Perspectives

Towards improving the utility of ketoses as organic raw materials[1,2]

Frieder W. Lichtenthaler *

Institut für Organische Chemie, Technische Universität Darmstadt, D-64287 Darmstadt, Germany

Abstract

Although three ketoses are bulk scale-accessible and inexpensive, i.e. D-fructose, L-sorbose, and isomaltulose, their utilization as organic raw materials in chemical industry is modest — not surprising in fact, as their chemistry has not developed at a rate comparable with the other common monosaccharides. This account gives an overview over older and very recent efforts of chemically transforming these three ketoses into building blocks with industrial application profiles, be it bulk, fine, or specialty chemicals, pharmaceuticals, or simply enantiopure building blocks for organic synthesis. © 1998 Elsevier Science Ltd. All rights reserved

Keywords: D-Fructose; L-Sorbose; Isomaltulose; Ketose-derived building blocks; Intermediate chemicals from sugars

1. Introduction

Carbohydrates are by far the most abundant organic compounds on earth, and represent the major portion of the annually renewable biomass of about 200 billion tons; of these, as of now, only 3% are used by man; the rest decays and recycles along natural pathways.

Despite substantial recent efforts to boost chemical industry's use of inexpensive, bulk scale accessible carbohydrates as organic raw materials [1–7], the systematic exploitation of the vast industrial potential lying in low- and high-molecular-weight carbohydrates is in the beginning – for several reasons: first, the use of fossil raw materials is, as of now, still more economic, and second, the process technology for the conversion of petrochemical raw materials into a broad range of products is not only exceedingly well developed but 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 already manifested in their structure-based names:

Our fossile resources are *hydrocarbons*, distinctly hydrophobic, oxygen-free and lacking functional groups, whereas the annually renewables are *carbohydrates*, overfunctionalized with hydroxyl groups and pronouncedly hydrophilic in nature. Needless to say, that the methods required for converting carbohydrates into viable industrial chemicals – reduction of oxygen content with simultaneous introduction of $C = C$ and $C = O$

---

* Corresponding author. Fax: 00 49 6151 166 674; e-mail: fwlicht@sugar.oc.chemie.tu-darmstadt.de
[1] Enantiopure building blocks from sugars, Part 24. For Part 23, see ref. [63].
[2] Dedicated to Professor Kurt Heyns on the occasion of his 90th birthday.

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

unsaturation – are diametrically opposed to those prevalent in petrochemical industry.

As our fossile resources become less and as the pressure on our environment is increasing, the presently still prevailing economic advantage of petrochemicals is going to change within the time frame of the next 10 to 20 years, emphasizing the need for developing appropriate process metho-

dology to convert carbohydrates into industrially useful products, be it fibers, packaging materials, fine or bulk chemicals, pharmaceuticals, or simply enantiopure building blocks for organic synthesis.

The bulk of the annually renewable carbohydrate-biomass are polysaccharides, e.g. cellulose, starch, chitin, and inulin, yet their non-food utilization is confined to textile, paper and coating

Table 1
Availability and prices of low molecular carbohydrates compared to petrochemically derived basic organic chemicals and solvents

		World production [a] (metric t/year)	Price [b] (DM/kg)	Source (supplier)
Sugars	Sucrose	123.000.000	0.75	World market
	D-Glucose	5.000.000	1.15	Cerestar
	Lactose	295.000	1.20	Borculo Whey
	D-Fructose	60.000	2.00	Südzucker
	Isomaltulose	35.000	4.00	Südzucker
	Maltose	3.000	5.–	Cerestar
	D-Xylose	16.000	12.–	Xyrofin
	L-Sorbose	25.000	15.–	Merck
	D-Galactose	?	85.–	Fluka
	Lactulose	10.000	90.–	Solvay Duphar
Sugar Alcohols	D-Sorbitol	650.000	2.–	Merck
	D-Mannitol	20.000	6.–	Cerestar
	D-Xylitol	15.000	12.–	Xyrofin
Sugar-derived Acids	L-Lactic acid	100.000	4.–	Purac
	D-Gluconic acid	60.000	7.–	Fluka
	L-Tartaric acid	?	10.–	Merck
	L-Ascorbic acid	60.000	12.–	Merck
Amino Acids	L-Glutamic acid	250.000	15.–	
	L-Lysine	40.000	20.–	
Industrial Organic Chemicals	Acetaldehyde	900.000 [c]	1.–	
	Aniline	1.320.000	1.–	
	Benzaldehyde	50.000	3.60	
Solvents	Methanol	6.500.000 [c]	0.50	
	Toluene	6.500.000 [c]	0.50	
	Acetone	3.200.000	0.75	

[a] Exact data are only available for the world production of sucrose, the figure given referring to the campaign 1996/97; for 1997/98 the world production is estimated to amount to over 125 mill. t [9]. All other data are average values based on more or less comprehensive estimations from producers and/or suppliers.
[b] Prices given are those attainable in mid-1997 on the world market for bulk delivery (ton range), or in the EU after allowing for EU refunds for industrial utilization of the sugars listed.
[c] Data from *The Chemical Industry in 1994*, UN Annual Review, New York/Geneva, 1995.

industries, either as such or in the form of simple esters and ethers. In terms of their use as basic organic raw materials for the chemical industry, however, the constituent monosaccharides of these polysaccharides – glucose, fructose (inulin), xylose (xylan), etc., or disaccharide versions thereof – are considerably more suited for straightforward chemical modifications and, hence, for the elaboration of products with tailor-made industrial applications. In addition, they are *inexpensive* and *ton scale-accessible* – a unique situation which becomes particularly evident by the data collected in Table 1. Therein, the bulk quantity prices of the nine least expensive sugars – all with kg prices well below DM 100. –, and, hence, ideal starting materials for organic synthesis – are set against those of other naturally occurring enantiopure compounds and of basic organic chemicals from petrochemical sources. The result is stunning, since the six least expensive sugars, some sugar alcohols and sugar-derived acids are not only cheaper than any other enantiopure product, such as amino acids or terpenoids, but they compare favorably with basic organic bulk chemicals such as benzaldehyde or aniline. Actually, the four cheapest sugars are in the price range of some of the standard solvents in which organic reactions are usually performed.

For centuries, sucrose, "the royal carbohydrate" [8], has been the worlds most abundantly produced organic compound of low molecular weight; its annual production is in the 120 million ton range [9], and the present state of its use as an organic raw material has recently been reviewed [6,10]. The

industrial, non-food valorization of glucose as the most readily accessible aldose is reasonably well developed, comprising its oxidation (→D-gluconic acid, a chelating agent and textile printing additive [11]), its reduction (→D-sorbitol→vitamin C [12]), and its acid-induced glycosidation with long-chain alcohols to provide alkyl polyglucoside surfactants ("APGs"), presently produced at about a 40.000 t scale per year [13].

In contrast thereto, the non-food utilization of the two comparatively inexpensive, ton – scale accessible ketose monosaccharides, i.e. D-fructose and L-sorbose (cf. Table 1) is particularly modest – expectedly, as their chemistry is considerably more capricious and less well understood than that of the common aldohexoses. This situation is most strikingly reflected by the fact that — except for a brief commentary on the status of D-fructose utilization by Heyns in 1978 [14] — exhaustive reviews on the chemistry of D-fructose [15] and L-sorbose [16] have appeared as far back as 1952, i.e. nearly half a century ago. Accordingly, in terms of the non-food industrial utilization of D-fructose and L-sorbose, as well as of the ton-scale accessible isomaltulose and lactulose (cf. Table 1), the exploitation of their practically feasible ensuing chemistry appears imparative, i.e. the systematic elaboration of simple and selective "reaction channels" towards products with broad industrial application profiles. Thus, this account, reviewing newer developments along these veins, is aimed at contributing to the increased use of these renewable ketoses as organic raw materials for chemical industry.
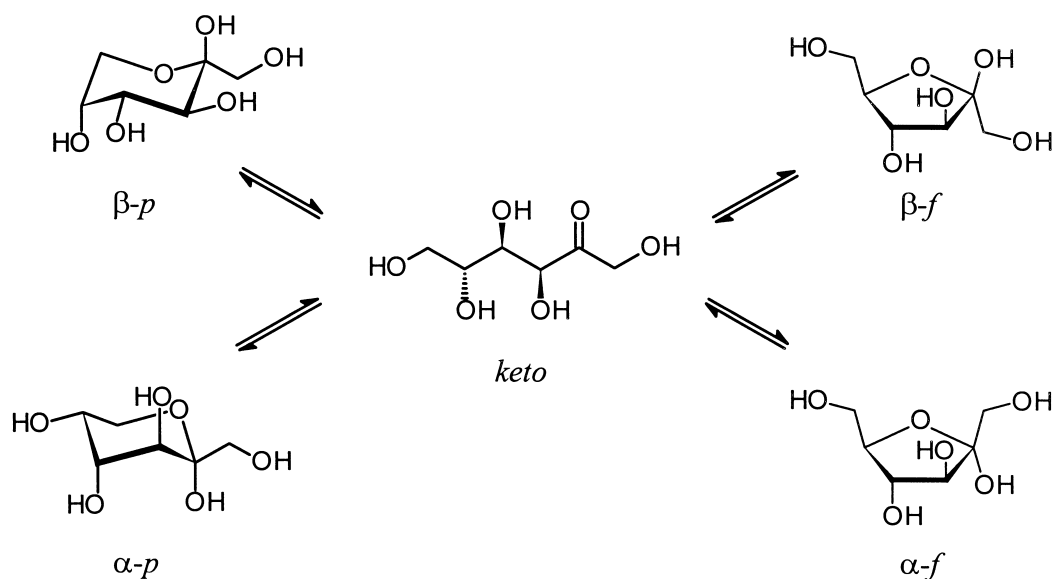
Scheme 1. Tautomeric forms of D-fructose in solution.

2. D-Fructose

Whilst D-fructose crystallizes in the β-pyranoid form as evidenced by X-ray structural analysis [17], in aqueous solution or when dissolved in dimethyl sulfoxide or pyridine, a mixture of the two pyranoid and two furanoid tautomers is invariably formed (cf. Scheme 1), its composition being strongly dependent on the solvent employed and on the temperature [18,19]; in fact, the only tautomer negligible in solution is the acyclic *keto*-form:

Due to this situation, simple derivatizations of D-fructose, such as glycosidations, acylations, and alkylations, usually yield product mixtures of, at worst, all five tautomeric forms, from which separation of the major component is cumbersome and highly detrimental to the yields obtainable. For pre-determining the outcome of such derivatizations as far as possible, all reaction parameters have to be considered as there are: (i) the different hydroxyl group reactivities within the various tautomeric forms, and (ii) the composition of tautomers during the reaction, which, in turn, is determined by the solvent, the rate of isomerization at the reaction temperature, and, if this isomerization is slow, on the time of pre-equilibration of the β-p tautomer (when dissolving crystalline fructose), before reagents are added.

