Unsaturated *O*- and *N*-Heterocycles from Carbohydrate Feedstocks

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ABSTRACT
With reference to the impending transition of chemical industry from depleting fossil raw materials to renewable feedstocks—the end of cheap oil is predicted for 2040 at the latest—this Account gives an overview on chemically transforming carbohydrates, by far the major part of the annually regrowing biomass, into the following unsaturated *O*- and *N*-heterocycles with versatile industrial application profiles: furans, pyrans, dihydropyranones, pyrroles, pyrazoles, imidazoles, pyridinols, pyrazines, and quinoxalines. Although the emphasis was laid on conversions that can be effected in practical one-pot procedures or in a few large-scale-adaptable steps, a broad structural variety of products emerges that have not only diverse chemical functionalities but also hydrophilic "residual sugar" portions that render them water-soluble and readily biodegradable.

"A raw material as feedstock should be renewable rather than depleting wherever technically and economically practicable." [1]

Introduction

This quotation, being one of the 12 principles of green chemistry,[1] is probably one of the least realized in chemical industry, since production of organic chemicals from renewable feedstocks is, with very few exceptions, neither technically nor economically practicable at present. However, as our fossil raw materials are irrevocably decreasing—the end of cheap oil is realistically prognosticated for 2040 at the latest[2−4]—and as the pressure on our environment is building up, the progressive changeover of chemical industry to renewable feedstocks emerges as an inevitable necessity.[4,5]

The terrestrial biomass, which Nature graciously provides us on an annual basis, is considerably more complex than fossil raw materials, constituting a multifaceted accumulation of low and high molecular weight products, exemplified by sugars, hydroxy and amino acids, lipids, and biopolymers such as cellulose, hemicelluloses, chitin, starch, lignin, and proteins. By far the most abundant of these organic materials, in fact, about two-third of the annually renewable biomass, are *carbohydrates*, a single class of natural products that, 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.

The bulk of the annually renewable carbohydrate biomass are polysaccharides, yet their nonfood utilization is confined to textile, paper, and coating industries, either as such or in the form of simple esters and ethers. Organic commodity chemicals, however, are low molecular weight products; hence, they are more expediently acquired from low molecular weight carbohydrates than from polysaccharides. Accordingly, the constituent repeating units of these polysaccharides—glucose (cellulose, starch), fructose (inulin), xylose (xylan), 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 sugars—all well below € 10/

Table 1. Annual Production Volume and Prices of Simple Sugars and Sugar-Serived Alcohols and Acids as Compared to Some Petrochemically Derived Basic Chemicals and Solvents

		world production[a] (metric t/year)	price[b] (Euro/kg)
sugars	sucrose	130 000 000	0.30
	D-glucose	5 000 000	0.60
	lactose	295 000	0.60
	D-fructose	60 000	1.00
	isomaltulose	50 000	2.00
	maltose	3 000	3.00
	D-xylose	25 000	4.50
	L-sorbose	60 000	7.50
sugar alcohols	D-sorbitol	650 000	1.80
	D-xylitol	30 000	5.00
	D-mannitol	30 000	8.00
sugar-derived acids	D-gluconic acid	60 000	1.40
	L-lactic acid	>100 000	1.75
	citric acid	500 000	2.50
	L-tartaric acid	35 000	6.00
amino acids	L-lysine	40 000	5.50
	L-glutamic acid	500 000	7.00
basic chemicals	aniline	1 300 000	0.95
	acetaldehyde	900 000	1.15
	adipic acid	1 500 000	1.70
solvents	methanol	25 000 000	0.15
	toluene	6 500 000	0.25
	acetone	3 200 000	0.55

[a] Reliable data are only available for the world production of sucrose, the figure given referring to the crop cycle 2000/2001.[6] All other data are average values based on estimates from producers and/or suppliers, as the production volume of many products is not publicly available. [b] Prices given are those attainable in early 2002 for bulk delivery of crystalline material (where applicable) based on pricing information from the sugar industry (sugars) and the *Chemical Market Reporter* **2002**, No. 2, 16−19 (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, sizeably lower, e.g. for the commercial sweetener "high fructose syrup", which contains up to 95% fructose, and, thus, may readily be used for large-scale preparative purposes.

Frieder Lichtenthaler studied chemistry at the University of Heidelberg and received his doctorate there in 1959 for research on enol phosphates with F. Cramer. After three postdoctoral years with H. O. L. Fischer at the University of California, Berkeley, he joined the faculty of the Technical University of Darmstadt, where he acquired his "Habilitation" in 1965, was appointed associate professor in 1968, and full professor in 1972. His research interests—generation of enantiopure building blocks from sugars, their use in the synthesis of non-carbohydrate natural products, molecular modeling of chemical and biological properties of sugars, and studies toward the utilization of carbohydrates as organic raw materials—are documented in over 250 publications.

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kg—as compared to some sugar-derived naturally occurring compounds and basic chemicals from petrochemical sources. The result is stunning, since the five cheapest sugars, some sugar alcohols, and sugar-derived acids are not only cheaper than any other enantiopure product, such as hydroxy or amino acids, but they compare favorably with basic organic bulk chemicals such as 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", has for centuries been the worlds most abundantly produced organic compound, the present annual production being an impressive 130 million tons.[6] Similarly bulk scale accessible are its component sugars D-*glucose*, produced by hydrolysis of starch,[7] and D-*fructose*, generated either from glucose by base-induced isomerization or from inulin or sucrose by hydrolysis.[8] *Isomaltulose*, an α(1→6)-isomer of sucrose, has recently become accessible on an industrial scale accessible through enzymatic transglucosylation,[9,10] *lactose* and *maltose* are available in large quantities from whey[11] and starch,[12] and D-*xylose*, the cheapest pentose, is generated from wood- or straw-derived xylans. L-*Sorbose* is the cheapest, large-scale accessible L-sugar due to its production from D-*sorbitol* (= D-*glucitol*) in the vitamin C fabrication process.[13] The sugar alcohols D-*xylitol*, D-*sorbitol*, and D-*mannitol*,[14] each of comparatively high yearly production via hydrogenation of their parent aldoses, are mainly used as food ingredients due to their sweetening properties, yet they also have potential as inexpensive raw materials for broad-scale preparative purposes. The same holds for D-*gluconic acid*[15] and the other sugar-derived acids listed in Table 1.

