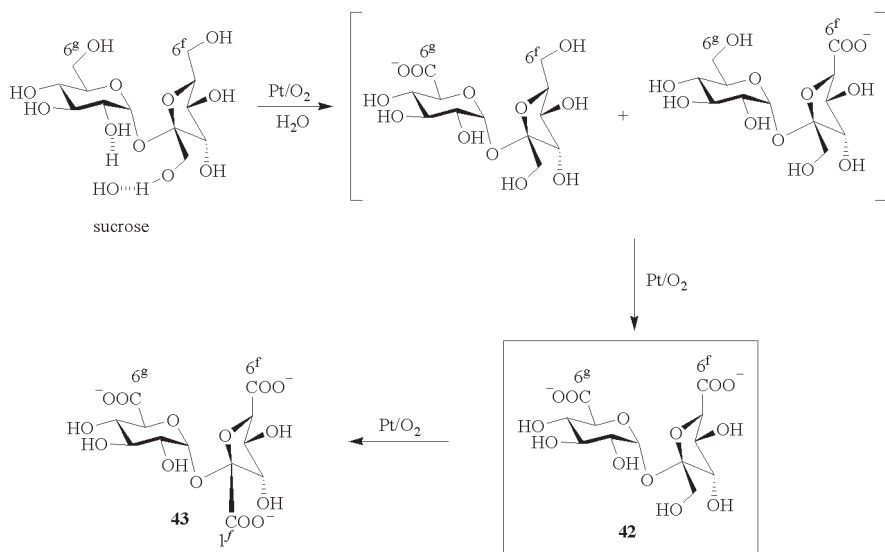
Through the persistence of an intersaccharidic water-bridge of the $2^g\text{-HO}\cdots\text{H}_2\text{O}\cdots\text{HO-1}^f$ type in aqueous solution [109], oxidation of sucrose with air in the presence of 0.5% Pt/C at 35 °C gives a 9:9:1 ratio of the 6^g -, 6^f - and 1^f -saccharonic acids [110] (Scheme 15). On further oxidation, particularly when using large amounts of the Pt catalyst and higher temperatures (80–100 °C), the formation of sucrose- $6^g,6^f$ -dicarboxylic acid **42** has been observed [111], yet a preparatively useful procedure for its acquisition was developed only end of the 1990s [112] by combining Pt/air-oxidation with continuous electro-dialytic removal of **42**, thereby protecting it from further oxidation. Otherwise, on letting the reaction proceed, the sucrose tricarboxylate **43** is obtained [113].

Levulinic acid (“LA”) and *formic acid* are end products of the acidic and thermal decomposition of lignocellulosic material, their multi-step formation from the hexoses contained therein proceeding through HMF as the key intermediate, the hemicellulosic part, mostly



Because sucrose is cheaper than its component sugars D-glucose and D-fructose, and available in large quantities (cf. Table 1) carboxylic acids resulting from selective oxidation of its primary hydroxyl groups are likely to be of even higher industrial relevance in the future.

xylans, furnishes furfural [26a, 26b]. A commercially viable fractionation technology for the specific, high-yield acquisition of LA has been developed (the “Biofine Process” [114]), rendering it an attractive option as an important biorefinery platform chemical [93g].

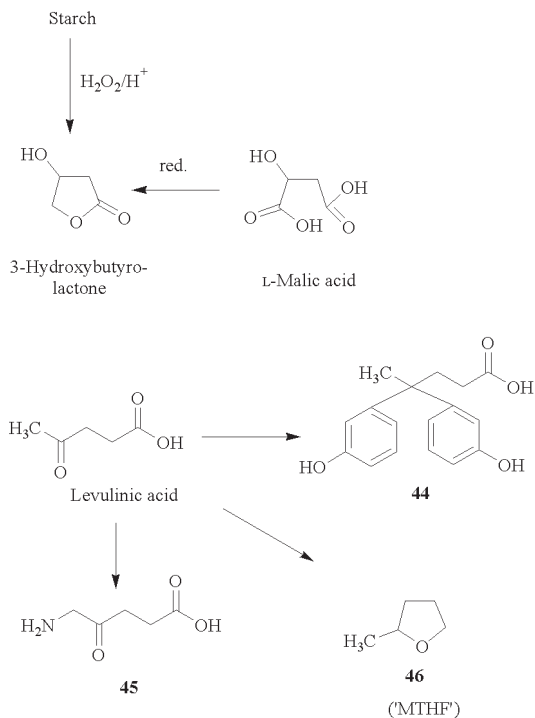


Scheme 15. Catalytic oxidation of sucrose [112, 113]

Levulinic acid is a starting material for a large number of higher-value products, because it can be converted by established procedures into products such as acrylic and succinic acids, pyrrolidines, and diphenolic acid (**44**), which has the potential of replacing bisphenol A in the manufacture of polycarbonate resins. Another derivative is 5-aminolevulinic acid (**45**), applied in agriculture as a herbicide and as a growth-promoting factor for plants. Another asset is that levulinic acid may be converted into 2-methyltetrahydrofuran (**46**), which is used as a liquid fuel extender (Scheme 16). The esters of LA, e.g., ethyl levulinate, have similar industrial potential as oxygenated additives to diesel fuels.

3-Hydroxybutyrolactone (3-HBL) is now a specialty chemical for fairly high-value pharmaceuticals. The 2004 DOE report [93h] places it in the list of the top twelve sugar-based candidates worthy of industrial exploitation. Its generation from starch by oxidative (H_2O_2) degradation is regarded as “messy”, because it involves multiple steps and results in a variety of side-products. Thus, this process must be improved, or alternatives found — one such alternative is reduction and cyclization of microbially produced L-malic acid (see Section Fumaric acid, Malic acid, Succinic acid) — to

fully utilize the potential of this four-carbon building block for the production of a variety of industrially important tetrahydrofuranoid derivatives.



Scheme 16.

4.7. Biopolymers from Polymerizable Sugar-Derivatives

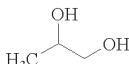

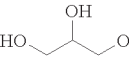
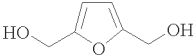
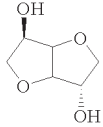
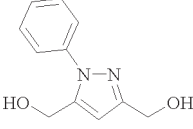
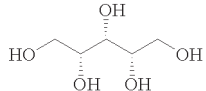
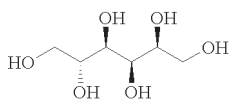
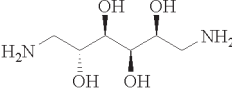
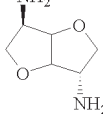
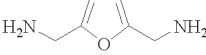
Today, biocompatibility and biodegradability are key functional requirements in the design of new polymeric materials, whether polyesters, polyamides, or polyurethanes (\rightarrow Polymers, Biodegradable). If composed of sugar-derived monomer components, such polymers are non-toxic and biodegradable and, hence, have minimal impact on waste management. They can be safely incinerated and, by composting, can be returned to the ecosystem harmlessly in a carbon dioxide-neutral process.