Whilst the OH group reactivities of the individual fructose tautomers are difficult to assess reliably – except for the preferential reaction of the primary hydroxyl functions (one in the pyranoid, two in the furanoid and acyclic forms) over the
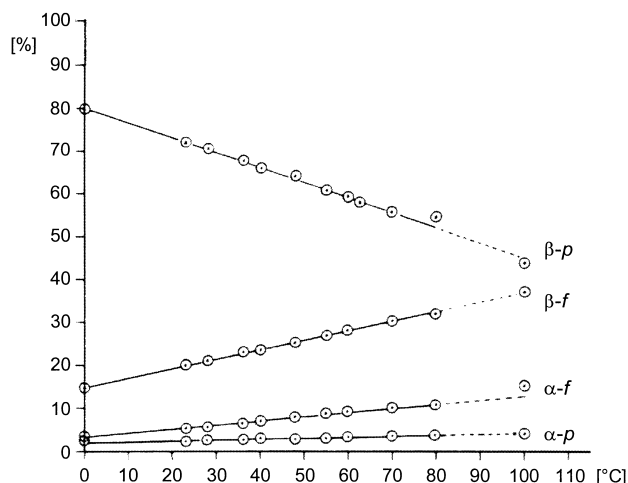

Fig. 1. Equilibrium composition of D-fructose tautomers in water as a function of temperature (4 M solution; values at 110 °C for the molten state), determined by ^{1}H NMR in dimethyl sulfoxide via the intensities of the well separated anomeric 2-OH protons [19], because the rate of equilibration in this solvent being exceedingly slow.

secondary ones, fairly exact data are available for the equilibrium composition of tautomers in water, dimethyl sulfoxide and pyridine (cf. Table 2), and for their rate of equilibration at a given temperature. In *water*, i.e. on dissolution of crystalline β-p fructose, equilibration with the other tautomers is fast at ambient or higher temperature; at 20 °C, for example, a constant rotational value is reached within 15 min [20]. As demonstrated by the data graphically presented in Fig. 1, there is also a distinct linear relationship between equilibrium composition

Table 2
Equilibrium composition in % of D-fructose tautomers [a] in water, dimethyl sulfoxide and pyridine [19]

Solvent	Temperature (°C)	β-p	α-p	β-f	α-f
Water	0	80	2	15	3
	25 [b]	73	2	20	5
	50	64	3	25	8
	70	56	4	30	10
Me$_2$SO	20	32	3	46	19
	25	27	4	48	20
	50	21	4	51	24
Pyridine	0	60	4	27	9
	20	54	5	30	11
	60	42	6	36	15

[a] The amount of acyclic *keto*-form present in these mixtures is, if detectable at all, in the 0.5–1% range.
[b] The commercial "high fructose syrup", widely used as a sweetener for soft drinks, corresponds closely to the 25 °C distribution of tautomers.
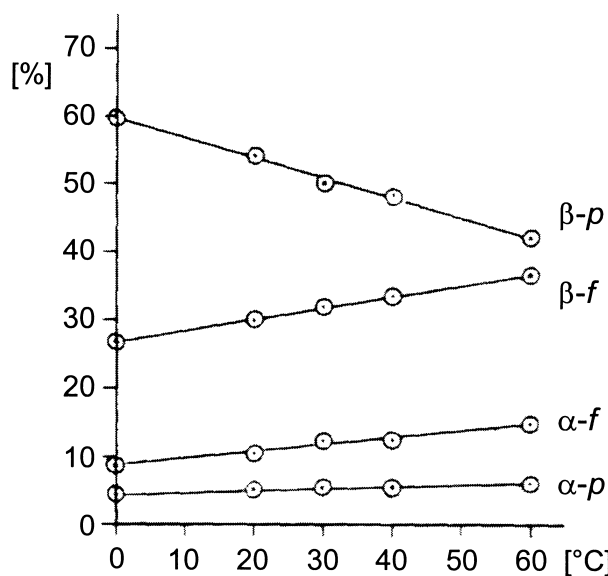

Fig. 2. Equilibrium composition of D-fructose tautomers in pyridine as a function of temperature [19].

and temperature such that the two fructofuranoses and the α-p-tautomer increase with temperature on expense of the β-p form, yet in different proportions. At 80 °C only 55% of the β-p form is still present, at 110 °C, i.e. in the molten state, even less (45%) [19].

In *dimethyl sulfoxide* and in *pyridine*, however, i.e. solvents in which simple derivatizations are usually performed, not only the tautomeric distribution is strongly temperature dependent (cf. Fig. 2 for pyridine), but the rate with which the β-p form equilibrates: at 0 °C, i.e. on dissolution of crystalline fructose in ice-cold pyridine by stirring for an hour or so, tautomerization is hardly detectable, resulting in a pyridine solution of the β-p form; at 60 °C, however, equilibration is essentially instantaneous to yield a 7:6:3:1 mixture of the β-p, β-f, α-f, and α-p tautomers (cf. Fig. 2 and Table 2), in which the two furanoid tautomers comprise more than 52%. The highest proportions of the two fructofuranose forms have been found in dimethyl sulfoxide, e.g. 51% β-f and 23% α-f tautomer for a solution equilibrated at 50 °C for 12 h [21], a fact that has been attributed [22] to their stabilization by intramolecular hydrogen bonds of the 1-OH···O-4 and 6-OH···O-3 tape as depicted in Fig. 3. The expectation though that the β-f form would eventually crystallize from such a solution — equilibration is exceedingly slow to ambient temperature already — has not materialized so far.
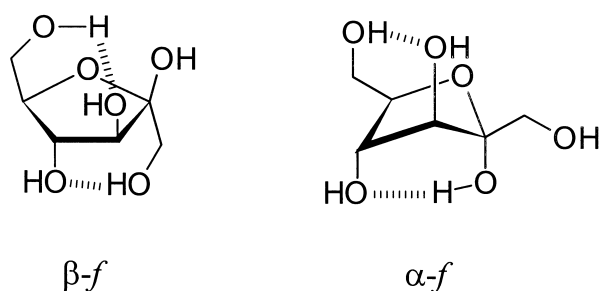

Fig. 3. Stabilization of D-fructofuranose forms in aprotic solvents (Me₂SO, pyridine) by intramolecular hydrogen bonds between primary and secondary hydroxyl groups [21,22].

From the foregoing, it is clear that derivatizations of fructose in pyridine or dimethyl sulfoxide not only depend on the reaction temperature, but on the way the crystalline β-p tautomer is dissolved in these solvents, and how long it had time to equilibrate before reagents were added. As the well-studied benzoylations of D-fructose in pyridine are particularly informative in this context, they are briefly discussed here in exemplary form.

In view of the exceedingly slow equilibration of tautomers at 0 °C, optimal conditions for the acquisition of pyranoid derivatives require that crystalline fructose (i.e. the β-p tautomer) is dissolved in cold pyridine and that the reaction is performed at low temperature. Brigl's empirically found procedure for the preparation of the pyranoid tetrabenzoate **1** in 80% yield [23] provides such conditions: gradual addition of fructose to a cooled (−10 °C) mixture of pyridine, chloroform and benzoyl chloride (4 molar equivalents), followed by warming to ambient temperature (Scheme 2). The anomeric hydroxyl group in **1**, being tertiary and, hence, less reactive, is nearly unaffected by these conditions, yet its conversion to the respective β-p-pentabenzoate **4** is smoothly accomplished by exposure to benzoyl chloride/pyridine in the presence of 4-dimethylaminopyridine (DMAP) [24].

When the benzoylation of D-fructose is performed at ambient temperature, the outcome is quite different: a mixture of **1**, **4**, the acyclic pentabenzoate **2**, and the furanoid tetrabenzoate **3α** is formed which requires column chromatography to be separated, and provides the products in yields up to 20% only [24]. Here, certain discrepancies between Brigl's work [23], who separated by fractional crystallization, and ours [24], could be traced back to a curious coincidence: the *keto*-pentabenzoate **2**, the furanoid tetrabenzoate **3α**, and the furanoid pentabenzoate **5**, each have melting points of 124–125 °C, which, in addition, is close to that of benzoic acid.

Dissolving fructose in pyridine, and reacting with benzoyl chloride at 60–70 °C again gives an entirely different product composition. The major product, isolable in yields of up to 60%, is the furanoid tetrabenzoate **3α** [25], with the respective α-f-pentabenzoate **5** and the acyclic isomer **2** as minor components [24]. This course of the benzoylation is readily rationalized: in pyridine at 65 °C, D-fructose equilibrates to a mixture of tautomers, in which the two furanoid forms comprise more than half (cf. Fig. 2), and their more reactive primary hydroxyl groups (1-OH and 6-OH, respectively) are benzoylated first, leading to the 1,6-dibenzoates in necessarily furanoid fixation, and, then to **3α** and **5**. Other conditions for the ready acquisition of **3α** (70%) comprise exposure of fructose in a 7:1 dichloromethane–pyridine solution to benzoyl chloride at ambient temperature, whereas the same reaction in 1:1 dichloromethane–pyridine
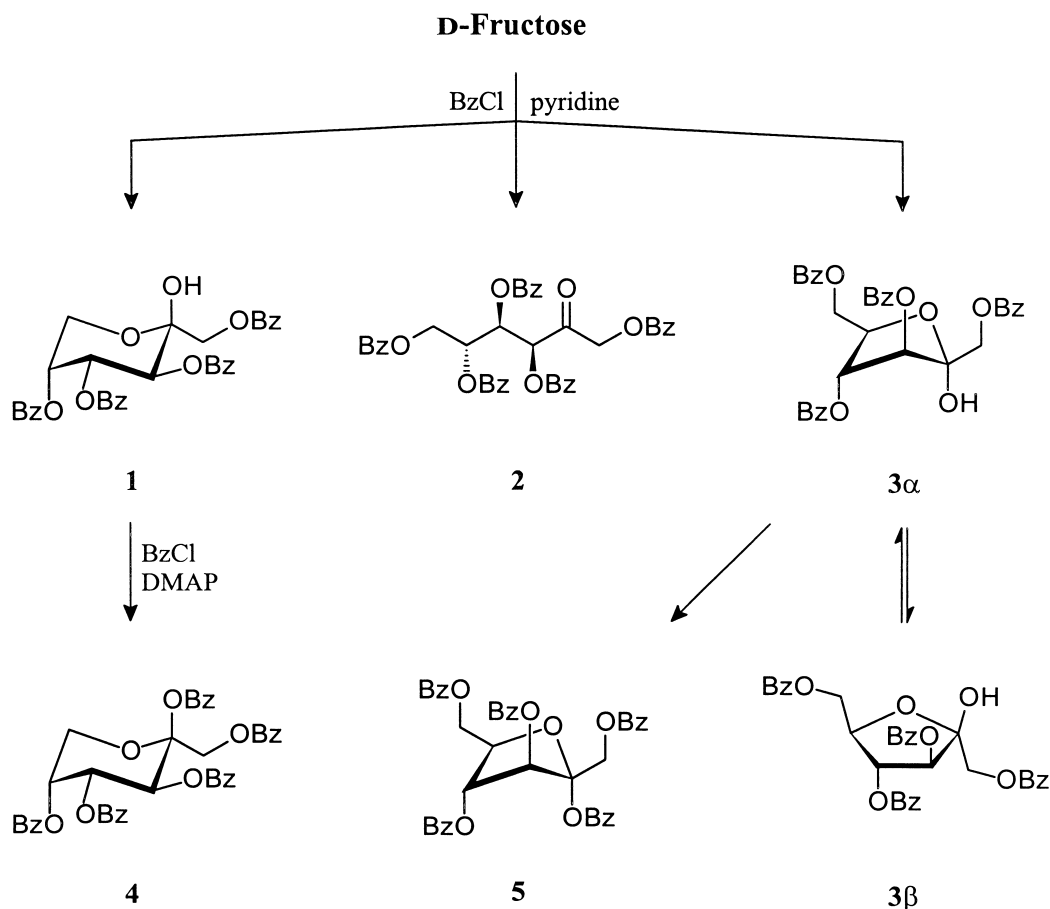
**D-Fructose**