In view of their large-scale accessibility, it must appear surprising that chemical industry, at present, utilizes these mono- and disaccharides only to a minor extent as feedstock for organic chemicals, a state of affairs amply documented by the fact that of the 100 major organic chemicals manufactured in the US in 1995,[16] only seven were derived from biofeedstocks, and five of these—ethanol, sorbitol, citric acid, lysine, and glutamic acid—used carbohydrates as the raw material source. Intense efforts within the past decade[17−21] to boost the acquisition of organic chemicals from the sugars in Table 1 have not basically changed this picture.

There are various reasons for that: at present, the use of fossil raw materials is more economic and, as importantly, the process technology for 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 materials, of which the essence is manifested in their structure-based names (Figure 1).

Our fossil resources are *hydrocarbons*, distinctly hydrophobic, oxygen-free, and lacking functional groups;

Fossil Resources:	Renewable Resources:
HYDRO-CARBONS	CARBO-HYDRATES
C_nH_{2n+2}	$C_n(H_2O)_n$
oxygen-free, lacking functional groups	overfunctionalized with hydroxyl groups

FIGURE 1. Hydrocarbons vs carbohydrates: more than a play on words, as their names, taken literally, reveal the basic differences in their utilization as organic raw materials.

annually renewables are *carbohydrates*, overfunctionalized with hydroxyl groups and pronouncedly hydrophilic. Needless to say, 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 transition to a biobased production system is unavoidable, strongly emphasizing the need for systematically elaborating appropriate process methodologies to convert carbohydrates—they are the major biofeedstock to fill the gap between dwindling oil supply and demand—into industrially useful products, be it bulk, intermediate, and fine chemicals, pharmaceuticals, agrochemicals, high-value-added speciality chemicals, or simply enantiopure building blocks for organic synthesis. Due to the plethora of potential industrial products derivable from carbohydrate feedstocks, this Account, compulsorily restricted in size, can cover only one aspect. It overviews *practical* procedures available to convert the sugars of Table 1 into unsaturated *O*- and *N*-heterocycles of established or presumed industrial relevance, with emphasis on those transformations that can be performed in either one-pot procedures or in a few simple steps and in which the carbon skeleton of the sugar becomes part of the heterocycle (rather than only attaching a heterocycle to the carbon chain at either end). This, naturally, necessitated a deliberate and inevitably subjective selection from the vast material available, to the detriment of much interesting academic work that, at least at present, was judged of lesser industrial significance.

Unsaturated *O*-Heterocycles from Sugars: Furans

Sugars invariably exist in furanoid and/or pyranoid cyclohemiacetal forms, which de facto are (saturated) *O*-heterocycles. This Account though focuses on their unsaturated analogues, i.e., *furan* and *pyran* or *dihydropyran* derivatives.

Furfural. With an annual production of about 200 000 tons, furfural (2-furaldehyde) appears to be the only unsaturated large-volume organic chemical prepared from carbohydrate sources. The technical process involves exposure of agricultural or forestry wastes (Figure 2) to aqueous acid and fairly high temperatures, the pentosans first being hydrolyzed to pentoses and then undergoing cyclodehydration.[22]

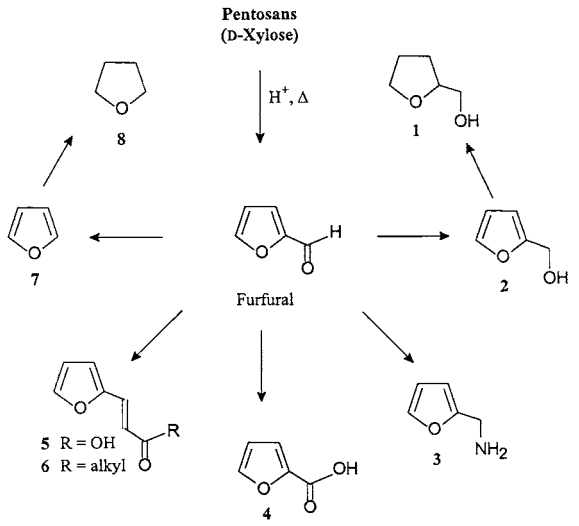


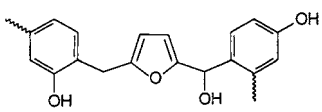
FIGURE 2. Furanic commodity chemicals derived from pentosans in agricultural wastes (corn cobs, oat hulls, wood chips, bagasse).

The chemistry of furfural is well-developed, providing a host of versatile industrial chemicals by simple straightforward operations (Figure 2): furfuryl alcohol (**2**) and its tetrahydro derivative **1** (hydrogenation), furfurylamine **3** (reductive amination), furoic acid **4** (oxidation) and furanacrylic acid **5** (Perkin reaction), or furylidene ketones **6** (aldol condensations).[22] Furfural is also the key chemical for the commercial production of furan (through catalytic decarbonylation) and tetrahydrofuran (**8**) (hydrogenation), thereby providing a biomass-based alternative to its petrochemical production via dehydration of 1,4-butanediol. The further importance of these furanic chemicals stems from their ring-cleavage chemistry, which has led to a variety of other established chemicals, e.g., levulinic acid and maleic anhydride.[22]

The bulk of the furfural produced is used as foundry sand linker, in the refining of lubricating oil, and, together with furfuryl alcohol and its tetrahydro derivative, in condensations with formaldehyde, phenol, acetone, or urea to yield resins of complex, ill-defined structures, with excellent thermosetting properties, high corrosion resistance, low fire hazard, and extreme physical strength.[22]

5-Hydroxymethylfurfural (HMF). Like many petroleum-derived basic chemicals, e.g., adipic acid and hexamethylenediamine, HMF is a six-carbon commodity with high industrial potential and, thus, has been termed "a key substance between carbohydrate chemistry and mineral oil-based industrial chemistry".[9] It is readily accessible from fructose or inulin hydrolysates by acid-induced elimination of 3 mol of water,[24] and even a pilot-plant-size process has been elaborated.[9]

HMF as such has been used for the manufacture of special phenolic resins of type **9**, as acid catalysis induces its aldehyde and hydroxymethyl group to react with phenol.[25]