4.7.1. Synthetic Biopolyesters

The polyester production worldwide is estimated to be approximately 2×10^7 t/a, of which only a small fraction is based on renewable monomers, such as polyols, dicarboxylic acids, or hydroxyalkanoic acids, despite the fact that a huge variety of these building blocks are amenable to either chemical or biotechnological production. As amply illustrated by the large variety of sugar-derived di- and polyols, hydroxyacids, and dicarboxylic acids shown in Tables 3 and 4 — only those which are reasonably accessible are listed — the number of possible polyesters is immense, and not all conceivable combinations have been implemented and evaluated for their application profiles. The only one of industrial relevance today is Cargill's polylactic acid (PLA), used as a benign, biodegradable material for packaging, for disposable single use items, and for medical devices (vide supra). Nevertheless on the verge of becoming an industrial bioproduct is Du Ponts's poly(trimethylene terephthalate) — its high-performance fiber Sorona. In this case one of the raw materials, presently petroleum-derived 1,3-propanediol, is being replaced the same component obtained from glucose by microbial fermentation.

Of the vast number of polyesters prepared from the monomers listed in Tables 3 and 4, those containing furan residues have attracted particular interest [27, 29]. 5-Hydroxymethyl-2-furoic acid, for example, gave a mixture of linear (**47**) and cyclic products (**48**) on polycondensation [115, 116], whereas the 2-furoy-

Table 3. Sugar-based alcohols and diamines suitable as monomers for polyesters, polyamides, or polyurethanes

Compound		Derivation
	1,2-Propanediol	D-glucose
	1,3-Propanediol	D-glucose
	Glycerol	fats (D-glucose)
	2,5-Bis(hydroxymethyl)furan	D-fructose
	1,6-Dianhydro-D-sorbitol	D-glucose
	3,5-Bis(hydroxymethyl)pyrazole	D-xylose
	Xylitol	D-xylose
	D-Sorbitol	D-glucose
	1,6-Diamino-1,6-dideoxy-D-glucitol	D-glucose
	2,5-Diamino-1,4:3,6-dianhydrosorbitol	D-glucose
	2,5-Bis(aminomethyl)furan	D-fructose

lactic acid analogue afforded the polyester **49**; 2,5-furandicarboxylic acid has been polyesterified with a series of aliphatic diols (\rightarrow **50** [116]), with dianhydrosorbitol (\rightarrow **52** [117]), or with bisphenols (\rightarrow **53** [118]) (cf. Fig. 6). Even the all-furan polyester **54** has been

Table 4. Sugar-derived carboxylic acids for potential use as monomers for polyesters and polyamides

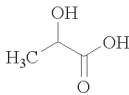
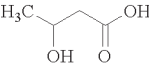
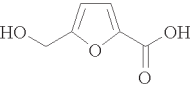
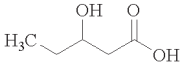
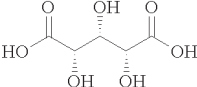
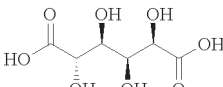
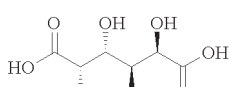
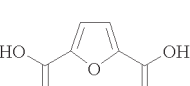
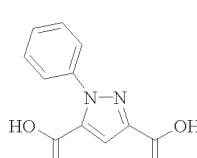
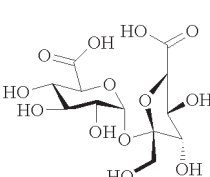
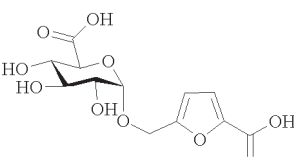
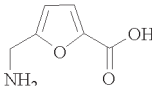
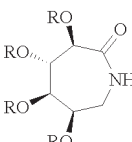
Compound	Derivation	
	Lactic acid	D-glucose
	3-Hydroxybutyric acid	D-glucose
	5-Hydroxymethylfuroic acid	D-fructose
	3-Hydroxyvaleric acid	D-glucose
	D-Xylaric acid	D-xylose
	D-Glucaric acid	D-glucose
	D-Galactaric acid	lactose
	Furan-2,5-dicarboxylic acid	D-fructose
	Pyrazole-3,5-dicarboxylic acid	D-xylose
	Sucrose-6,6'-dicarboxylic acid	sucrose
	GMF-6,6'-dicarboxylic acid	isomaltulose (sucrose)

Table 4. (Continued)

Compound	Derivation	
	5-Amino-methylfuroic acid	D-fructose
	6-Amino-D-gluconic acid lactam (R = H, CH ₃)	D-glucose

successfully prepared from its respective monomeric components [27] — like polyesters **47–50**, **52** and **54**, a “fully green”, naturally resourced product. The same applies to polyester **51**, composed of 1,3-propanediol and the furan-2,5-diacid. This polyester is in fact an analogue of Du Pont’s Sorona wherein the terephthalic acid portion is replaced by a bio-counterpart. Given the same fiber properties it would rightfully deserve the “clothing from a cornfield” attribute.

Despite the versatile application profiles of these polyesters — and a vast number of others that have been synthesized — they have been prepared only on the laboratory scale and used in experimental applications and so currently are “academic curiosities”. They will remain so, however, only as long as the economics are in favor of the production of the monomeric components from fossil raw materials — a situation that will change within the near future [5].

4.7.2. Microbial Polyesters

Microbial polyesters, or PHA for poly(hydroxyalkanoates) [119, 120], constitute a large and versatile family of polyesters produced by various bacteria in which they are deposited within the bacterial cell wall as a storage polymer. Industrial processes have been developed that deliver poly(3-hydroxybutyrate) [poly(3HB)] and a polymer consisting of 3-hydroxybutyric and 3-hydroxyvaleric acid [poly(3HB)-*co*-3(HV), trade name Biopol]. Both polyesters have outstanding properties in respect to thermoplastic behavior, biocompatibility, and

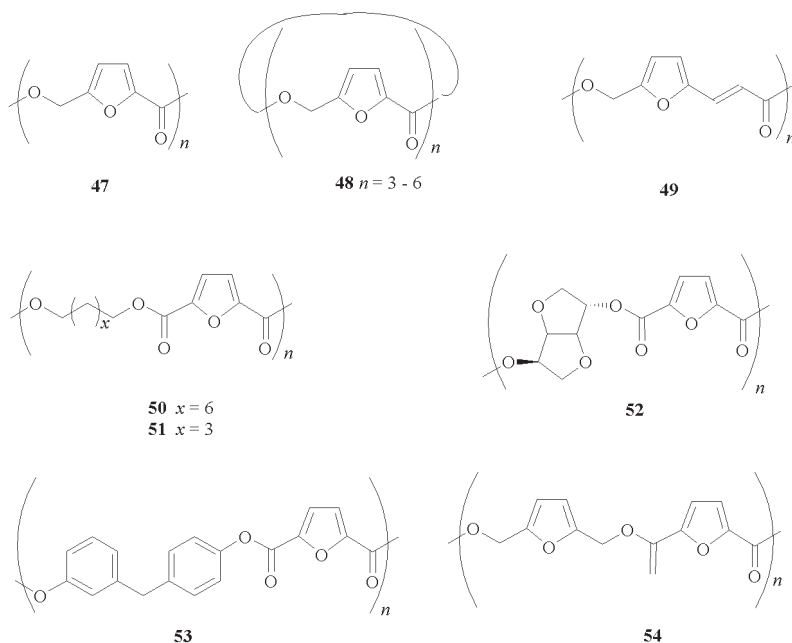
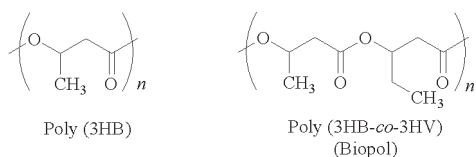


Figure 6. Polyesters containing furan moieties

biodegradability, and hence have wide applications in cosmetics, hygiene and agricultural materials, in drug delivery systems, and in medical surgery.