Scheme 2. Benzoylations of D-fructose [23–26].

provides high yields (80%) of the furanoid α-pentabenzoate **5** [26].

That the outcome of an acylation of fructose depends not only on the hydroxyl group reactivities of the individual tautomers and on their distribution in pyridine solution, but also on the steric bulk of the acylating agent, is revealed by its pivaloylation. Addition of crystalline fructose to a cooled (−10 °C) mixture of pyridine, dichloromethane and pivaloyl chloride — conditions that yield pyranoid products **1** and **4** with benzoyl chloride — gives the furanoid tetrapivalate nearly exclusively, isolable as the β-anomer (**3β** with *t*BuCO instead of Bz) in a yield of over 70% [24]. Since crystalline fructose, when dissolved in cold pyridine, retains the β-*p*-tautomeric form [19], the pivaloylation at −10 °C is conceivably initiated by esterification of the primary 1-OH group, generating a tautomeric mixture of the pyranoid (axial 5-OH) and furanoid fructose-1-pivalates (primary 6-OH), of which the latter — present in the mixture to a minor extent only — is more readily acylated due to being more reactive and better accessible to

pivaloyl chloride than secondary hydroxyl functions in the pyranoid form.

While the furanoid tetrabenzoate crystallized as its α-anomer (**3α**), the respective tetrapivalate, for steric reasons obviously, prefers the β-form in the solid state. In chloroform solution, however, α⇌β equilibration takes place as revealed by ¹H NMR: **3α** forms a 1:1 mixture of anomers, the respective β-*f*-pivalate one in favor of the β-form (2:1); on removal of the solvents, however, both regenerate their original anomers [24].

This brief excursion into the capricious preparative subtleties of acylations of fructose amply demonstrates the difficulties encountered in "entry reactions", i.e. in the straightforward conversion of D-fructose into simple, tautomerically fixed derivatives. As such derivatives, however, are the key compounds for exploiting the chemistry of fructose towards products with industrial application profiles, it is imperative to have profound knowledge of those "entry reactions" that meet preparative criteria of practicability, as there are simple reagents, a fairly uniform reaction course, and
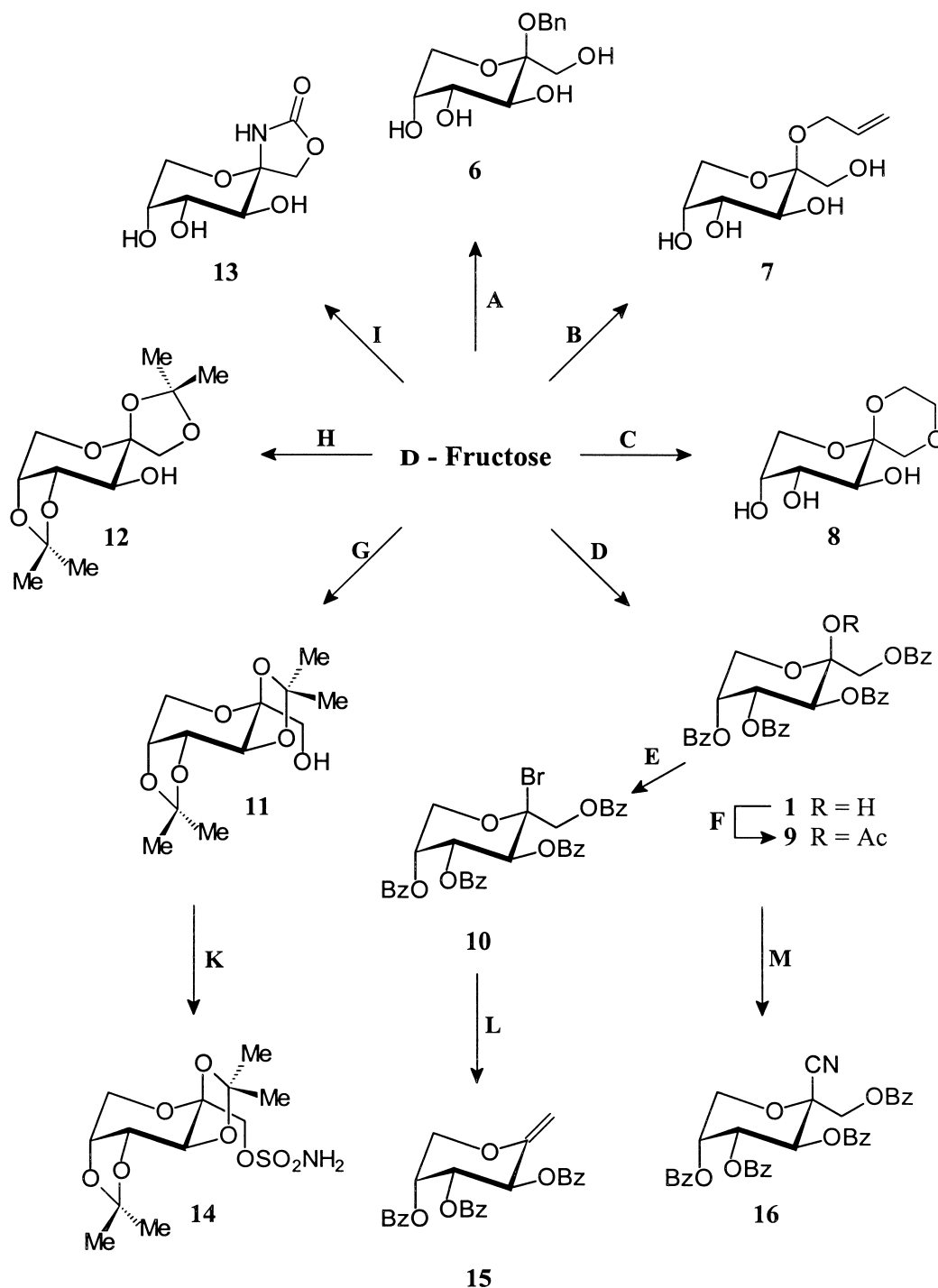
A	BnOH / HCl, 30% [33]	G	acetone / 5% H$_2$SO$_4$, 80% [42,43]
B	allyl alcohol / AcCl, 49% [35]	H	acetone / cat. H$_2$SO$_4$, 45% [42,44]
C	2-chloroethanol / HCl, then	I	KOCN, buffer, 31% [24]
	NaOMe /MeOH, 74% [36]	K	ClSO$_2$NH$_2$ / Et$_3$N, 46% [45]
D	BzCl / pyridine, -10 °C, 78% [23,24]	L	Zn / methylimidazole, 90% [40]
E	HBr, CH$_2$Cl$_2$, 0 °C, 90% [40]	M	Me$_3$SiCN / BF$_3$, MeNO$_2$, 90% [38]
F	Ac$_2$O / NaOAc, 100 °C, 90% [23]		

Scheme 3. "Entry reactions" from D-fructose to simple derivatives fixed in pyranoid form.

useful yield of the product without recourse to tedious chromatography. Accordingly, in the sequel, only those "entry reactions" from fructose to simple derivatives are documented, that comply with these practicality criteria.

Pyranoid fructose derivatives.— The "entry reactions" compiled in Scheme 3 provide a variety of pyranoid fructose derivatives in useful yields. Of these, acid-catalyzed glycosidations are particularly capricious, as exposure of a methanol solution of fructose to an acid (HCl [27], H_2SO_4 [28], or mesoporous silica-alumina cracking catalysts [29]) or simply to iodine [30] leads to complex anomeric mixtures of methyl furanosides and pyranosides which require chromatography for their separation, and, thus, curtail yields of pure products to about 20–40%. In addition, the composition of the fructoside mixture strongly depends on the amount of acid used, since exposure of fructose to 0.1% methanolic HCl at ambient temperature generates a 46 (*β-p*) : 26 (*β-f*) : 25 (*α-f*) : 3 (*α-p*) mixture of methyl fructosides, whereas under kinetic conditions (0.001% HCl in methanol) the anomeric methyl fructofuranosides accumulate as the major products [27]. Substantial efforts have been made towards the preparation of long-chain alkyl fructosides [31,32], as they are deemed to have similar industrial potential as biodegradable detergents as the alkyl polyglucosides (APGs) [13]. However, direct silica–alumina catalyzed glycosidations of fructose with 1-octanol and 1-dodecanol not only proceed sluggishly but cannot be led to completion, the extent of conversion remaining below 50% [32]. Better results are achievable in a two-stage process, i.e. generation of an *n*-butyl fructoside mixture followed by acid-catalyzed transacetalization with a long-chain alcohol [32].