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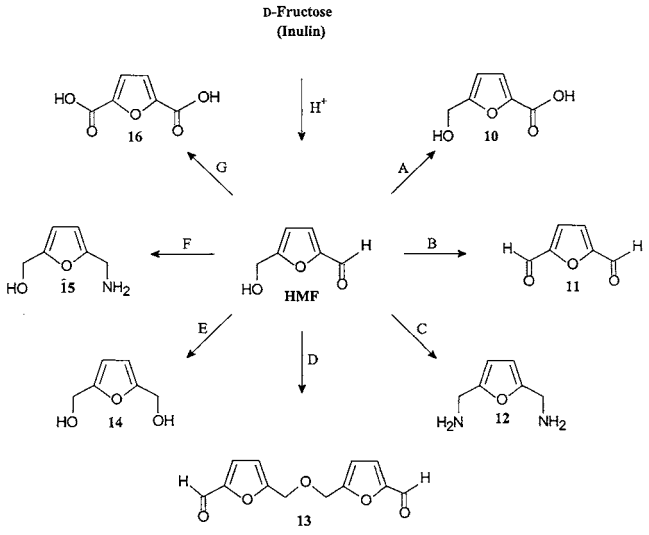
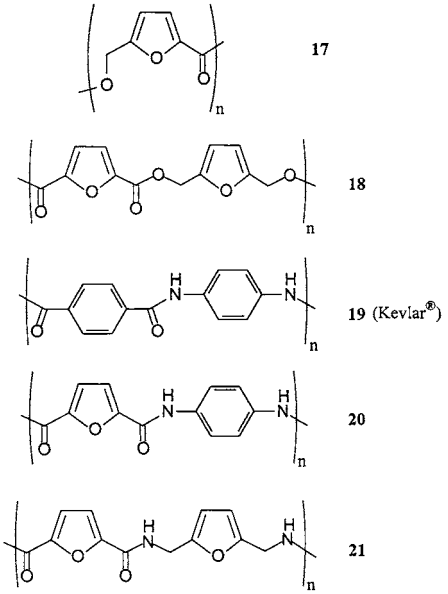


Key: A Ag_2O, 100 °C, 75% [26] E $Pt,C / H_2$, quant. [28]
B $BaMnO_4$, 93% [26] F Ni/H_2, NH_3, 72% [29]
C NH_2OH, then Ni/H_2, 33% [26] G $Pt,C / O_2$, pH 7, 91% [30]
D TsOH (H_2O↑), 89% [27]

FIGURE 3. Versatile intermediate chemicals derived from hydroxymethylfurfural (HMF).

Of higher industrial potential as intermediate chemicals are the various ensuing products of HMF, i.e., **10**−**16** (Figure 3), for which well worked out, large-scale-adaptable protocols are available.

Of these products, the 2,5-bis(hydroxymethyl)furan **14**, the 5-hydroxymethyl-2-furoic acid **10**, and the 2,5-dicarboxylic acid **16** have extensively been exploited for the preparation of furanoic polyesters.[23] The diol **14** has been reacted with various aliphatic and aromatic diacids; the ethyl ester of **10**, upon polycondensation, gave a mixture of linear (**17**) and cyclic products, while the furan-diacid **16** has been polyesterified with a series of aliphatic diols or bisphenols. Even the all-furanic polyester **18** has been successfully prepared from its respective monomeric components.[23]



17

18

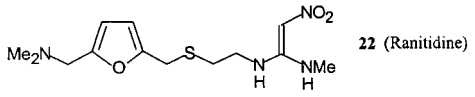
19 (Kevlar®)

20

21

Another obvious outgrowth from diamine **15** and dicarboxylic acid **16** was the preparation of furanic polyamides, as they could potentially replace the present, petroleum-based diamines and diacids in the industrially produced polyamides. Of the series of furanic polyamides prepared[23] by utilizing **16** and aliphatic or aromatic diamines, polyamide **20**, an analogue of Kevlar (**19**), has particularly promising decomposition and glass temperature parameters, distinctly better than those found for the all-furanic polyamide **21**.

Despite this impressive array of useful HMF-derived intermediate chemicals, HMF is, as of now, not produced on an industrial scale. Obviously, the economic preconditions are not yet favorable enough. A recent assessment of the economics of HMF against competitive petrochemical raw materials[31] gives ample evidence thereof: ton prices of naphtha and ethylene are in the 150−400 Euro range and that of inulin (500 Euros/t) or fructose (~1000 Euros/t), entailing an HMF-marketing price of at least 2500 Euros/t, is too expensive at present for a bulk-scale industrial product. Accordingly, as long as the economic situation favors fossil raw materials, applications of HMF lie in high value-added products, such as pharmaceuticals or special niche materials. A prototype along this vein is Ranitidine (**22**),[32] an efficient antiulcer drug due to its potent oral inhibition of histamine-induced gastric acid secretion. Although **22** is presently prepared from furfural,[32]



22 (Ranitidine)

its manufacture from HMF, whose structural features are contained in it, may be considerably more economic.

5-(Glucosyloxymethyl)furfural (GMF). The industrial production of isomaltulose (Table 1)—for food reasons, as it is hydrogenated to isomalt **23**, a low calorie sweetener with the same taste profile as sucrose[10]—has made it a lucrative target for generating disaccharide intermediates of industrial potential. For example, air oxidation in strongly alkaline solution smoothly provides the glucosyl-α(1→5)-D-arabinonic acid in the form of its lactone **24** in excellent yield,[33] which on perbenzoylation and SmI_2-mediated elimination affords the 2-furanone **25**.[33] Another industrially relevant reaction of isomaltulose comprises the acid-induced dehydration of the fructose portion to give α-D-glucosyloxymethylfurfural (GMF, **26**) (Figure 4). As this process is also feasible in a continuous flow reactor,[33] it may be readily produced on large scale.