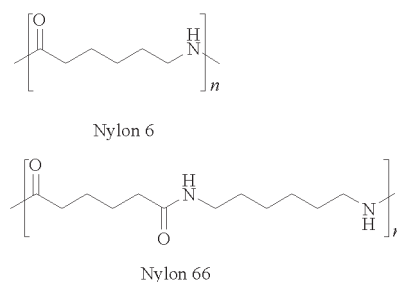


Other representative PHA's synthesized by microorganisms contain 3-hydroxyhexanoic, 3-hydroxyoctanoic and malic acid as repeating units. It is to be expected that improvement of fermentation strategies, e.g. by recombinant *E. coli* harboring the microbial PHA biosynthesis genes, will enhance the economic viability of PHA production, currently on an approximate 3×10^3 t/a level, as they have the potential to replace numerous chemosynthetic polymers in many applications.

4.7.3. Polyamides

More than 90% of the polyamides produced worldwide, amounting to approximately

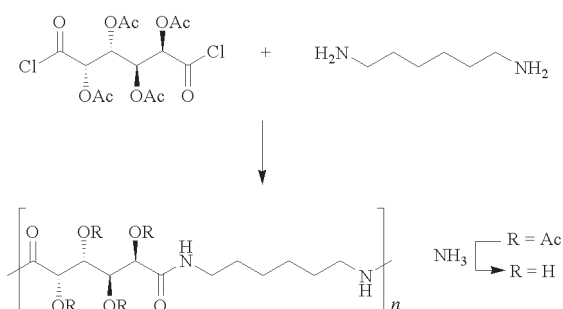
5.8×10^3 t in 1998 [121], are based on six-carbon monomers, i.e. caprolactam (Nylon 6), and adipic acid/hexamethylenediamine (Nylon 66), the manufacture of which is based exclusively in petroleum-based pathways [121].



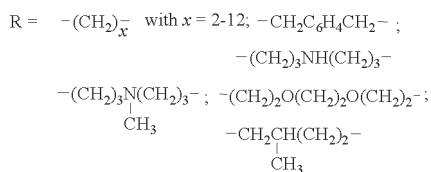
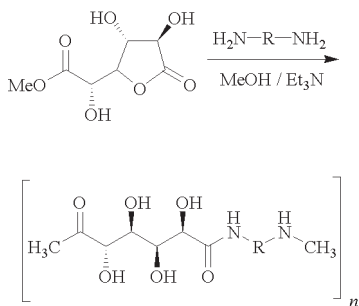
When considering the large variety of aminocarboxylic acids, dicarboxylic acids and diamines reasonably accessible from the common six-carbon sugars [122, 123] — expedient examples are listed in Tables 3 and 4 — substitution of the petroleum-based monomers of these polyamides by those derived from sugars seems particularly obvious and promising. Of the myriad of possible combinations of these sugar-derived monomers either with themselves or with the common, petrochemically-derived diamines and dicarboxylic acids, an immense

number have been realized. Here, only a few of these polyamides are covered as examples.

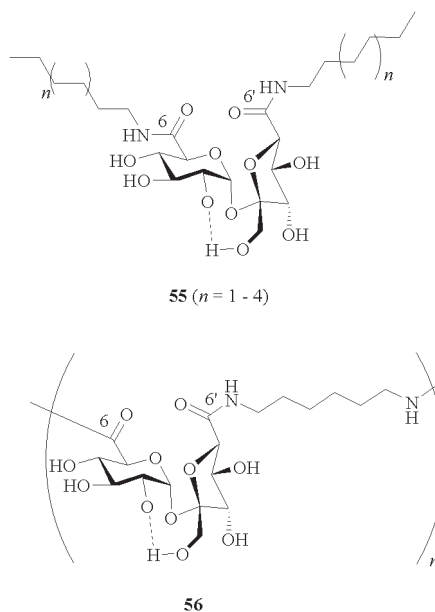
Solution or interfacial polycondensation of galactaric acid dichloride in its acetylated form with a variety of aliphatic and aromatic diamines yield a series of polyamides [124], that resulting from 1,6-diaminohexane, resembles a Nylon 6,6 in which half of the methylene hydrogen atoms of the usual adipic acid are substituted by acetoxy groups ($R = \text{Ac}$). These groups can be deacylated with aqueous ammonia to give the tetrahydroxylated Nylon 66.



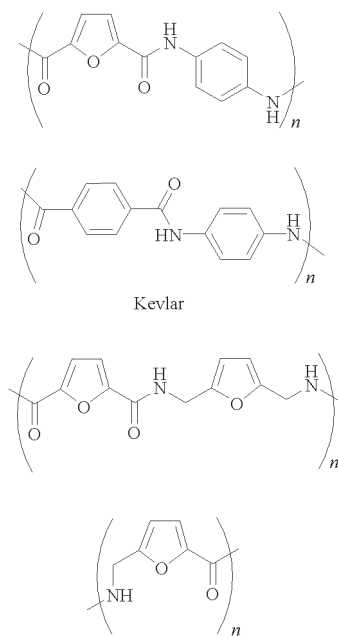
Use of the lactone monomethyl ester of D-glucaric acid proves advantageous in the generation of stereoregular polyglucaramides, leading to an impressive array of aliphatic and aromatic diamines [124].



Of similar practical utility is sucrose-6,6'-dicarboxylic acid (**42**), readily obtained from sucrose by Pt-catalyzed oxidation with oxygen in aqueous medium (cf. Scheme 15), which on amidation of its dimethyl ester with fat amines provides surface-active diamines of type **55** with remarkable tensidometric properties, whereas a reaction with hexamethylenediamine furnishes the interesting, highly hydrophilic polyamide **56** [125]



Sugar-based “quasi-aromatic” monomers for polyamides, i.e. the furan-2,5-dicarboxylic acid, seem particularly relevant because they have the potential to replace petrochemically derived terephthalic or isophthalic acid in current industrial products. The furan-1,6-diamine has similar potential as a substitute for *p*-phenylenediamine. Indeed, a series of such furan polyamides has been prepared [126] using the dicarboxylic acid and aliphatic and aromatic diamines. Of these, the polyamide resulting from condensation with hexamethylenediamine, which de facto is an analog of the commercially introduced Kevlar, has particularly promising decomposition and glass temperature properties [127] distinctly better than those of the all-furan polyamides:



Despite the impressive array of highly useful products — their application profiles compare favorably with those of well-known commercial polyamides — none of these sugar-derived polyamides is currently produced on an industrial scale; the reasons are purely economic, because the products derived from fossil raw material sources are still cheaper, on average by a factor of five. Eventually, however, with the end of cheap oil in sight [5], and the pressure on our environment increasing, this untoward situation for products from carbohydrate feedstocks will change.

5. Outlook

The unusually diverse stock of readily accessible products described within this account, which covers a wide range of industrial application profiles, lies mostly unexploited — mainly for economic reasons, because equivalent products based on petrochemical raw materials are distinctly cheaper. Notwithstanding this fact, a basic change in the current situation is clearly foreseeable. As the depletion of our fossil raw materials progresses, chemical

products derived from them will inevitably increase in price, such that biobased products will become competitive. Realistic estimates [5–7] expect this to occur by 2040.