More propitious appears to be the glycosidation of D-fructose with benzyl alcohol/HCl [33], not because of the higher uniformity of the glycoside mixture generated but because of the fact, that the benzyl *β*-D-fructopyranoside (**6**) can be isolated by crystallization. Due to this, **6** has been used as the starting material for the preparation of various 4-aminohexuloses via the dialdehyde–nitromethane approach [34]. Other, well accessible fructopyranosides are the allyl derivative **7** (49%) [35], and, most notably, the *spiro*-glycoside **8**, formed on HCl-promoted glycosidation with 2-chloroethanol and subsequent base-induced spirocyclization (74%) [36].

The most readily accessible acylated fructopyranose is tetrabenzoate **1**, smoothly acquirable from a low temperature benzoylation [23,24], which happens to be a versatile key intermediate for the generation of various pyranoid building blocks [37]; acetylation of the anomeric OH group (**1**→**9** [23]) followed by BF_3-promoted cyanation smoothly provides the nitrile of a 2-hydroxymethyl branched 2,6-anhydrogluconic acid (**16**) [38], whilst HBr treatment converts **1** into fructosyl bromide **10** [39,40], which in turn is a propitious intermediate for the generation of *exo*- and *endo*-fructal esters, e.g. **15** [40], or the respective hydroxyfructals [37,41]. Of similar preparative importance are the two diacetone-fructopyranoses **11** [42,43] and **12** [44], as only one of the five OH groups is unblocked and, hence, available for versatile further modifications; sulfamoylation of the primary OH group in **11**, for example, leads to topiramate **14**, a novel drug with high antiepileptic efficacy [45]. Similar synthetic as well as conceivable pharmaceutical potential may apply to the cyclic carbamate **13**, smoothly generated on reaction of fructose with potassium cyanate [24].

Acyclic derivatives of D-fructose.— The few preparatively relevant "entry reactions" from fructose to acyclic derivatives are compiled in Scheme 4.
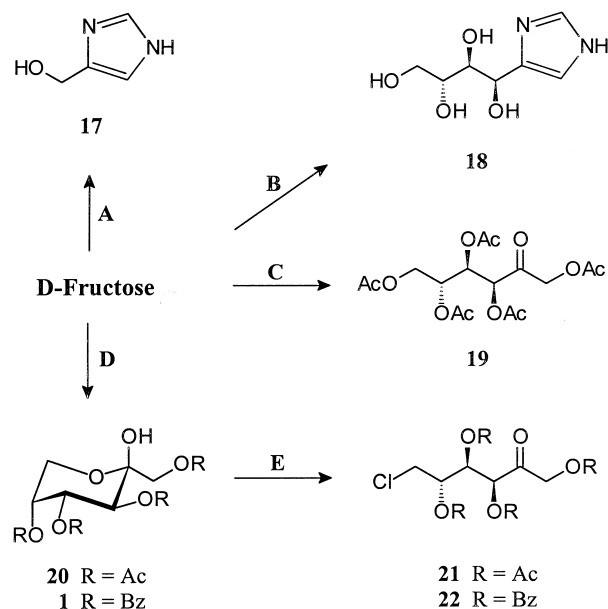
A CH_2O / aq NH_3 / $CuCO_3\cdot Cu(OH)_2$, 2 h, 100 °C, 60% [46]

B $H_2NCH=NH\cdot HOAc$ / liq NH_3, reflux, 38% [47]

C Ac_2O / $ZnCl_2$, 5 h, 0 °C, 2 h, 50 °C, 48% [48]

D Ac_2O / H_2SO_4, 3 h, 0 °C, 60% [49b]
     BzCl / pyridine, -10 °C, 78% [24]

E PCl_5 / toluene, 30 min reflux, 84 and 78% [24]

Scheme 4. Acyclic derivatives of D-fructose.

Of those, the formation of the 4-hydroxymethyl-imidazole **17** on Cu(II)-promoted reaction with formaldehyde and conc. ammonia [46] is rather unique in such as obviously retroaldolization to glyceraldehyde and dihydroxyacetone is involved, of which only the latter is believed [46a] to give rise to the product. The retroaldol fission can be partially suppressed though on treating D-fructose with formamidinium acetate in liquid ammonia at 75 °C in a pressure bottle, **18** can be isolated from the resulting mixture with **17** in 38% yield [47].

The most readily accessible acylated *keto*-fructose is the pentaacetate **19**, as it crystallizes on work up of an acetic anhydride/ZnCl$_2$ acylation

[48]. Well accessible also are the acylated 6-chloro-6-deoxy-*keto*-fructoses **21** and **22**, as they are formed in high yields on briefly refluxing the pyranoid tetraacetate **20** [49] and tetrabenzoate **1**, respectively, with PCl$_5$ in toluene [24,50].

Furanoid derivatives of D-*fructose.*— The simple fructose derivatives fixed in pyranoid and acyclic form discussed, are complemented by an equally multifaceted array of readily accessible furanoid compounds, i.e. products **24–29**, of which structures and mode of synthesis are compiled in Scheme 5.

Of the simple furanoid products, by far the highest industrial potential appertains to 5-hydroxy-


Scheme 5. Simple furanoid derivatives of D-fructose.
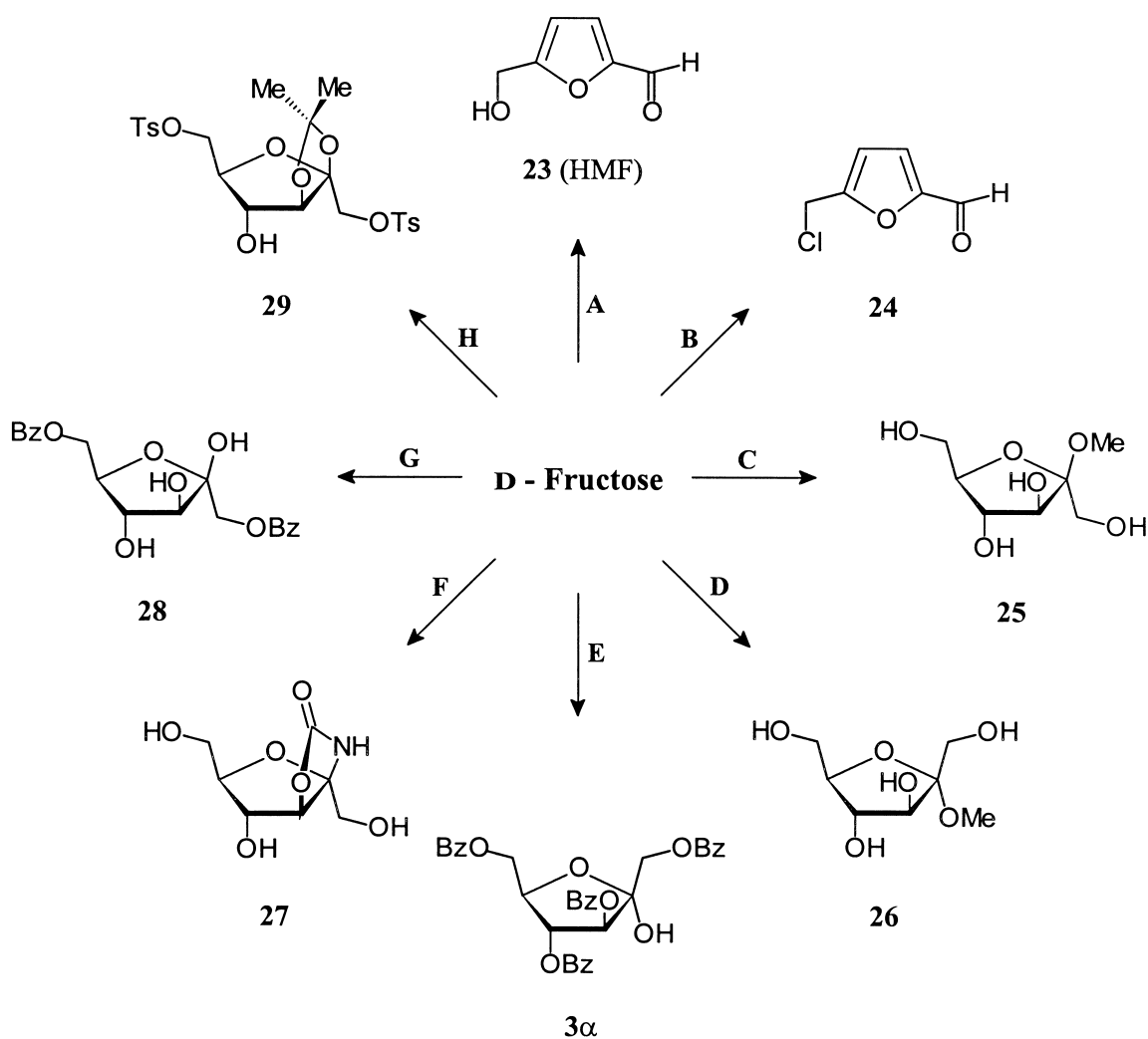
|			
A	H$^+$, 90% [52,53]	**F**	KOCN / buffer, 32% [24]
B	HCl / toluene, 60-85 °C, 65% [54]	**G**	HCN / NH$_3$, then BzCl / pyridine, finally
C	MeOH / HCl, 33% [28]		Ag$_2$CO$_3$ / EtOAc / reflux, 60% [55]
D	MeOH / silica-alumina catalyst, 30% [29]	**H**	TsCl / pyridine, then Me$_2$CO / H$^+$, 20% [56]
E	BzCl / pyridine, 60 °C, 60% [25]		

methylfurfural ("HMF", **23**), which has been termed one of the few "petrochemicals" readily accessible from regrowing resources [51] and as a key substance between carbohydrate chemistry and mineral oil-based industrial organic chemistry [52]. It is readily accessible by acid-induced elimination of three moles of water [53], and even a pilot plant size process has been elaborated [52].

HMF has been used—as such, or upon generation *in situ* from starch hydrolysates—for the manufacture of special phenolic resins of type **30**, as acid catalysis induces its aldehyde as well as the hydroxymethyl group to react with phenol [57]:

30
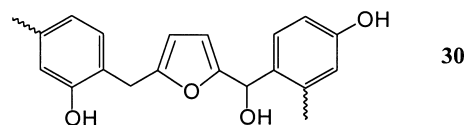
Of higher potential as basic organic intermediate chemicals are the various ensuing products of HMF, i.e. **31–38** (Scheme 6), for which well worked-out, large scale-adaptable reaction procedures have been developed [58–64].