As a glucosylated HMF, **26** provides a rich ensuing chemistry toward products with broad application profiles.[34] Oxidation with chlorite gives the glucosylfuroic acid **27** and heating with hydroxylamine its nitrile **28**, usable as dipolarophile in a [3 + 2]-cycloaddition with azide toward tetrazolide **32**.[34] Aldol-type condensations deliver derivatives with polymerizable double bonds, most notably the methylenation product **29**, which polymerizes spontaneously, and acrylic acid **30**,[34] expected to yield novel, hydrophilic polymers with interesting performance profiles. Reductive amination provides GMF-amine **31**, its *N*-acylation with fatty acid chlorides giving compounds of type **33**, nonionic surface-active agents in which their hydrophobic fat-alkyl residue and hydrophilic glucose part are separated by a quasiaromatic spacer. They also exhibit useful liquid crystalline properties,[35] as do esters of glucosylfuroic acid **27** with long-chain alcohols (e.g. **34**), which combine high surface activity with biocompatibility,

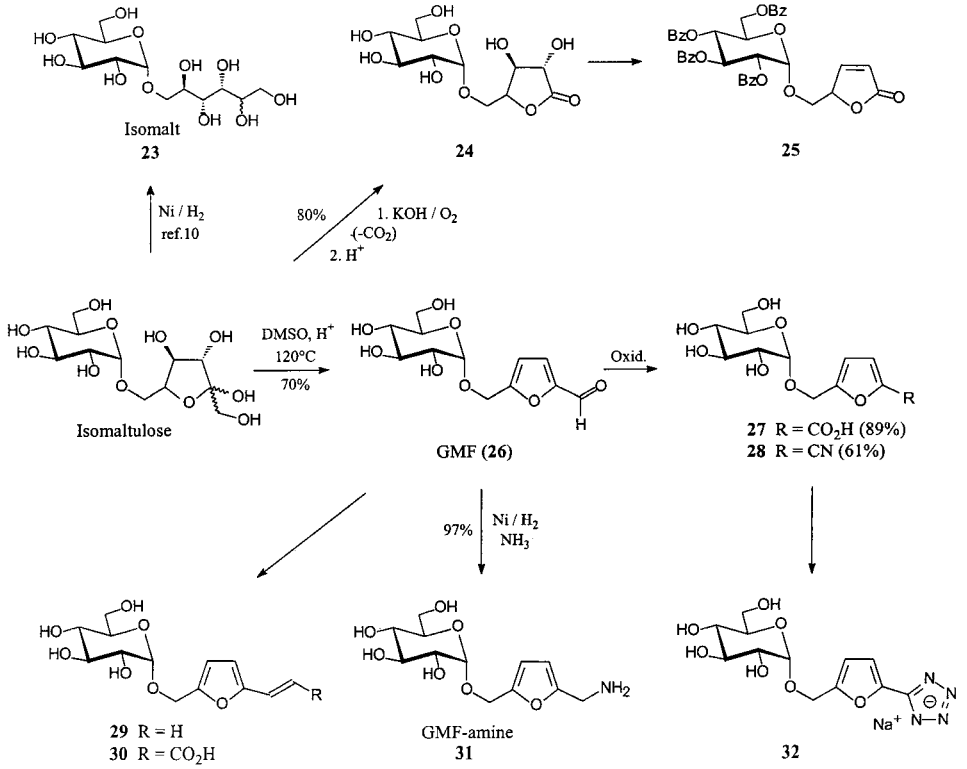
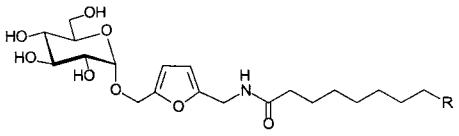
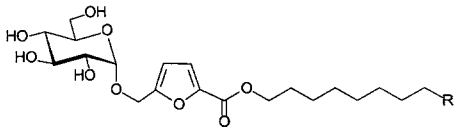


FIGURE 4. Transformation of isomaltulose into products with industrial application profiles.[33,34]

rendering them promising candidates for biomedical applications.

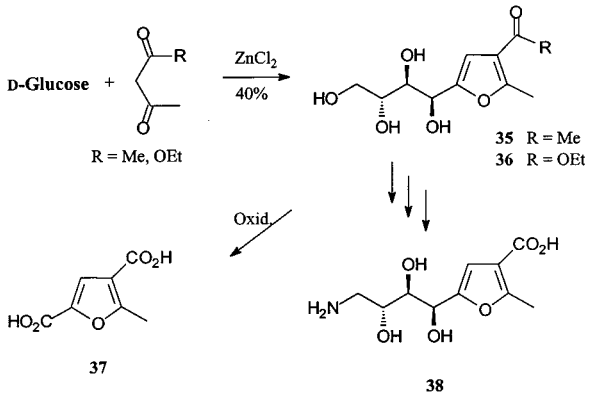


33 R = Et, Bu



34 R = H, Bu

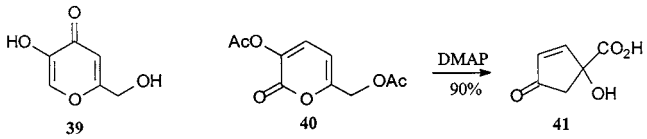
Furans with a Tetrahydroxybutyl Side Chain. Another simple, one-step entry from hexoses to more highly substituted furans involves their $ZnCl_2$-mediated reaction with 1,3-dicarbonyl compounds such as ethyl acetoacetate or 2,4-pentanedione. As only the first two sugar carbons contribute to the formation of the furan, a distinctly hydrophilic tetrahydroxybutyl side chain is elaborated. Thus D-glucose smoothly provides furans **35** and **36** with D-*arabino*-configuration in the polyol fragment,[36] which can be shortened oxidatively to the dicarboxylic acid (**36** → **37**) or a variety of other furanic building blocks. Of biological relevance appear to be ensuing products of type **38**, i.e., amino acids with the carboxyl group in the hydrophobic and the amino group in the hydrophilic portion of the molecule, as they have been used for preparing hetarylene-carbopeptoid libraries via combinatorial techniques.[37]



Pyrones and Dihydropyranones

The bulk scale-accessible mono- and disaccharides of Table 1 invariably adopt pyranoid cyclohemiacetal forms, from which well-elaborated, efficient reaction channels lead to an unusually large variety of unsaturated pyranoid building blocks, such as pyrones, dihydropyrans, and dihydropyranones, of which the latter two have the additional advantage of being enantiopure. In the context of this Account, they are treated only cursorily inasmuch as none of these products have reached commodity status so far; they may be considered though as high-value-added speciality chemicals.