In the meantime, it is imperative that carbohydrates are systematically further exploited leading toward efficient, environmentally benign, and economical process methods for their large-scale conversion into industrially viable products, whether bulk, intermediate, or fine chemicals, pharmaceuticals, or polymeric. General conceptual formulations toward this goal are available [2, 3, 128], yet their straightforward implementation is exceedingly slow. To enhance this, it is essential that national and supranational funding institutions — in Europe the corresponding EU bodies — recognize this. Thus, any promising, innovative research project, irrespective of involving mission-oriented, applied investigations or non-predefined basic explorations, should receive generous support either by funding institutions or by the chemical industry and/or both. Economically sound biobased alternatives to petrochemicals — various potential examples are contained in this account — will then become available as a matter of course.

References

- 1 C. Okkerse, H. van Bekkum: "From Fossil to Green", *Green Chem.* **1999**, 107–114.
- 2 *The Roadmap for Biomass Technologies in the U.S.*, Biomass R&D Technical Advisory Committee, US Department of Energy, Accession No. ADA 436527, 2002.
- 3 R.D. Perlack, L.L. Wright, A. Turhollow, R.L. Graham, B. Stokes, D.C. Erblich: *Biomass as Feedstock for a Bioenergy and Bioproducts Industry: The Technical Feasibility of a Billion-Ton Annual Supply*, Report No. DOE//GO-102995-2135; Oak Ridge National Laboratory, Oak Ridge, TN, 2005. Available electronically at <http://www.osti.gov/bridge>.
- 4 W. Umbach, in H. Eierdanz (ed.): *Perspektiven Nachwachsender Rohstoffe in der Chemie*, VCH Publ., Weinheim 1996, pp. IXXX–XLI.
- 5 (a) C.J. Campbell, J.H. Laherrère: "The End of Cheap Oil", *Sci. Am.* **3** (1998) 60–65. (b) J. Attarian: "The Coming End of Cheap Oil: Hubbert's Peak and Beyond", *The Social Contracts* **12** (2002) 276–286. (c) C. J. Campbell: "Industry Urged to Watch for Regular Oil Production Peaks, Depletion Signals", *Oil & Gas J.* **101** (2003) 38–45.
- 6 D.H. Klass: "Fossil Fuel Reserves and Depletion", *Biomass for Renewable Energy, Fuels, and Chemicals*, Acad. Press, San Diego 1998; pp. 10–19.
- 7 R.H. Hirsch, R. Bezdek, R. Wendling: "Peaking of World Oil Production: Impacts, Mitigation, and Risk Management", US

- National Energy Technology Laboratory Report, Febr. 2005, 91 pp; <http://www.oilcrisis.com/US/NETL/OilPeaking.pdf>.
- 8 A. Hugill: *Sugar and All That—A History of Tate & Lyle*, Introductory Dedicational Metaphor, Entry Books, London 1978.
 - 9 UN Food & Agriculture Organization: World Sugar Production, 2007/08. http://www.fao.org/es/esc/en/20953/21032/highlight_25853en.html (accessed 15 October 2009).
 - 10 (<http://www.eridex.com/html> (accessed 1 October 2009). <http://www.micchem.com/products/Erythritol.htm> (accessed 1 October 2009). P. De Cock, C.-L. Bechert: "Erythritol in Non-caloric Functional Beverages", *Pure Appl. Chem.* **74** (2002) 1281–1289.
 - 11 D.L. Klass: "Organic Commodity Chemicals from Biomass", [6], pp. 495–546.
 - 12 F. W. Lichtenthaler (ed.): *Carbohydrates as Organic Raw Materials*, vol. I, VCH Publ., Weinheim 1991, p. 365; G. Descotes (ed.): vol. II, VCH Publ., Weinheim 1993, p. 278; H. van Bekkum, H. Röper, A.G.J. Voragen (eds.): vol. III, VCH Publ., Weinheim 1996, p. 358; W. Praznik (ed.): vol. IV, Wiener Univ. Verlag, Vienna 1998, p. 292.
 - 13 F.W. Lichtenthaler, S. Mondel: "Perspectives in the Use of Low-molecular-weight Carbohydrates as Organic Raw Materials", *Pure Appl. Chem.* **69** (1997) 1853–1866.
 - 14 F.W. Lichtenthaler: "Towards Improving the Utility of Ketoses as Organic Raw Materials", *Carbohydr. Res.* **313** (1998) 69–89.
 - 15 J.J. Bozell (ed.): "Chemicals and Materials from Renewable Resources", *ACS Symposium Series* **784** (2001) 226.
 - 16 F.W. Lichtenthaler: "Unsaturated *O*- and *N*-Heterocycles from Carbohydrate Feedstocks", *Acc. Chem. Res.* **35** (2002) 728–737.
 - 17 F.W. Lichtenthaler, in Z.J. Witeczak, K. Tatsuta (eds.): "Carbohydrate Synthons in Natural Product Chemistry", *ACS Symposium Series*, **841** (2003) 47–83.
 - 18 F.W. Lichtenthaler, S. Peters: "Carbohydrates as Green Raw Materials for the Chemical Industry", *Comptes Rendue Chimie*, **7** (2004) 65–90.
 - 19 J.J. Bozell, M.K. Patel (eds.): *Feedstocks for the Future: Renewables for the Production of Chemicals and Materials*, Oxford University Press, New York 2006.