Of these readily accessible intermediate chemicals, the 2,5-bis(hydroxymethyl)furan **31**, the 5-hydroxymethyl-2-furoic acid **32**, and the 2,5-dicarboxylic
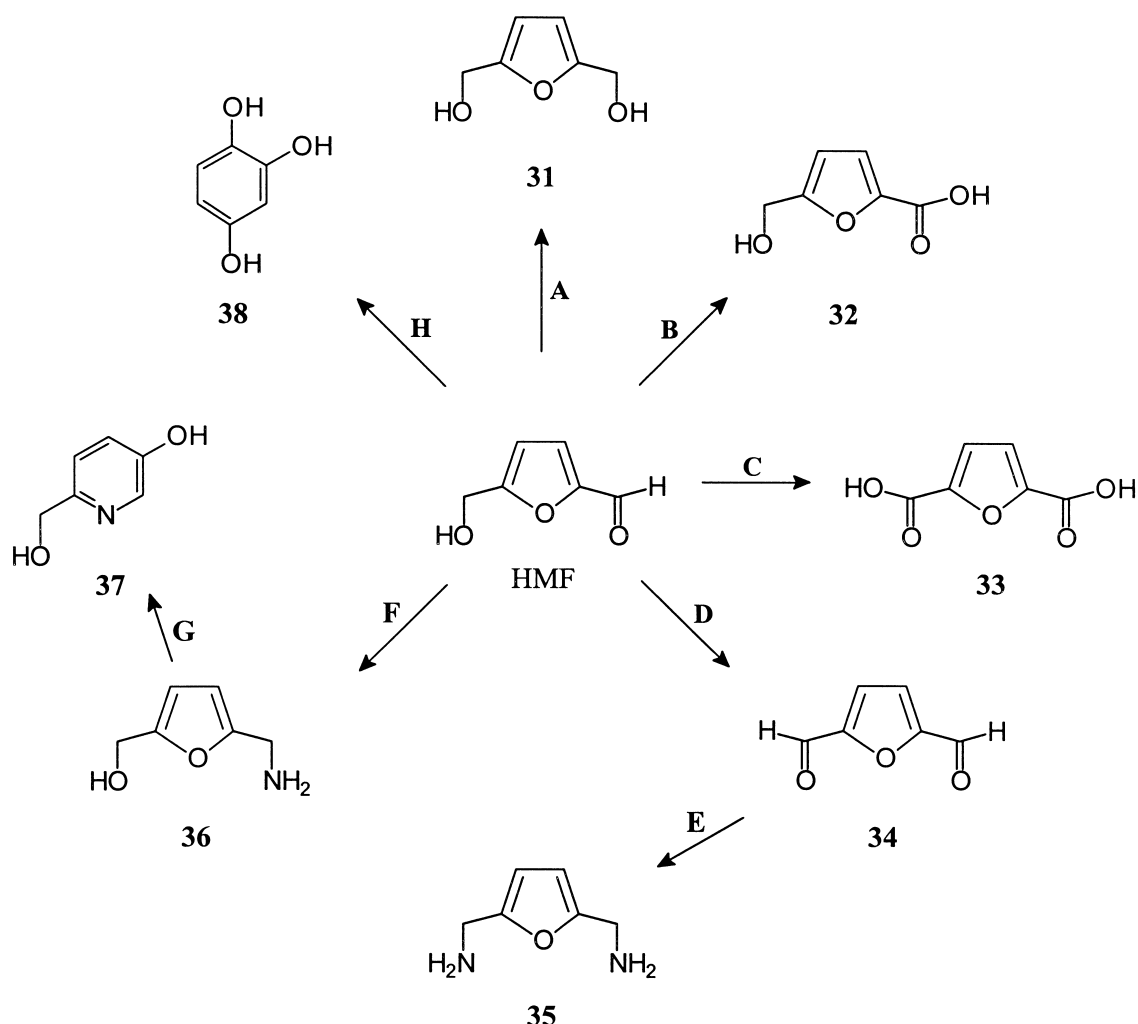

A Pt, C / H_2, quant. [58]	**E** NH_2OH, then Ni / H_2, 33% [59]
B Ag_2O, 100 °C, 75% [59]	**F** Ni / H_2, NH_3, 72% [62]
C Pt, C / O_2, pH 7, 91% [60]	**G** Br_2 / MeOH, 85% [63]
D $BaMnO_4$, 93% [59]	**H** H_2O / 330 °C / Δp [64]
$Ca(OCl)_2$ / TEMPO, 81% [61]	

Scheme 6. Versatile intermediate chemicals derived from hydroxymethylfurfural (HMF).

acid **33** have extensively been exploited for the preparation of furanoic polyesters: the diol **31** has been reacted with various aliphatic and aromatic diacids [65]; the ethyl ester of furoic acid **32**, upon polycondensation, gave a mixture of linear and cyclic products [66], whilst the furan-diacid **33** has been poly-esterified with a series of aliphatic diols or bisphenols [65]. Even the all-furanic polyester **39** has been successfully prepared from its respective monomeric components [65].
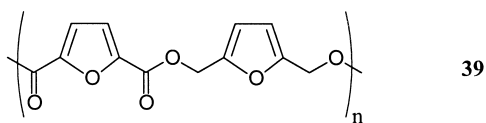
39
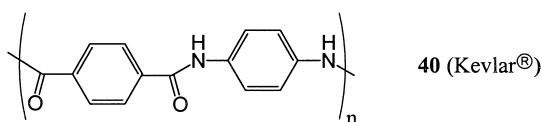
40 (Kevlar®)
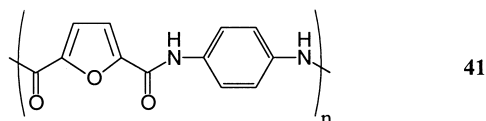
41
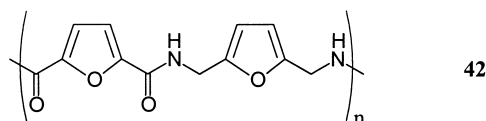
42

Another obvious development was the generation of furanic polyamides from the dicarboxylic acid **33** and the respective diamine, 2,5-bis(aminomethyl)furan **35**, as they can replace adipic or terephthalic acid, and, correspondingly, hexamethylene diamine or *p*-diaminobenzene, in the common industrially produced polyamides. Indeed, a series of such furanic polyamides has been prepared [67–70], utilizing **33** and aliphatic as well as aromatic diamines, of which polyamide **41** — an analog of Kevlar® (**40**) — had particularly promising decomposition and glass temperature parameters [70], distinctly better than those found for the all-furanoic polyamide **42**.

Despite of the impressive array of highly useful organic intermediate chemicals and marketable products derived from HMF, this fructose-based key compound is, as of now, not produced on an industrial scale. Obviously, the economic pre-conditions are not yet favorable enough to do so. A recent assessment of the economics of HMF against competitive petrochemical raw materials [71] gives ample evidence thereof: prices of naphtha

and ethylene are in the DM 300–800 range per ton, that of inulin (DM 1000/t) or fructose (~DM 2000/t) entailing a marketing price of HMF of at least DM 5000 per ton, certainly too expensive at present for a bulk scale industrial product. Accordingly, as long as the present economic situation in favor of fossil raw materials is prevailing, the applications of fructose-derived HMF lie in high value-added products, such as pharmaceuticals or other special niche materials, to be elaborated by further developmental exploitations. Prototype along this vein is Ranitidine (Zantac®, **43**) [72], a highly efficient anti-ulcer drug due to its potent, oral inhibition of histamine-induced gastric acid secretion [73], which was the first prescription drug exceeding $1 billion in annual sales [52]. Although **43** is presently prepared from furfural, its manufacture from HMF, whose structural features are contained in it, may be considerably more economic, if properly worked out.
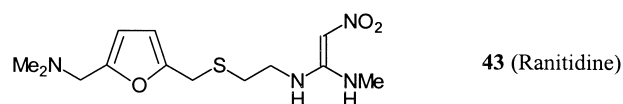
43 (Ranitidine)

3. L-Sorbose

L-Sorbose, the 5-epimer of D-fructose, is the most readily, large-scale available L-sugar (cf. Table 1) due to its technical production from D-sorbitol in the vitamin C fabrication process [12]. However, its non-food utilization has been exceedingly poor despite of the fact that the α-pyranoid tautomeric form is highly favored in solution (87–98%) in the temperature range of 27–85 °C [18], on account of which the "entry reactions" to pyranoid derivatives are proceeding in a more uniform manner and allow better yields than in the fructose case.
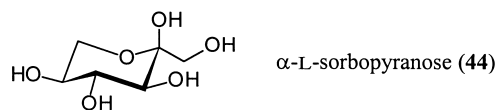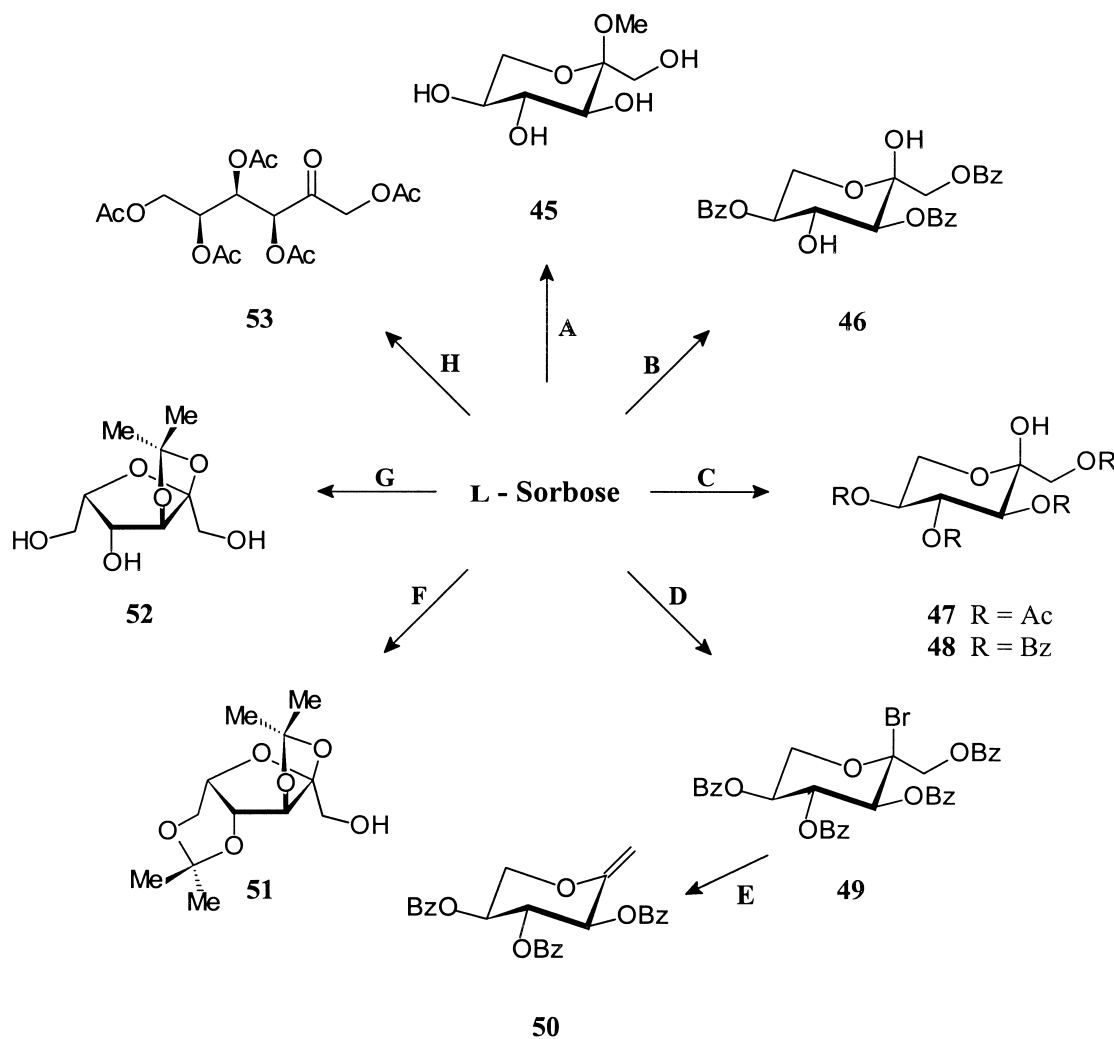