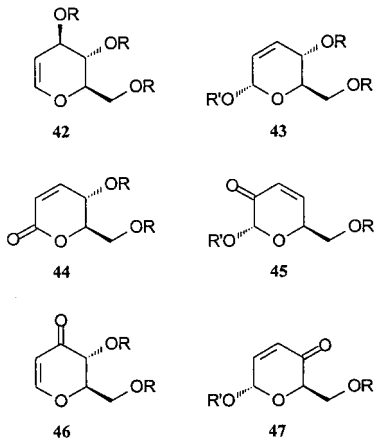
The pyrones **39** (kojic acid) and **40** are readily obtained from D-glucose, the former either enzymatically by *Aspergillus oxyzae* growing on steamed rice[38] or chemically via pyranoid 3,2-enolones[39,40] and the latter by oxidation to D-gluconic acid[15] and acetylation.[41] Both, at present, are of little significance as six-carbon building blocks, despite a surprisingly effective route from **40** to cyclopentanoid products of type **41**,[42] which are surmised to have industrial potential.



39 **40** **41**

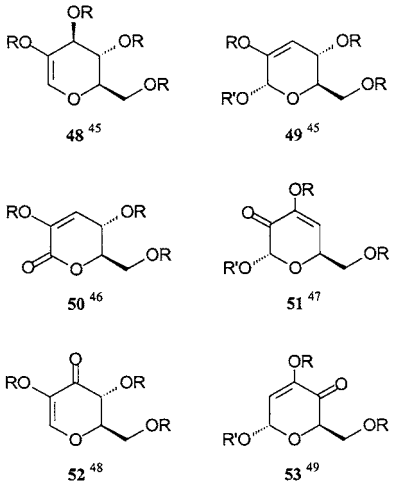
Of higher interest, at least with respect to their extensive use for the total synthesis of non-carbohydrate natural products,[40,43] are the bevy of enantiopure six-carbon building blocks of the dihydropyran and dihydropyranone type in Figures 5 (**43**−**47**) and 6 (**49**−**53**), all compounds being readily accessible from D-glucose in no more than three to five straightforward steps.[40,44]

Some of these pyranoid building blocks are accessible even more directly, e.g., levoglucosenone (**54**), which has



42 **43** **44** **45** **46** **47**

FIGURE 5. Enantiopure six-carbon building blocks accessible in three to five straightforward steps from D-glucose via D-glucal **42** as the key intermediate (R = Ac, Bz).[40,44]

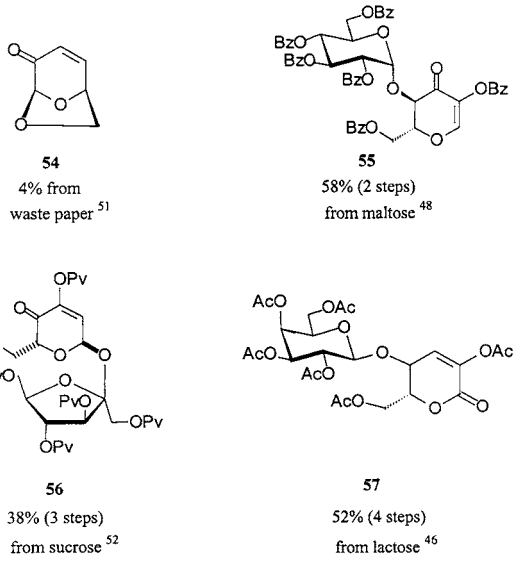


48 [45] **49** [45] **50** [46] **51** [47] **52** [48] **53** [49]

R = Ac, Bz; R' = Me, Et

FIGURE 6. Pyranoid building blocks from D-glucose via hydroxyglucal esters (**48**) as key intermediates.[45−49]

been used for the synthesis of a diverse variety of natural products.[50] Although the yield attainable on pyrolysis of waste paper[51] is relatively low (3−4%), relative large quantities of **54** can be amassed quickly. Similarly convenient are the acquisitions of the three dihydropyranones **55**−**57**, requiring two, three, and four steps from maltose, sucrose, and lactose, respectively.



54
4% from waste paper [51]

55
58% (2 steps) from maltose [48]

56
38% (3 steps) from sucrose [52]

57
52% (4 steps) from lactose [46]

Ac : acetyl; Bz : benzoyl; Pv : pivaloyl

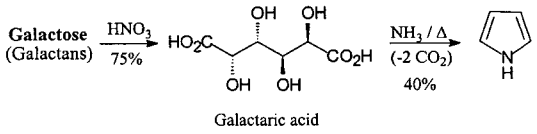
All of these pyranoid building blocks are enantiopure and have a unique, highly diverse array of functional groups to which the armory of preparative organic methodology can directly be applied. The enolone esters **51**, **53**, and **56**, for example, possess three differently functionalized carbonyl groups, one being free, the other two masked in enol ester and acetal form. In addition, the enolone structural unit is flanked by chiral centers, so any addition reaction to either carbonyl or enolic double bond proceeds with high stereoselectivity. As for the disaccharide-derived building blocks **55**−**57**, they feature functionality in one of the units and—in the form of the intact glycosyl moiety—a cheap acid-sensitive protecting group in the other.

Aside from their extensive use in the total synthesis of enantiopure non-carbohydrate natural products,[40,43,50] these pyranoid building blocks have found little use as high-value-added chemicals. If finding suitable targets and appropriate preparative outlets, however, particularly toward pharmaceutically hopeful compound libraries via combinatorial techniques, these pyranoid building blocks are apt to become a plethora of attractive, industrially relevant speciality chemicals.

Sugar-Derived Unsaturated *N*-Heterocycles

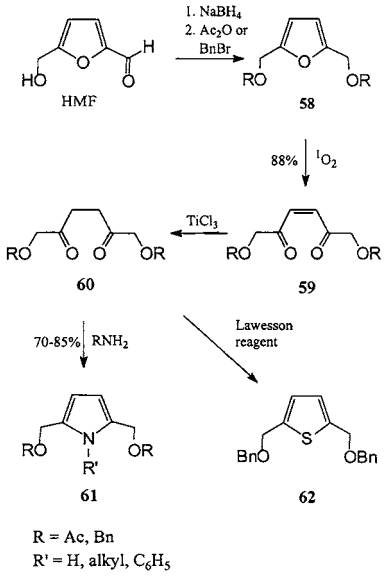
Although tranformation of sugars into trace amounts of *N*-heterocycles occurs extensively on exposure of foodstuffs to heat (Maillard reaction), and despite the fact that various *N*-heterocycles have been generated from saccharide derivatives,[53−55] procedures meeting preparative standards are exceedingly scarce, those allowing large-scale adaptation being essentially nonexistent. Only recently, improvement of existing procedures and development of new methodologies have led to the more ready acquisition of various *N*-heterocycles from carbohydrates: imidazoles, pyrroles, pyrazoles, pyridines, and pyrazines, which due to their sugar derivation have hydrophilic side chains. The following survey again stresses practicality of procedures, mainly focusing on advancements within the past decade.