 - 20 A. Corma, S. Iborra, A. Velty: "Chemical Routes for the Transformation of Biomass into Chemicals", *Chem. Rev.* **107** (2007) 2411–2502.
 - 21 F.O. Licht: "2008 World Fuel Ethanol Production". Renewable Fuels Association. <http://www.ethanolrfa.org/industry/statistics/#E>. (accessed 1 October 2009).
 - 22 M.E. Himmel, W.A. Adney, J.O. Baker, R. Elander, J.D. McMillan, R.A. Nieves, J.J. Sheehan, S.R. Thomas, T.B. Vinzant, M. Zhang: "Advanced Bioethanol Production Technologies", in B.C. Saha, J. Woodward (eds.): "Fuels and Chemicals from Biomass", *ACS Symposium Series* **666** (1997) 2–45.
 - 23 H.G. Lawford, J.D. Rousseau: "Cellulosic Fuel Ethanol—Alternative Fermentation Process Design with Wild-type and Recombinant *Zymomonas mobilis*", *Appl. Biochem. Biotechnol.* **105** (2003) 457–469.
 - 24 J.A. Matthews: "Is Growing Biofuel Crops a Crime against Humanity?", *Biofuels, Biocrops and Biorefining* **2** (2008) 97–99. J. A. Matthews, H. Tan: "Biofuels and Indirect Land Use Change Effects: The Debate Continues", *Biofuels, Bioproducts, and Biorefining* **3** (2009) 305–317.
 - 25 N. Qureshi, T.C. Ezeji: "Butanol, a Superior Biofuel Production from Agricultural Residues", *Biofuels, Biocrops, and Biorefining* **2** (2008) 319–330.
 - 26 (a) A.S. Mamman, J.-M. Lee, Y.-C. Kim, I.T. Hwang, N.-J. Park, Y.K. Hwang, J.-S. Chang, J.-S. Hwang: "Furfural: Hemicellulose/xylose-derived Biochemical", *Biofuels, Bioproducts, Biorefineries* **2** (2008) 438–454. (b) K.J. Zeitsch: *The Chemistry and Technology of Furfural and its many Byproducts*, Elsevier, Amsterdam 2000, p. 374.
 - 27 A. Gandini, M.N. Belgacem: "Furans in Polymer Chemistry", *Prog. Polym. Sci.* **22** (1997) 1203–1379.
 - 28 M.S. Hoflinger, A.H. Conner, D.R. Holm, C.G. Gill, Jr.: "Difurfuryl Diamines by the Acidic Condensation of Furfurylamine with Aldehydes", *J. Org. Chem.* **60** (1995) 1595–1598.
 - 29 C. Moreau, M.N. Belgacem, A. Gandini: "Substituted Furans from Carbohydrates and Ensuing Polymers", *Topics in Catalysis* **27** (2004) 11–30.
 - 30 P. Gruber, D.E. Henton, J. Starr: "Polylactic Acid from Renewable Resources", in *Biorefineries—Industrial Processes and Products*, vol. 2, Wiley-VCH, Weinheim 2006, pp. 381–407.
 - 31 <http://www.natureworkslc.com> (accessed 30 September 2009).
 - 32 M. McCoy: "Seeking Biomaterials", *Chem. Eng. News* **81** (2003) no. 8, 18; **81** (2003) no. 45, 17–18. S.K. Ritter: "Green Chemistry Progress Report", *Chem. Eng. News* **80** (2002) no. 47, 20.
 - 33 <http://www.vertecbiosolvents.com/> (accessed 15 October 2009).
 - 34 W. von Rybinski, K. Hill: "Alkyl Polyglycosides—Properties and Applications of a New Class of Surfactants", *Angew. Chem.* **110** (1998) 1394–1412; *Angew. Chem. Int. Ed.* **37** (1998) 1328–1345.
 - 35 K.-H. Hill, O. Rhode: "Sugar-based Surfactants for Consumer Products and Technical Applications", *Fett/Lipid* **101** (1999) 27–33.
 - 36 P. Jürgens, A. Turowski: "Vergleichende Untersuchung von Zuckerestem, *N*-Methylglucamiden und Glycosiden am Beispiel von Reinigungsprodukten", in *Perspektiven Nachwachsender Rohstoffe in der Chemie*, VCH, Weinheim 1996, pp. 61–70.
 - 37 N.B. Desai: "Esters of Sucrose and Glucose as Cosmetic Materials", *Cosmetics & Toiletries* **105** (1990) 109–107. Mitsubishi-Kagaku Foods Corp.: "Sugar Esters"; <http://www.mfc.co.jp/english/whatsse.htm> (accessed 20 February 2010).
 - 38 L.A. Silviri, N.J. DeAngelis: "Isosorbide Dinitrate", *Anal. Profiles Drug Subs.* **4** (1975) 225–244.
 - 39 B.E. Maryanoff, S.O. Nortey, J.F. Gardocki, R.P. Shank, S.P. Dodgson: "Anticonvulsant Sulfamates. 2,3:4,5-Di-*O*-isopropylidene- β -D-fructopyranose Sulfamate. *J. Med. Chem.* **30** (1987) 880–887.
 - 40 For pertinent reviews, see: J.N. Chheda, Y. Roman-Leshkov, J. A. Dumesic: "Production of 5-Hydroxymethylfurfural and Furfural by Dehydration of Biomass-derived Mono- and Polysaccharides", *Green Chemistry* **9** (2007) 342–350. J. Lewkowski: "Synthesis, Chemistry and Applications of 5-Hydroxymethylfurfural and its Derivatives", *ARKIVOC* (2001) 17–54. B.F.M. Kuster: "Manufacture of 5-Hydroxymethylfurfural", *Starch/Stärke* **42** (1990) 314–321.
 - 41 H. Schiweck, M. Munir, K. Rapp, M. Voge: "New Developments in the Use of Sucrose as an Industrial Bulk Chemical", in F. W. Lichtenthaler (ed.): *Carbohydrates as Organic Raw Materials*, VCH, Weinheim 1991, pp. 57–94; *Zuckerind. (Berlin)* **115** (1990) 555–565.
 - 42 H. Koch, J. Pein: "Condensations between 5-Hydroxymethylfurfural, Phenol, and Formaldehyde", *Polym. Bull. (Berlin)* **13** (1985) 525–532; *Starch/Stärke* **35** (1983) 304–313.