α-L-sorbopyranose (**44**)

Accordingly, Fischer-type glycosidation of L-sorbose with methanol/HCl at ambient temperature affords a mixture of methyl sorbosides in which the methyl α-L-sorbopyranoside (**45**) is highly preponderant (92% [27]), and may be isolated in yields of up to 90% [74]. Low temperature benzoylation proceeds selectively to the 1,3,5-tribenzoate **46** [75], whilst acylation under standard conditions at low temperature and prolonged

reaction times smoothly affords the pyranoid tetraacetate **47** [76] and tetrabenzoate **48** [77], respectively. If benzoylation is followed by exposure to hydrogen bromide, the sorbopyranosyl bromide **49** is obtained [40,47], which serves as an ideal precursor for the generation of the highly versatile *exo*-sorbal building block **50** [40].

Of the two well-accessible L-sorbose derivatives fixed in furanoid form, the 2,3:4,6-di-*O*-isopropylidene acetal **51** is available on ton-scale due to being a key intermediate in the vitamin C fabrication process [12,78], whilst the acquisition of the

mono-*O*-isopropylidene compound **52**, primary product of the acid-catalyzed acetonation towards **51**, is less optimized [79]. Of the various acyclic *keto*-L-sorbose derivatives known, the pentaacetate **53**, smoothly formed on zinc chloride-promoted acetylation [80] (cf. Scheme 7), appears to be the most easily preparable.

The array of well accessible pyranoid, furanoid and open-chain derivatives of L-sorbose is very similar to that derivable from D-fructose — as expected, as the two hexoses are 5-epimers only. The major difference in their preparative utilities appears to

|		
A	MeOH / 0.5% HCl, 15 h, 20 °C, 90% [74b]	
B	BzCl / pyridine, −10 °C, 43% [75]	
C	Ac$_2$O / pyridine, −10 °C, 65% [76] BzCl / pyridine, −10 °C, 71% [77]	
D	BzCl / pyridine, −10 °C [77], then HBr, 82% [40]	
E	Zn / methylimidazole, 80% [40]	
F	Me$_2$CO / H$_2$SO$_4$, 4 °C, >90% [78]	
G	Me$_2$CO / H$_2$SO$_4$, 40% [79]	
H	ZnCl$_2$ / Ac$_2$O, 70% [80]	

Scheme 7. Simple L-sorbose derivatives fixed in pyranoid, furanoid and open-chain form.

lie in the structures of their isopropylidene acetals, D-fructose invariably yielding pyranoid diaceto-nides with either 1-OH and 3-OH free (**11** and **12**, respectively), whilst L-sorbose only elaborates the furanoid mono- (**52**) or di-acetonide (**51**) with the hydroxyl groups at C-1, C-4 and C-6, or at C-1 unprotected. The use of L-sorbose derivatives, of course, will also be advantageous if the configura-tion of a given enantiopure target molecule mat-ches better with its array of chiral centers than with those of D-fructose.

4. Isomaltulose

This disaccharide, a 6-*O*-D-glucosyl-D-fructose (**55**), has also been designated "palatinose" due to its first isolation from molasses [81] in the Südzucker Research Laboratories at Offstein in the Palatinate section of central Germany. It is produced by Südzucker on a 35.000 ton per year scale presently by causing sucrose to undergo a *Protaminobacter rubrum*-induced glucosyl-shift [82,83] — a transfor-mation, that most likely proceeds via a closed-shell transition state of type **54** [10], as due to the water bridge between 2^g-O and 1^f-OH [84] both mono-saccharide portions conceivably exist as a glucosyl-cation/fructosyl-anion ion pair, in which the 6^f-OH is sterically close to the glucosyl-C-1 (Scheme 8).

In a very strict sense, however, this enzymatically promoted sucrose→isomaltulose conversion is not intramolecular, since the glucosyl transfer involved may be intercepted by other mono-saccharide acceptors, such as D-glucose, D-man-nose, and D-arabinose when added to the fermentation broth in fairly high concentration; although the major product is still isomaltulose (**55**), the corresponding disaccharides isomaltose, 6-*O*-α-D-glucosyl-D-mannose [85] and 5-*O*-α-D-glucosyl-D-arabinose [86] have been unequivocally identified. Another indication that the *Protamino-bacter rubrum*-promoted glucosyl transfer from sucrose to isomaltulose is neither rigidly intramo-lecular nor regiospecific follows from the findings [87,88], that the fermentation conditions (con-centration of sucrose, temperature, duration) can be modified in such a way as to make 1-*O*-α-D-glucosyl-D-fructose (trehalulose) the major product. When fermenting sucrose solutions with certain strains of *Pseudomonas mesoacidophila* or *Agro-bacterium radiobacter*, trehalulose and isomaltulose even accumulate in as high a ratio as 10:1 [89].
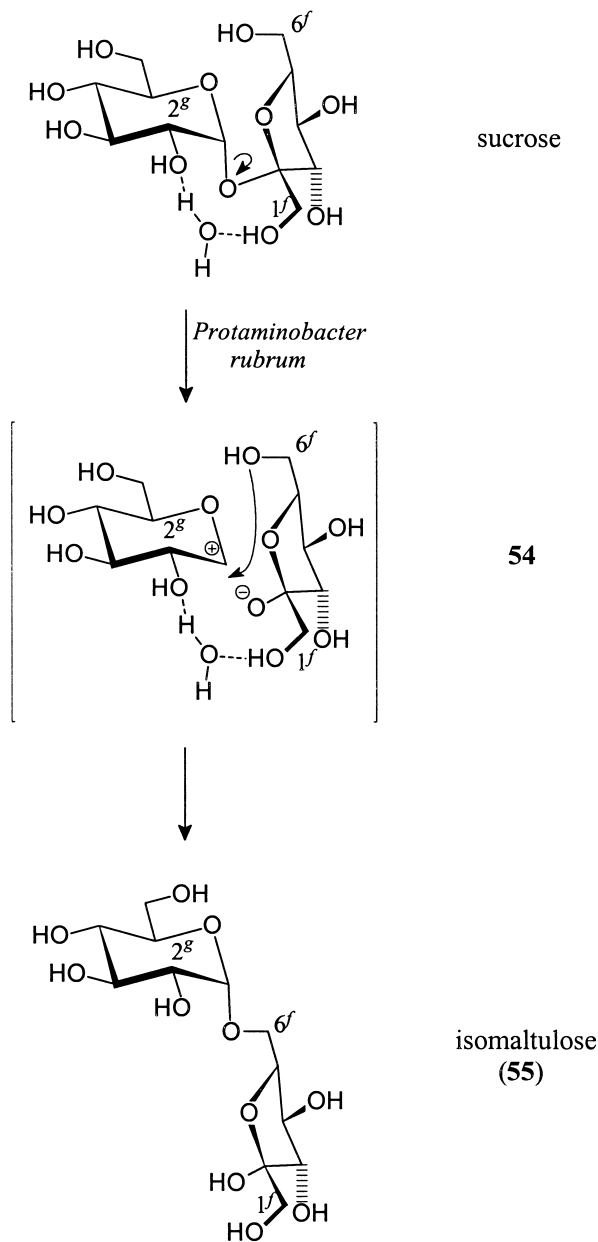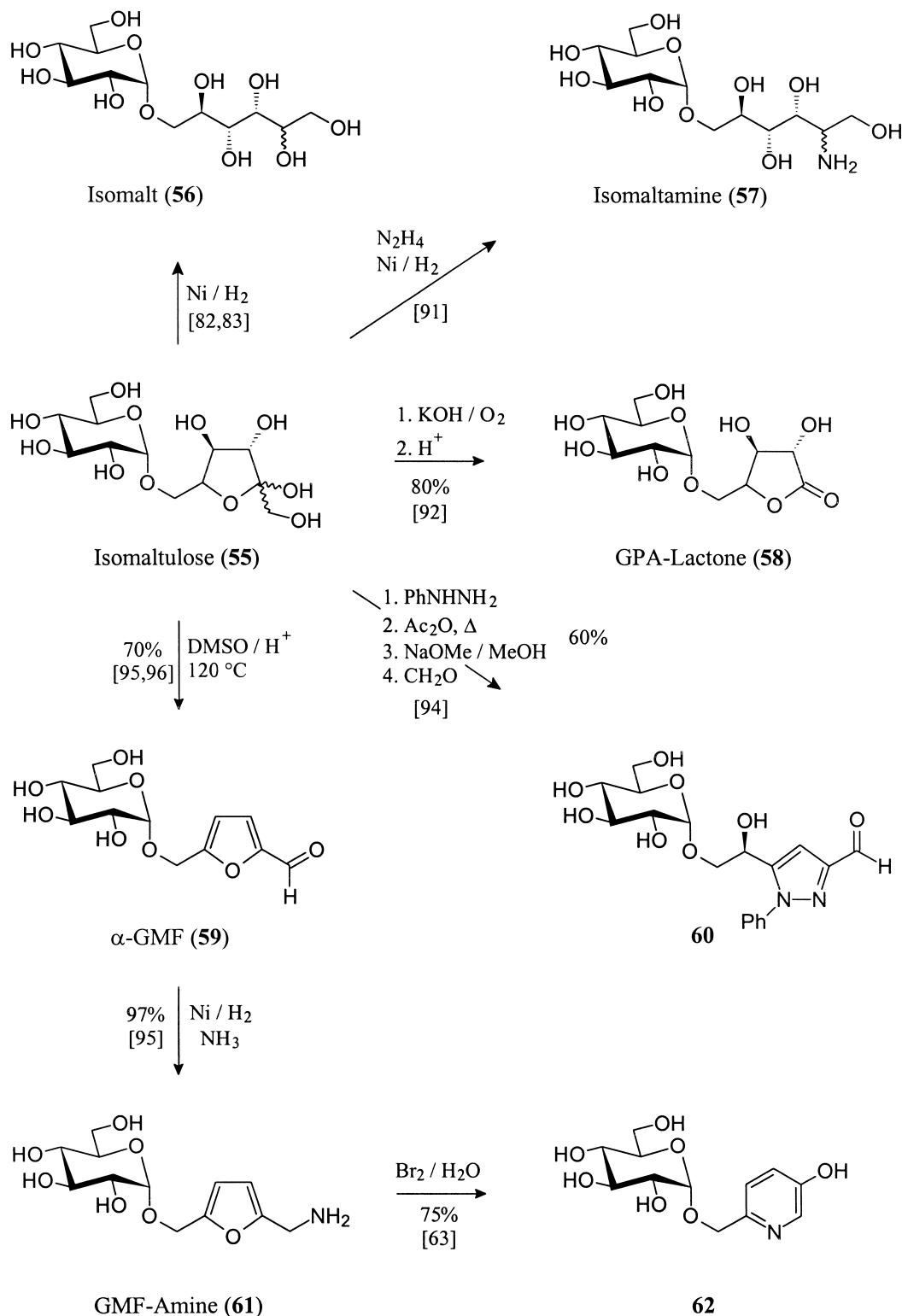