Pyrroles. Thermal decomposition of the galactose-derived ammonium mucate[56] appears to be the only generation of pyrrole itself from a carbohydrate source, a process not exploited industrially due to more efficient accesses from petrochemicals.



Galactaric acid

2,5-Disubstituted pyrroles have recently become accessible from HMF in a preparatively straightforward reaction sequence, involving photooxidative furan ring opening (**58** → **59**) and cyclization of the saturated 2,5-diketones with ammonia or amines (**60** → **61**).[57] Using a thiation reagent, thiophenes, e.g., **62**, can similarly be obtained.[57]



HMF

58

60

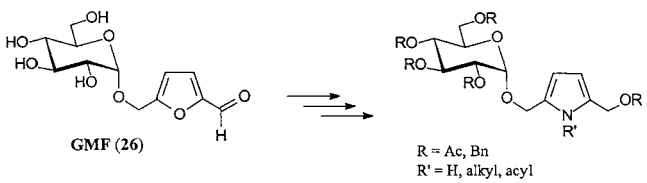
59

61

62

R = Ac, Bn
R' = H, alkyl, C_6H_5

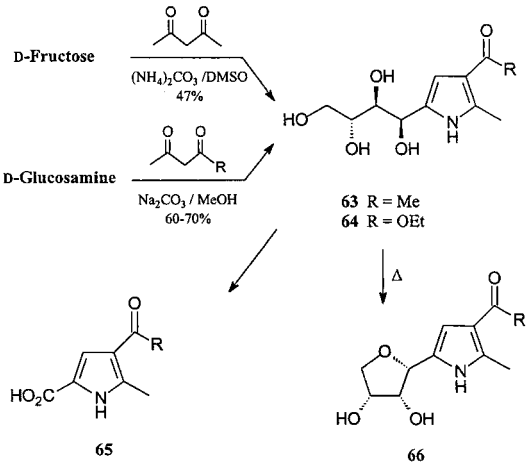
These reaction sequences can directly be transferred to GMF, leading to pyrroles carrying an additional glucosyl residue:[57]



GMF (26)

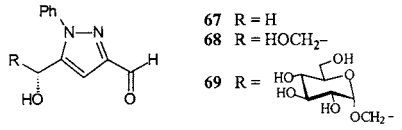
R = Ac, Bn
R' = H, alkyl, acyl

Pyrroles with an equally hydrophilic tetrahydroxybutyl substituent are available from D-glucosamine by exposure to acetylacetone or acetoacetate under mildly basic conditions, smoothly affording products **63** and **64**, respectively.[58,59] Of these, **63** may also be obtained in a one-pot reaction from D-fructose by heating with acetylacetone and ammonium carbonate in DMSO.[59]



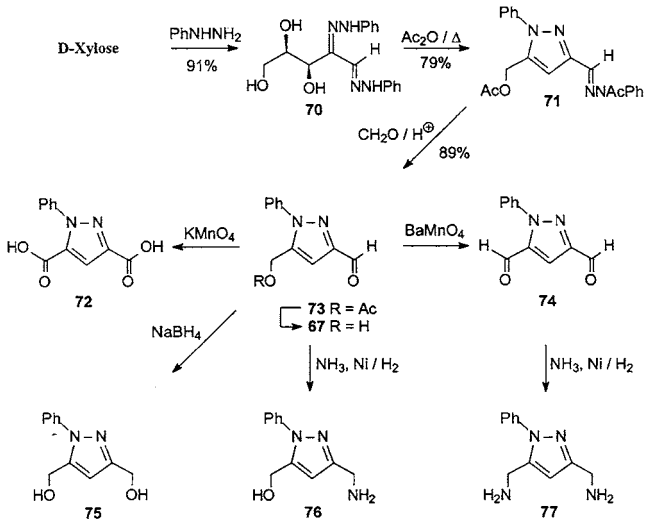
The hydroxylated side chain can, of course, be modified in many ways: oxidative shortening provides simple pyrrole building blocks (e.g., **65**)[58] and heating elaborates a furanoid ring, as in **66**.[59]

Pyrazoles. An expeditious four-step approach to 1-phenylpyrazol-3-carboxaldehydes with 5-hydroxymethyl (**67**), 5-dihydroxyethyl (**68**), or 5-glucosyloxymethyl substituents (**69**) has been elaborated starting from D-xylose,[60] D-glucose, and isomaltulose,[61] respectively.



As illustrated for D-xylose, its phenyl osazone **70**, formed on reaction with phenylhydrazine, straightforwardedly elaborates the pyrazole **71** upon addition to refluxing acetic anhydride. Subsequent liberation of the *N*-acetylphenylhydrazone-blocked aldehyde group (**71** → **73**) can be equally well accomplished by heating in aqueous formaldehyde/acetic acid and exposure to K_2CO_3 in aqueous methanol then generating pyrazolaldehyde **67**.[60] Thus, a preparatively simple route is established from D-xylose, the cheapest pentose available from renewable resources, to versatile *N*-heterocyclic building blocks, the overall yield for the four steps required being 57%.[60]

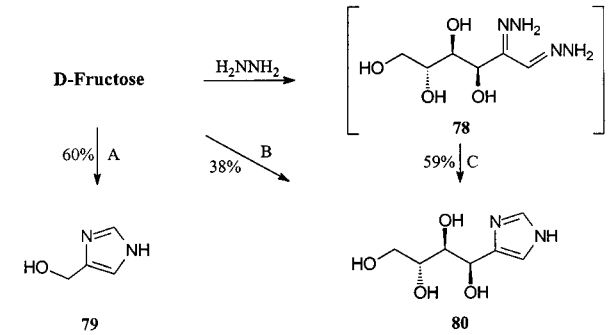
Further modifications of pyrazole aldehyde **67** toward products with industrial application profiles, e.g., compounds **72**−**77**, followed standard methodology.[60] Aside from being useful pharmaceutical intermediates, these products can also be utilized for the generation of novel polyamides by condensation of **72** with suitable diamines (**77** included), as well as of **77** with appropriate dicarboxylic acids such as adipic acid or **72**. Similarly, esterification of **72** with long-chain alcohols or *N*-acylation of



76 with fatty acid chlorides are to lead to products with novel surfactant and/or liquid crystalline properties.