- 43 T. El Haj, A. Masroua, J.C. Martin, G. Descotes: "5-Hydroxymethylfurfural and Derivatives by Acid Treatment of Sugars on Ion-exchange Resins", *Bull. Soc. Chim. Fr.* **1987**, 855–860.
- 44 Y. Roman-Leshkov, C.J. Barret, Z.Y. Liu, J.A. Dumesic: "Production of Dimethylfuran for Liquid Fuels from Biomass-derived Carbohydrates", *Nature* **447** (2007) 982–985.
- 45 N. Schiavo, G. Descotes, J. Mentech: "Catalytic Hydrogenation of 5-Hydroxymethylfurfural in aqueous Medium", *Bull. Chem. Soc. Chim. Fr.* **128** (1991) 704–711.
- 46 N. Elming, N. Clauson-Kaas: "6-Methyl-3-pyridinol from 2-Hydroxymethyl-5-aminomethylfuran", *Acta Chem. Scand.* **10** (1956) 1603–1605.
- 47 Hoechst AG: "Catalytic Oxidation of 5-Hydroxymethylfurfural", DE 3826073, 1988 (E.I. Leupold, M. Wiesner, M. Schlingmann, K. Rapp). M.L. Ribeiro, U. Schuchardt: "Cooperative Effect of Cobalt Acetylacetonate and Silica in the Catalytic Cyclization and Oxidation of Fructose to 2,5-Furandicarboxylic acid", *Catalysis Commun.* **4** (2003) 83–86. O. Casanova, S. Iborra, A. Corma: "One-pot, Base-free Oxidative Esterification of 2-Hydroxymethylfurfural into 2,5-Dimethylfuroate", *J. Catalysis* **265** (2009) 109–116.
- 48 J.B. Binder, R.T. Raines: "Simple Chemical Transformation of Lignocellulosic Biomass into Furans for Fuels and Chemicals", *J. Am. Chem. Soc.* **131** (2009) 1979–1985.
- 49 M. Mascal, E.B. Nikitin: "Direct, High-yield Conversion of Cellulose into Biofuel", *Angew. Chem. Int. Ed.* **47** (2008) 7924–7926.
- 50 F. García-González: "Reactions of Monosaccharides with β -Ketooesters", *Adv. Carbohydr. Chem.* **11** (1956) 97–143.
- 51 F. Rodrigues, Y. Canac, A. Lubineau: "A Convenient, One-step Synthesis of β -C-Glycosidic Ketones in Aqueous Media", *Chem. Commun.* **2000**, 2049–2050. I. Riemann, M.A. Papadopoulos, M. Knorst, W.-D. Fessner: "C-Glycosides by Aqueous Condensation of β -Dicarbonyl Compounds with Unprotected Sugars", *Aust. J. Chem.* **55** (2002) 147–154.
- 52 S. Peters, F.W. Lichtenthaler, H.J. Lindner: "A C-Fructosylpropanone Locked in a 2,7-Dioxabicyclo[3,2,1]octane Framework", *Tetrahedron: Asymmetry* **14** (2003) 2475–2479.
- 53 Y. Chapleur (ed.): *Carbohydrate Mimics*, Wiley-VCH, Weinheim, New York 1998, p. 604ff. and references cited therein.
- 54 A. Beélik: "Kojic Acid", *Adv. Carbohydr. Chem.* **11** (1956) 145–183.
- 55 F.W. Lichtenthaler: "Sugar Enolones and γ -Pyrone-Formation", *Pure Appl. Chem.* **50** (1978) 1343–1362.
- 56 F.W. Lichtenthaler: "Building Blocks from Sugars and their Use in Natural Product Synthesis", in R. Scheffold (ed.): *Modern Synthetic Methods*, vol. 6, VCH, Weinheim 1992, pp. 273–376.
- 57 C. Nelson, J. Gratzl: "Conversion of D-Glucono-1,5-lactone into an α -Pyrone", *Carbohydr. Res.* **60** (1978) 267–273.
- 58 K. Tajima: "Cyclopentenones from 3-Acetoxy-6-acetoxymethyl-2-pyrone", *Chem. Lett.* **1987**, 1319–1322.
- 59 For useful preparative procedures, see: *Methods Carbohydr. Chem.* **2** (1963) 318, 326, 405, 427.
- 60 F.W. Lichtenthaler: "Sugar-derived Building Blocks for the Synthesis of Non-carbohydrate Natural Products", in S. J. Witzak, K. Tatsuta (eds.): "Carbohydrate Synthons in Natural Product Chemistry", *ACS Symposium Series* **841** (2003) 47–83. S. Hanessian: *Total Synthesis of Natural Products: The Chiron Approach*, Pergamon, Oxford 1983.
- 61 R.J. Ferrier, N. Prasad: "Synthesis of 2,3-Dideoxy- α -D-erythro-hex-2-enopyranosides from Tri-O-acetyl-D-glucal", *J. Chem. Soc. C* **1969**, 570–575.
- 62 F.W. Lichtenthaler, S. Rönninger, P. Jarglis: "Expedient Approach to Pyranoid Ene and Enol Lactones", *Liebigs Ann.* **1989**, 1153–1161.
- 63 S. Hanessian, A.M. Faucher, S. Leger: "Total Synthesis of Meroquiene", *Tetrahedron* **46** (1990) 231–234. N. Ohyabu, T. Nishikawa, M. Isobe: "First Asymmetric Total Synthesis of Tetrodotoxin", *J. Am. Chem. Soc.* **125** (2003) 8798–8805.
- 64 S. Czernicki, K. Vijayakuraman, G. Ville: "Convenient Synthesis of Hex-1-enopyran-3-uloses: Selective Oxidation of Allylic Alcohols using Pyridinium Dichromate", *J. Org. Chem.* **51** (1986) 5472–5475.
- 65 B. Fraser-Reid, A. McLean, E.W. Usherwood, M. Yunker: "Synthesis and Properties of some Alkyl 2,3-Dideoxy-2-enopyranosid-4-uloses", *Can. J. Chem.* **48** (1970) 2877–2884.
- 66 R.J. Ferrier: "Modified Synthesis of 2-Hydroxyglycalesters", *Methods Carbohydr. Chem.* **6** (1972) 307–311.
- 67 F.W. Lichtenthaler, U. Kraska: "Preparation of Sugar Enolones", *Carbohydr. Res.* **58** (1977) 363–377.
- 68 F.W. Lichtenthaler, S. Nishiyama, T. Weimer: "2,3-Dihydro-pyranones with Contiguous Chiral Centers", *Liebigs Ann.* **1989**, 1163–1170.
- 69 F.W. Lichtenthaler, S. Ogawa, P. Heide: "Synthesis of Unsaturated Hexopyranosid-4-uloses", *Chem. Ber.* **110** (1977) 3324–3332.
- 70 J. Gravitis, N. Vedernikov, J. Zandersons, A. Kokorevics: "Furfural and Levoglucosan Production from Deciduous Wood and Agricultural Wastes", in J. J. Bozell (ed.): "Chemicals and Materials from Renewable Resources", *ACS Symposium Series* **784** (2001) 110–122. R.C. Brown, D. Radlein, J. Piskorz: "Pretreatment Processes to increase Pyrolytic Yield of Levoglucosan from Herbaceous Feedstocks", in J. J. Bozell (ed.): "Chemicals and Materials from Renewable Resources", *ACS Symposium Series* **784** (2001) 123–132. F. Shafizadeh, R. Furneaux, T. Stevenson: "Reactions of Levoglucosone", *Carbohydr. Res.* **71** (1979) 169–191.
- 71 Z. J. Witzak: "Synthesis of Natural Products from Levoglucosone", *Pure Appl. Chem.* **66** (1994) 2189–2192.
- 72 F. Ledl, E. Schleicher: "The Maillard Reaction in Foodstuffs and the Human Body", *Angew. Chem.* **102** (1990) 597–626; *Angew. Chem. Int. Ed.* **29** (1990) 565–594.
- 73 (a) H. El Khadem: "N-Heterocycles from Saccharide Derivatives", *Adv. Carbohydr. Chem.* **25** (1970) 351–405. (b) E.S.H. El Ashry, N. Rashad: "Carbohydrate Hydrazones and Osazones as Raw Materials for Nucleosides and N-Heterocycles", *Curr. Org. Chem.* **4** (2000) 609–657.
- 74 S.M. McElvain, K.M. Bolliger: "Pyrrole", *Org. Synth., Coll. Vol. 1* **1941**, 473–474.
- 75 F. García-González, A. Gómez Sánchez: "Reactions of Amino Sugars with β -Dicarbonyl Compounds", *Adv. Carbohydr. Chem.* **20** (1965) 303–355.
- 76 A. Rozanski, K. Bielawski, J. Boltryk, D. Bartulewicz: "Simple Synthesis of 3-Acetyl-5-(tetrahydroxybutyl)-2-methylpyrrole", *Akad. Med. Juliana Marchlewskiego Białymstoku* **1991**, 35–36, 57–63; *Chem. Abstr.* **118** (1992) 22471m.
- 77 V. Diehl, E. Cuny, F.W. Lichtenthaler: "Conversion of D-Xylose into Hydrophilically Functionalized Pyrazoles", *Heterocycles* **48** (1998) 1193–1201.
- 78 M. Oikawa, C. Müller, M. Kunz, F.W. Lichtenthaler: "Hydrophilic Pyrazoles from Sugars", *Carbohydr. Res.* **309** (1998) 269–279.
- 79 R. Weidenhagen, R. Hermann: "4-Hydroxymethylimidazole", *Ber. Dtsch. Chem. Ges.* **70** (1937) 570–583; *Org. Synth., Coll. Vol. III* **1955**, 460–462.