Scheme 8.

Isomaltulose (**55**) crystallizes in its α-furanoid tautomeric form as a dihydrate [90]. In solution, the number of tautomers are reduced to half (as compared to D-fructose), because due to the non-availability of the 6-OH group in the fructose portion, only the two furanoid tautomers are pre-vailing, of which the β-*f*-form usually pre-ponderates by about 3:1 [21]. In any of its derivatives, the fructose portion will either be fur-anoid or acyclic. Thus, catalytic hydrogenation yields a 1:1 mixture of the 6-*O*-glucosylated D-mannitol and D-glucitol (**56**), which has been named "isomalt"® and is used as a low caloric

sweetener with essentially the same taste profile as sucrose [82,83]. Non-food applications result from its reductive amination with hydrazine on a nickel catalyst, that smoothly generates a 1:1-mixture of α-glucosyl-(1→6)-2-amino-2-deoxy-D-glucitol and the

respective D-mannitol isomer [91], appropriately termed isomaltamine (57) in analogy to isomalt® (cf. Scheme 9). Air oxidation of isomaltulose in strongly alkaline solution (KOH) gives the potassium salt of the next lower aldonic acid, i.e. α-glucosyl-
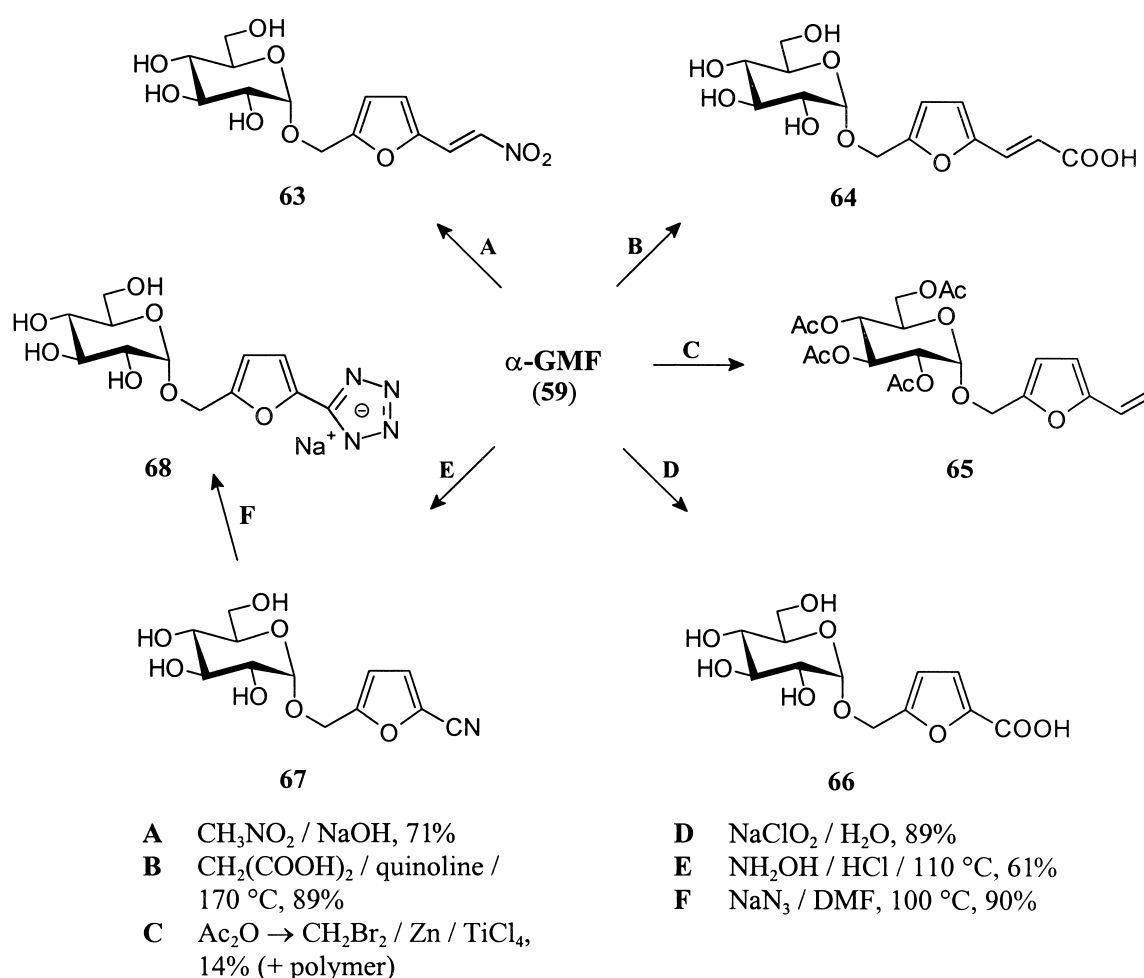

Scheme 9. Transformations of isomaltulose (palatinose, 55) into products with industrial application profiles.

(1→5)-D-arabinonic acid ("GPA"), isolable as the potassium salt or, after neutralization, as the GPA-lactone **58** in high yields each [92]. Gratifyingly, a recently developed preparatively useful 4-step procedure for the conversion of D-xylose into hydrophilically functionalized pyrazole-aldehydes [93] could be transferred to isomaltulose without affecting its glycosidic linkage: acetic anhydride-induced dehydrative cyclization of its phenylosazone and subsequent liberation of the *N*-acetylphenylhydrazone-blocked aldehyde function provided **60** [94], a versatile *N*-heterocyclic building block.

Another industrially relevant reaction of isomaltulose comprises its ready conversion into 5-glucosyloxymethyl-furfural ("α-GMF", **59**) by acidic dehydration of the fructose portion under conditions that retain the intersaccharidic linkage [95]. This process, i.e. **55** → **59**, can also be performed in a continuous flow reactor [96], and, hence, has the potential of being readily large-scale accessible. As a glucosylated HMF, α-GMF (**59**) provides a

rich ensuing chemistry towards products with broad application profiles. Reductive amination, for example, smoothly generates the α-GMF-amine **61**, from which a preparatively useful one-step oxidative ring expansion leads to glucosyloxymethyl-substituted 3-pyridinols of type **62** [63], which are of potential pharmaceutical interest as analogs — upon carbamoylation — of the para-sympathomimetic pyridostigmine. Aldol-type condensations with α-GMF deliver derivatives with polymerizable double bonds, e.g. routes A, B, and C in Scheme 10, most notably the acrylic acid **64** and the methylenation product **65**, that are expected to yield novel, hydrophilic polymers with interesting performance profiles [95]. Oxidation with sodium chlorite in a slightly acidic aqueous solution smoothly converted α-GMF into the respective furoic acid **66**, whereas brief exposure to hydroxylammonium chloride in dimethyl sulfoxide at 100 °C elaborated the nitrile **67**, which may be used as a dipolarophile in [3 + 2]-cycloadditions since

A   CH$_3$NO$_2$ / NaOH, 71%
B   CH$_2$(COOH)$_2$ / quinoline / 170 °C, 89%
C   Ac$_2$O → CH$_2$Br$_2$ / Zn / TiCl$_4$, 14% (+ polymer)

D   NaClO$_2$ / H$_2$O, 89%
E   NH$_2$OH / HCl / 110 °C, 61%
F   NaN$_3$ / DMF, 100 °C, 90%

Scheme 10. Ensuing chemistry of 5-(α-D-glucosyloxy)methyl-furfural (α-GMF, **59**) [95].

heating with sodium azide in *N,N*-dimethylformamide readily (91%) affords the tetrazolide **68** [95].

Various products with industrial application profiles have been prepared from the diversely modified isomaltulose building blocks **57–66** (Scheme 11). As a pronouncedly hydrophilic amine of a disaccharide alcohol, isomaltamine (**57**) is a versatile intermediate for further derivatization, e.g. with fatty acid halides to non-ionic, biologically degradable detergents of type **69** [97], or with methacrylic acid derivatives to provide polymerizable acrylamido-disaccharides of type **70** [91]. Amidation of GPA-lactone **58** with long-chain amines, e.g. the C_8- and C_{12}-"fat amines", provided the GPA-amides **71** and **72** [92], which not only exhibit promising detergent profiles, but also surprising liquid crystalline properties, such as S_{Ad}-phases over a broad temperature range [98]; in these, the X-ray-derived layer thickness was less than twice the extended molecular length indicating partial overlap of the hydrocarbon "tails".