Similar potential applies to the more hydrophilic pyrazole building blocks **68** and **69**, equally well accessible in an analogous four-step sequence from D-glucose and isomaltulose in overall yields of 55−60%.[61]

Imidazoles. Various imidazoles carrying hydrophilic substituents in the 4-position are readily accessible in one-pot procedures from the standard monosaccharides. Of those, the formation of 4-hydroxymethylimidazole (**79**) on Cu(II)-promoted reaction with formaldehyde and concentrated ammonia[62] is rather unique as retro-aldolization to glyceraldehyde and dihydroxyacetone is involved. The retro-aldol fission can be partially suppressed though by heating D-fructose with formamidinium acetate in liquid ammonia in a pressure vessel, allowing the isolation of **80** in albeit modest yield (38%).[63] These somewhat impractical conditions can be simplified by briefly heating fructose with formamidinium acetate in the presence of boric acid and a dehydrating agent (hydrazine), the imidazole **80** (now isolable in 59% yield) obviously being elaborated via a borate complex of the bis-hydrazone **78**.[64]



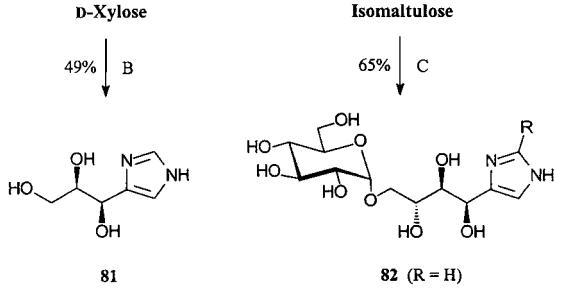
Conditions A CH_2O, aq. NH_3, $CuCO3/Cu(OH)_2$, 2 h, 100 °C[62]

B $HC(=NH)NH_2 \cdot HOAc$ / liq. NH_3, 15 h, 75 °C[63]

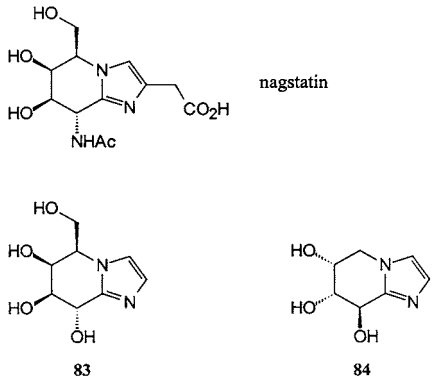
C N_2H_4 / $HC(=NH)NH_2 \cdot HOAc$ / aq. HOAc, H_3BO_3, 3 h reflux[64]

These conditions can be readily applied to pentoses and disaccharides, as exemplified with the simple acquisi-

tion of **81** from D-xylose[63] and **82** from isomaltulose,[64] in acceptable yields for one-pot procedures. Further substitution into the imidazole ring can be effected by reacting sugars with ethyl acetimidate/ammonium carbonate, isomaltulose yielding the 2-methylimidazole derivative **82** (R = Me, 53%).[64]

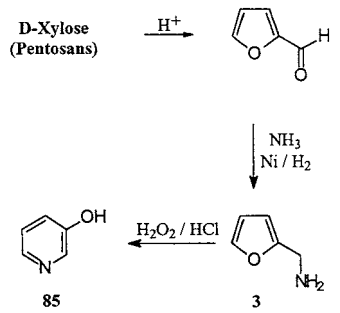


Sugar-annulated imidazoles have recently gained particular interest due to the remarkable capacity of naturally occurring nagstatin to inhibit β-glycosidases. Substantial synthetic efforts[65,66] have led to a series of imidazolo sugars, e.g., **83** and **84** via compounds of type **80**,[66] that proved the inhibitory activity to be associated with their imidazole portion. In preparative terms, however, these multistep approaches are all but practical, as of now.

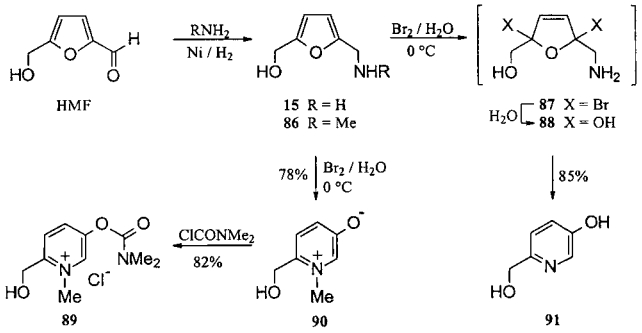


3-Pyridinols. The conversion of pentoses into 3-pyridinol (**85**) can be effected in a practical three-step sequence, involving acid-induced dehydration to furfural, reductive amination to furfurylamine (→**3**), and oxidation with hydrogen peroxide,[29,67] the last step conceivably proceeding through the stage of a 2,5-dihydroxy-2,5-dihydrofurfurylamine, which elaborates the pyridine nucleus via dehydration to a 5-aminopentenal intermediate and cycloaldimine formation. **85** figures as an intermediate chemical for herbicides and insecticides,[68] as well as for cholinergic drugs of the pyridostigmine type.

For conversion of furfurylamines with oxidizable hydroxyl groups, e.g., HMF-derived **15**, either *O*-protection had to precede oxidation (this approach has been implemented for **15** → **91** in four steps,[29] comprising electrochemical oxidation and tedious workup) or milder oxidants had to be used. Best results were obtained by simply exposing **15** to bromine in water/methanol (0 °C, 45 min), affording the 3-pyridinol **91** in crystalline form (85%).[69] Thus, the entire multistep conversion **15** → **91**—1,4-addition of bromine (→**87**), hydrolysis (→**88**), elimination

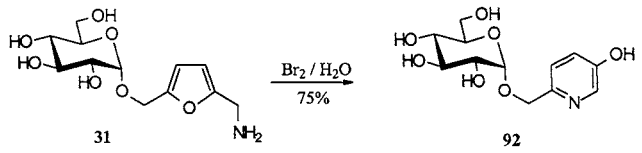


of water and cyclo-imine formation—can be effected in an exceedingly mild one-pot procedure.