- 80 (a) J. Streith, A. Boiron, A. Frankowski, D. LeNouen, H. Rudyk, T. Tschamber: "One-pot Synthesis of Imidazolozugars", *Synthesis* **1995**, 944–946. (b) F.W. Lichtenthaler, A. Brust, TU Darmstadt, unpublished results.
- 81 Sadolin & Holmblad A/S: "Improvement in Preparing 3-Pyridinol", GB 862581, 1961 (N. Elming, S.V. Carlsten, B. Lennart, I. Ohlsson); *Chem. Abstr.* **56** (1962) 11574g.
- 82 Hoechst AG: "Heterocyclic Phenoxypyridines as Herbicidal Agents and Insecticides", EP 227045, 227046, 1987 (V. Koch, L. Willms, A. Fuss, K. Bauer, H. Bieringer, H. Buerstell); *Chem. Abstr.* **107** (1987) 175892, 134217.
- 83 C. Müller, V. Diehl, F.W. Lichtenthaler: "3-Pyridinol from Fructose and Isomaltulose", *Tetrahedron* **54** (1998) 10703–10712.
- 84 I. Forsskahl, T. Popoff, O. Theander: "Reactions of D-Xylose and D-Glucose in alkaline Aqueous Solutions", *Carbohydr. Res.* **48** (1976) 13–21. T. Popoff, O. Theander: "Formation of Aromatic Compounds from D-Glucose and D-Fructose in slightly Acidic Aqueous Solution", *Acta Chem. Scand.* **B30** (1976) 397–402.
- 85 K.M. Drahts, D.R. Knop, J.W. Frost: "Shikimic acid and Quinic acid: Replacing Isolation from Plant Sources with Recombinant Microbial Catalysis", *J. Am. Chem. Soc.* **121** (1999) 1603–1604.
- 86 J.C. Rolloff, K.M. Kent, M.J. Postich, M.W. Beeker, H.H. Chapman, D.E. Kelly, W. Lew, M.S. Louie, L.R. McGee, E. J. Priske, L.M. Schultze, R.H. Yu, L. Zhang: "Practical Total Synthesis of the Anti-influenza Drug GS-4104", *J. Org. Chem.* **63** (1998) 4545–4550.
- 87 N. Ran, D.R. Knop, K.M. Drahts, J.W. Frost: "Benzene-free Synthesis of Hydroquinone", *J. Am. Chem. Soc.* **123** (2001) 10927–10934.
- 88 J.M. Gibson, P.S. Thomas, J.D. Thomas, J.L. Barker, S.S. Chandran, M.K. Harrup, K.M. Drahts, J.W. Frost: "Benzene-free Synthesis of Phenol", *Angew. Chem. Int. Ed.* **40** (2001) 1945–1948.
- 89 K.M. Drahts, J.W. Frost: "Environmentally Compatible Synthesis of Catechol from D-Glucose", *J. Am. Chem. Soc.* **117** (1975) 2395–2400. W. Li, D. Xie, J.W. Frost: "Benzene-free Synthesis of Catechol: Interfacing Microbial and Chemical Synthesis", *J. Am. Chem. Soc.* **127** (2005) 2874–2882.
- 90 S. Kambourakis, K.M. Drahts, J.W. Frost: "Synthesis of Gallic Acid and Pyrogallol from Glucose: Replacing Natural Product Isolation with Microbial Catalysis", *J. Am. Chem. Soc.* **122** (2002) 9042–9043.
- 91 J. Achkar, M. Xian, H. Zhao, J.W. Frost: "Biosynthesis of Phloroglucinol", *J. Am. Chem. Soc.* **127** (2005) 5332–5333.
- 92 P. Präve, U. Faust, W. Sittig, D.A. Sukatsch (eds.): *Fundamentals of Biotechnology*, VCH, Weinheim 1987.
- 93 T. Werpy, G. Petersen (eds.): "Top Value Added Chemicals from Biomass vol 1—Results of Screening for Potential Candidates from Sugars and Synthesis Gas", Report No. NREL/TP-510-35523, National Renewable Energy Laboratory, Golden, CO, 2004, p. 67. Available electronically at <http://www.osti.gov/bridge>. (a) "Glutamic Acids", pp. 39–42; (b) "Aspartic Acid", pp. 31–35; (c) "3-Hydroxypropionic Acid (3-HPA)", pp. 29–31; (d) "Four-carbon 1,4-Diacids", pp. 22–25; (e) "Itaconic Acid", pp. 42–44; (f) "Glucaric Acid", pp. 36–38; (g) "Levulinic Acid", pp. 45–48; (h) "3-Hydroxybutyrolactone", pp. 49–51.
- 94 S.Y. Lee, S.H. Park, S.H. Hong, Y. Lee, S.H. Lee: "Fermentative Production of Building Blocks for Chemical Synthesis of Polyesters", *Biopolymers*, Wiley-VCH, Weinheim 2001, vol. **3b**, chap. 10, p. 265ff.
- 95 For pertinent reviews, see: (a) S.Y. Lee, S.H. Hong, S.H. Lee, S. J. Park: "Fermentative Production of Chemicals that can be used for Polymer Synthesis", *Macromol. Biosci.* **4** (2004) 157–164. G.T. Tsao, N.J. Cao, J. Du, C.S. Gong: "Production of Multifunctional Organic Acids from Renewable Resources", *Adv. Biochim. Eng. Biotechnol.* **65** (1999) 243–280.
- 96 Press release by Cargill and Novozymes in January 2008.
- 97 F.S. Carta, C.R. Soccol, L.P. Ramos, J.D. Fontana: "Production of Fumaric Acid by Fermentation of Enzymic Hydrolyzates Derived From Cassava Bagasse", *Bioresour. Technol.* **68** (1999) 23–28.
- 98 G.N. Vemuri, M.A. Eiteman, E. Altman: "Succinate Production in Dual-phase *E. coli* - Fermentations depends on the Time of Transition from Aerobic to Anaerobic Conditions", *J. Ind. Microbiol. Biotechnol.* **28** (2002) 325–332. G.N. Vemuri, M.A. Eiteman, E. Altman: "Effects of Growth Mode and Pyruvate Carboxylase on Succinic Acid Production by Metabolically Engineered *E. coli* Strains", *Appl. Environ. Microbiol.* **68** (2002) 1715–1727. R.R. Gokarn, M.A. Eiteman, J. Sridhar: "Production of Succinate by Anaerobic Microorganisms", in B. D. Saha, J. Woodard (eds.): "Fuels and Chemicals from Biomass", *ACS Symposium Series* **666** (1997) 237–279.
- 99 A. Cukalovic, C.V. Stevens: "Feasibility of Production Methods for Succinic Acid Derivatives", *Biofuels, Bioproducts and Biorefining* **2** (2008) 505–529.
- 100 M. Okabe, D. Lies, S. Kanamasa, E.Y. Park: "Biotechnological Production of Itaconic Acid and its Biosynthesis from *Aspergillus terreus*", *Appl. Microbiol. Biotechnol.* **84** (2009) 597–606. C.S. Reddy, R.P. Singh: "Enhanced Production of Itaconic Acid from Corn Starch and Market Refuse Fruits by Genetically Manipulated *Aspergillus terreus* SKR 10", *Bioresour. Technol.* **85** (2002) 69–71. T. Wilke, K. Welter, K.D. Vorlop: "Biotechnical Production of Itaconic Acid from Sugar", *Appl. Microbiol. Biotechnol.* **56** (2001) 289–295.
- 101 DuPont PTT (Sorona®): http://www2.dupont.com/Sorona/en_US/ (accessed 20 February 2010)
- 102 M.M. Zhu, P.D. Lawman, D.C. Cameron: "Improving 1,3-Propanediol Production from Glycerol in a Metabolically Engineered *E. coli* by Reducing Accumulation of Glycerol-3-phosphate", *Biotechnol. Prog.* **18** (2002) 694–699.
- 103 For an informative review, see: A.N. Zeng, H. Biebl: "Bulk Chemicals from Biomass: Ease of 1,3-Propanediol Production and New Trends", *Adv. Biochem. Engineering/Biotech.* **74** (2002) 239–259.
- 104 N.E. Altaras, D.C. Cameron: "Metabolic Engineering of a 1,2-Propanediol Pathway in *E. coli*", *Appl. Environ. Microbiol.* **65** (1999) 1180–1185. N.E. Altaras, D.C. Cameron: "Enhanced Production of (R)-1,2-Propanediol by Metabolically Engineered *E. coli*", *Biotechnol. Progr.* **16** (2000) 940–946. N.E. Altaras, M.R. Etzel, D.C. Cameron: "Conversion of Sugars to 1,2-Propanediol by *Thermoanaerobacterium thermoaccharolyticum*", *Biotechnol. Progr.* **17** (2001) 52–56.
- 105 N. Nishino, M. Yochida, H. Shiota, E. Sakaguchi: "Accommodation of 1,2-Propanediol and Enhancement of Aerobic Stability in Whole Crop Maize Silage Inoculated with *Lactobacillus buchneri*", *J. Appl. Microbiol.* **94** (2003) 800–807.
- 106 W. Niu, M.N. Molefe, J.W. Frost: "Microbial synthesis of the energetic material precursor 1,2,4-butanetriol", *J. Am. Chem. Soc.* **125** (2003) 12998–12999.
- 107 C.L. Mehltretter: "D-Glucaric Acid", *Methods Carbohydr. Chem.* **2** (1963) 46–48.
- 108 B.A. Lewis, F. Smith, A.M. Stephen: "Galactaric Acid and its Derivatives", *Methods Carbohydr. Chem.* **2** (1963) 38–46.