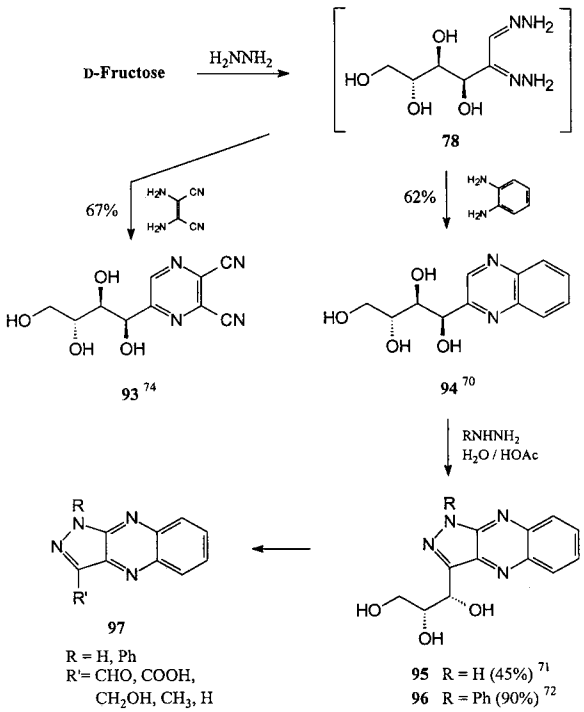
The procedure can also be applied to furfurylamines with secondary amino groups by replacing ammonia with a primary amine in the reductive amination, e.g., HMF → **86** (91%). On exposure to bromine water, the *N*-methyl-3-oxidopyridinium betaine **90** is obtained, which, through selective *O*-carbamoylation, is cleanly converted into **89**, a 6-hydroxymethyl analogue of the parasympathomimetic pyridostigmine.

Similarly, glucosylated furfurylamines are converted to the respective 3-pyridinols, e.g., **31** → **92**, the bromine/water treatment not affecting the glycosidic linkage. The overall yield of **92** for the three steps from isomaltulose amounts to a satisfactory 51%.[69]



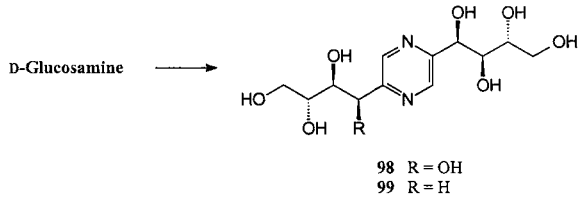
Pyrazines and Quinoxalines. Useful one-pot procedures are also available for the conversion of monosaccharides into tetrahydroxybutyl-substituted pyrazines and quinoxalines. As exemplified for D-fructose, exposure to hydrazine and diaminomaleodinitrile gives the pyrazine **93**,[64] the decisive intermediate obviously being the D-glucosone-bis-hydrazone **78**. For the quinoxaline analogue **94**, the preparatively most favorable conditions seem to be reaction of fructose with hydrazine, *o*-phenylenediamine, and boric acid in dilute acetic acid with bubbling of oxygen through the solution.[70]

On refluxing the quinoxaline **94** in aqueous acid with excess hydrazine or phenylhydrazine, an oxidative cyclization takes place with elaboration of the trihydroxypropyl-substituted flavazoles **95**[71] and **96**.[72] In each of



these *N*-heterocycles, the polyhydroxyalkyl side chain can be oxidatively shortened to aldehyde or carboxyl functions, or removed altogether (decarboxylation), a route by which flavazole itself (**97**, R = R′ = H) was prepared for the first time.[71]

Two rather unique pyrazines, the fructosazine **98** and/or its monodeoxy derivative **99**, are similarly accessible in a one-pot transformation, comprising an oxidative dimerization of D-glucosamine. When allowed to stand in aqueous ammonia for 3 weeks, the fructosazine **98** was obtained (47%),[72] while simple stirring in aqueous NaOH in the presence of phenylboronic acid at room-temperature elaborated the 1-deoxy derivative **99**, isolable in 58% yield.[73]



Conclusion

In the quest for unfolding new application fields for the nonfood utilization of low molecular weight carbohydrates, this Account outlines the current status for practical conversions of inexpensive, bulk-scale-available sugars into unsaturated *O*- and *N*-heterocycles with versatile industrial application profiles. Although the emphasis was laid on those sugar → heterocycle transformations that can be performed in one-pot procedures or in a few simple, large-scale-adaptable steps, an unusually broad structural variety of products emerges. These not only have highly diverse chemical functionalities with which a straightforward ensuing chemistry can be elaborated, but they carry distinctly hydrophilic "residual sugar" portions that render them water-soluble—an important issue in their use as intermediates for pharmaceuticals—and readily biodegradable.

At present, however, the industrial utilization of this promiscuous stock of readily bioaccessible *O*- and *N*-heterocycles is dissappointingly modest: furfural and some of its ensuing products being the only established bulk and/or intermediate chemicals so far. Notwithstanding, a basic change in this scenario is clearly foreseeable. As depletion of our fossil raw materials is progressing, chemical products derived therefrom will inevitably increase in price, such that biobased products will eventually become competitive. Realistic prognoses expect this for 2040 at the latest.[2−4]

In the meantime, it is imperative that carbohydrates, whose huge potential as organic raw materials is far from being exhausted, are systematically further exploited toward efficient, environmentally benign, and economical process methodologies for their large-scale conversion into industrially viable products, such as bulk or intermediate chemicals, pharmaceuticals, and polymeric organic materials. In this endeavor, national and supranational funding institutions—in Europe the EU most notably—will have to play an active role, not only by generously funding corresponding activities in a broad time frame (5−10 years) but by first elaborating a concise long-term strategy that takes root in academia and chemical industry. The basic strategy, thereby, is not to be directed toward the very same basic chemicals that are well-accessible from petrochemical sources but toward the development of products with analogous industrial application profiles, with as little alteration of the carbohydrate structural framework as possible. Only then will economically sound biobased alternatives to petrochemicals—various potential examples are contained in this Account—become available.

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