- 109 S. Immel, F.W. Lichtenthaler: "The Conformation of Sucrose in Water: A Molecular Dynamics Approach", *Liebigs Ann. Chem.* **1995**, 1938–1947.
- 110 Südzucker AG: "Process and Apparatus for the Preparation of Mono-oxidized Products from Carbohydrates", DE 4307388, 1994 (M. Kunz, H. Puke, C. Recker, L. Scheiwe, J. Kowalczyk); *Chem. Abstr.* **122** (1995) 56411.
- 111 L.A. Edye, G.V. Meehan, G.N. Richards: "Platinum-catalyzed Oxidation of Sucrose", *J. Carbohydr. Chem.* **10** (1991) 11–23; **13** (1994) 273–283.
- 112 Südzucker AG: "Process for Continuous Manufacture of Di- and Higher-oxidized Carboxylic Acids from Carbohydrates", DE 19542287, 1996 (M. Kunz, A. Schwarz, J. Kowalczyk); *Chem. Abstr.* **127** (1997) 52504.
- 113 Hoechst AG: "Preparation of Sucrose Tricarboxylic Acid", DE 3535720, 1987 (W. Fritsche-Lang, E.I. Leupold, M. Schlingmann); *Chem. Abstr.* **107** (1987) 59408.
- 114 Biofine Inc.: "Production of Levulinic Acid by Hydrolysis of Carbohydrate-containing Materials", US 475630, 1996 (S.W. Fitzpatrick); *Chem. Abstr.* **126** (1996) 117739. D.J. Hayes, S. Fitzpatrick, M.H.B. Hayes, J.R.H. Ross: "The Biofine Process—Production of Levulinic Acid, Furfural and Formic Acid from Lignocellulose Feedstocks", in B. Kamm, P. R. Gruber (eds.): *Biorefineries—Industrial Processes and Products*, vol. **1**, Wiley-VCH, Weinheim 2006, pp. 113–164.
- 115 J.A. Moore, J.E. Kelly: "Poly(hydroxymethylfuroate)", *J. Polym. Sci., Polym. Chem. Ed.* **22** (1984) 863–864.
- 116 H. Hirai: "Synthesis of Macrocyclic Oligoesters from 5-Hydroxymethyl-2-furancarboxylic Acid", *J. Macromol. Sci., Chem. Part A* **21** (1984) 1165–1179.
- 117 R. Storbeck, M. Ballauf: "Synthesis and Thermal Analysis of Copolyesters Derived from 1,4:3,6-Dianhydrosorbitol", *J. Appl. Polymer Sci.* **59** (1996) 1199–1202.
- 118 J.A. Moore, J.E. Kelly: "Polymerization of Furandicarbonyl Chloride with Bisphenol A", *Polymer* **20** (1979) 627–628.
- 119 "Polyesters—Properties and chemical Synthesis" in Y. Doi, A. Steinbüchel (eds.): *Biopolymers*, vols. **3a**, **3b**, Wiley-VCH, Weinheim 2001, 468 pp. "Polyesters—Applications and Commercial Products" in A. Steinbüchel, Y. Doi (eds.): *Biopolymers*, vol. **4**, Wiley-VCH, Weinheim 2002, 398 pp.
- 120 Y.B. Kim, R.W. Lenz: "Polyesters from Microorganisms", *Adv. Biochem. Engineering/Biotechnol.* **71** (2001) 51–79.
- 121 H.-P. Weiss, W. Sauerer: "Polyamides", *Kunststoffe* **89** (1999) 68–74.
- 122 J. Thiem, F. Bachmann: "Carbohydrate-derived Polyamides", *Trends Polym. Sci.* **2** (1994), 425–432. E.M.E. Mansur, S.H. Kandil, H.H.A. M. Hassan, M.E.E. Shaban: "Synthesis of Carbohydrate-containing Polyamides and Study of their Properties", *Eur. Polym. J.* **26** (1990) 267–276.
- 123 O. Varela, H.A. Orgueira: "Synthesis of chiral Polyamides from Carbohydrate-derived Monomers", *Adv. Carbohydr. Chem. Biochem.* **55** (1999) 137–174.
- 124 L. Chen, E. Kiely: "Synthesis of Stereoregular Head/Tail Hydroxylated Nylons Derived from D-Glucose", *J. Org. Chem.* **61** (1996) 5847–5851; US 5 329 044, 1994 (L. Chen, D.E. Kiely); *Chem. Abstr.* **122** (1994) 56785. D. E. Kiely: "Carbohydrate Diacids: Potential as Commercial Chemicals and Hydrophobic Polyamide Precursors", in J. J. Bozell (ed.): "Chemicals and Materials from Renewable Resources", *ACS Symposium Series* **784** (2001) 64–80.
- 125 E. Cuny, S. Mondel, F.W. Lichtenthaler: "Novel Polyamides from Disaccharide-derived Dicarboxylic Acids", *Internat. Carbohydr. Symp.*, Whistler 2006, <http://csi.chemie.tu-darmstadt.de/ak/fwlicht/PAPERS/paper292.pdf> (accessed 20 February 2010).
- 126 A. Gandini, M.N. Belgacem: "Furanic Polyamides Chemistry", *Prog. Polym. Sci.* **22** (1977) 1238–1246.
- 127 A. Mitiakoudis, A. Gandini: "Poly(*p*-phenylene)-2,5-furandicarbonamide and Conversion into Filaments and Films", *Macromolecules* **24** (1991) 830–835.
- 128 M. Eissen, J.O. Metzger, E. Schmidt: U. Schneidewind, "Concepts on the Contribution of Chemistry to a Sustainable Development", *Angew. Chem.* **114** (2002) 402–424; *Angew. Chem. Int. Ed.* **41** (2002) 414–436.