Similarly, *N*-acylation of GMF-amine **61** with fatty acid chlorides affords compounds of type **73–75** [95], i.e. non-ionic surface-active agents, in which the hydrophobic fat-alkyl residue and the hydrophilic glucose part are separated by a quasi-aromatic spacer; similar application potential

pertains to the esters of *α*-GMF-acid **66** with long-chain alcohols, e.g. **76** and **77** [95].
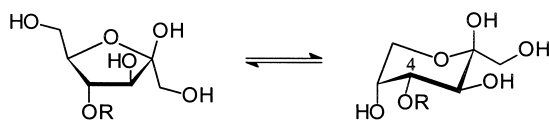
5. Lactulose

In terms of accessibility, lactulose, a 4-*O*-*β*-D-galactopyranosyl-D-fructose (**78**), is—after isomaltulose—the second most important keto-disaccharide. It is presently manufactured on an approximate 10.000 t/a scale (cf. Table 1) by base-catalyzed isomerization of lactose [99,100], its main use being in the medical treatment of several intestinally-related disorders [101]. Unlike lactose, it resists hydrolysis in the human intestine [102], and appears to act as an extremely mild purgative and, because of its stimulation of the colonic lactobacilli, helps minimize the formation of ammonia-producing organisms.

The commercial crystalline lactulose is normally anhydrous and comprises a rarely observed 75:15:10 mixture of the *β-f*, *β-p*, and *α-f* tautomers [103], yet under special crystallization conditions the pure *β*-furanoid form can be obtained as a trihydrate, of which an X-ray structure has been performed [104]. An aqueous solution at 25 °C has the *β-p* anomer as the major component (61%) with
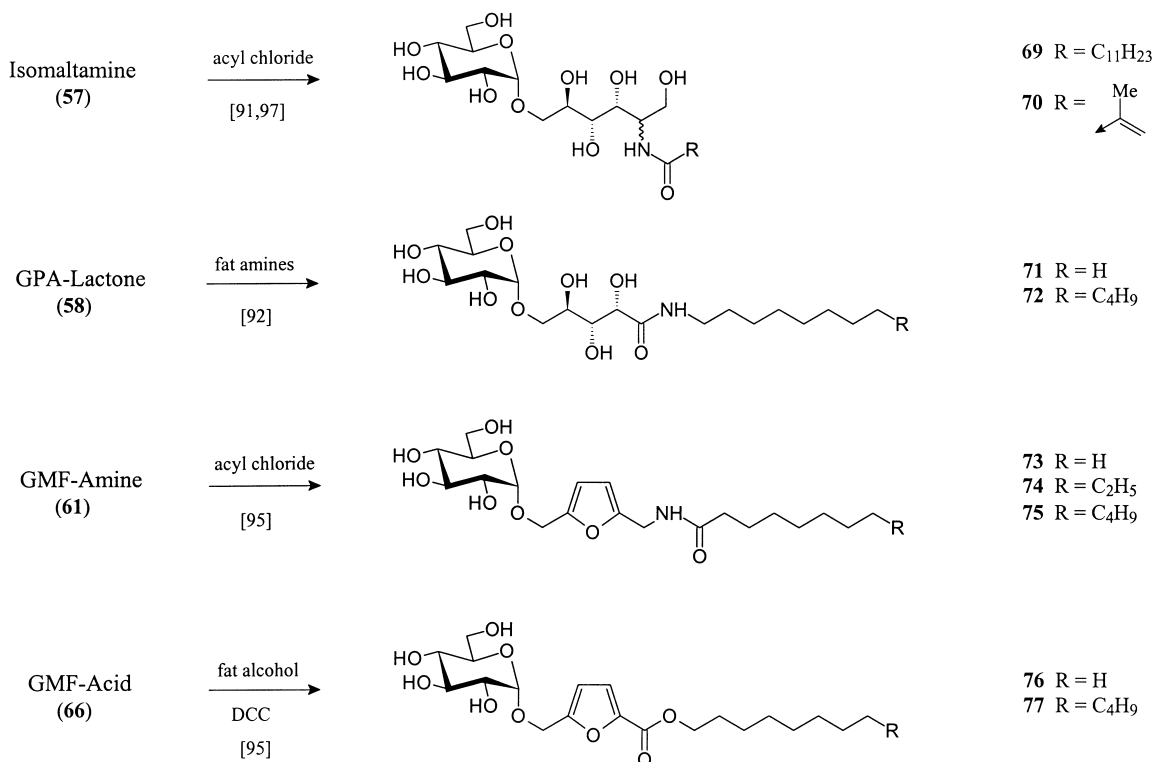
Scheme 11. Isomaltulose-derived products with useful application profiles.

the *β-f* and *α-f* forms following (29 and 8%, respectively) [105], whereas in dimethyl sulfoxide the two furanoid tautomers are dominating the equilibrium mixture [106], presumably due to enhanced intramolecular hydrogen bonding of the type depicted in Fig. 3.


Lactulose (**78**, R = β-Gal*p*)

Maltulose (**79**, R = α-Glc*p*)

With respect to the exploitation of the chemistry of lactulose towards industrially useful intermediate or speciality chemicals, exceedingly little has been done, such that only a few simple derivatives — e.g. the octaacetate [107] — have been prepared which are of no use in this context. This state of affairs is not surprising as milk processing industry — whey is the raw material for the acquisition of lactose and, hence, lactulose — exhibits a pronounced reluctance towards either doing the basic exploratory research necessary itself, or sponsoring it at academic institutions. Another impediment for a straightforward capitalization on these readily accessible disaccharides (cf. Table 1) appears to be a preconceived opinion in various grant-giving institutions that basic research on lactose and lactulose should not be funded since as animal products they have no bearing on agricultural farming regulations.

There are several other fructose-containing disaccharides which are readily accessible and, due to worked-out process methodology, could be produced on an industrial scale, if required: maltulose (**79**), available from maltose by base-promoted isomerization [21,108], trehalulose (**81**), obtainable from sucrose by enzymatic transfer of its glucosyl portion to the 1-OH of fructose [87–89] (vide supra), and leucrose (**80**), similarly generated by *Leuconostoc mesenteroides*-promoted glucosyl transfer from sucrose to the fructose-5-OH [109].
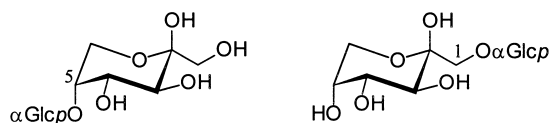
Of these ketose-disaccharides, leucrose, as a 5-*O*-α-D-glucopyranosyl-D-fructose (**80**), is unique in such as it can only adopt pyranoid tautomeric forms in the fructose portion. As evidenced by an X-ray structural analysis [110], it crystallizes as a monohydrate in its *β-p* anomeric form, and even in aqueous solution this *β-p* form is highly preponderant (98% at 20 °C) [21]. The hydrophobicity potential profile based on its solvent accessible surface has also been generated by molecular modeling [111]. The chemistry of leucrose has been fairly well exploited, such that not only simple derivatives have been prepared but, for example, a benzoylated *exo*-fructal (a 5-*O*-glucosylated analog of **15**) or *N*-glycosides [112], each of potential utility as versatile building blocks.

By contrast, the ensuing chemistry of maltulose (**79**) and of trehalulose (**81**) is, as of now, totally undeveloped. It is to be considerably more capricious than that of isomaltulose (**55**) and leucrose (**80**), as all four cyclic tautomeric forms are present in aqueous or pyridine solution [21], so despite the preponderance of the respective *β-p* forms (as depicted in formulae **79** and **81**), derivatizations are expected to yield complex mixtures. This particularly holds for trehalulose, which has not been obtained in crystalline (and, hence, pure tautomeric) form, but as an amorphous product comprising a 75:12:6:2 mixture of the *β-p*, *β-f*, *α-f*, and *α-p* tautomers [88].

6. Coda[3] — Conclusions

Despite of the various new "entry reactions" and "reaction channels" advanced here for the three bulk-scale accessible ketoses, their potential as an organic raw material for the elaboration of industrially useful chemicals is far from being fully exploited; numerous further reactions are conceivable through application of modern methodologies and wait for elaboration – a situation that holds globally for all carbohydrates.

This, unambiguously, points towards broad-scale, practically-oriented basic research to be performed in the entire spectrum of promising applications, in order to decisively improve the competitiveness of well-accessible low-molecular-weight carbohydrates as basic organic raw materials.

Leucrose (**80**)   Trehalulose (**81**)

---

[3] According to Websters Dictionary, in music, a passage which brings a composition to a definite, formal close.

A pre-condition for auspicious advances towards this end is, however, that the chemical industry becomes actively engaged in the basic research to be performed and gives up its present wait-and-see attitude: wait for industrially interesting results elaborated in academic institutions, and only then see, how they can be exploited towards lucratively marketable products.

In striving for the replacement of fossil raw materials by those annually regrowing, it would be an unrealistic strategy trying to generate from carbohydrates, i.e. 95% of the biomass annually regrowing, the very same basic chemicals that are well accessible from petrochemical sources. The objective emerging from the present scenario is another one, the only reasonable one, in fact: development of products from renewable resources with analogous industrial application profiles and with as little alteration of their structural framework as possible. Only then economically sound alternatives to petrochemicals will become available.

Acknowledgements

References

[1] F.W. Lichtenthaler (Ed.), *Carbohydrates as Organic Raw Materials*, VCH Publ., Weinheim/New York, 1991.

[2] G. Descotes (Ed.), *Carbohydrates as Organic Raw Materials II*, VCH Publ., Weinheim/New York, 1993.

[3] M. Eggersdorfer, S. Warwel, and G. Wulff (Eds.), *Nachwachsende Rohstoffe: Perspektiven für die Chemie*, VCH Publ., Weinheim/New York, 1993.

[4] H. van Bekkum, H. Röper, and A.G.J. Voragen (Eds.), *Carbohydrates as Organic Raw Materials III*, VCH Publ., Weinheim/New York, 1996.

[5] H. Eierdanz (Ed.), *Perspektiven nachwachsender Rohstoffe in der Chemie*, VCH Publ., Weinheim/New York, 1996.

[6] F.W. Lichtenthaler and S. Mondel, *Pure Appl. Chem.*, 69 (1997) 1853–1866.

[7] W. Praznik and A. Huber (Eds.), *Carbohydrates as Organic Raw Materials IV*, Wiener Universitätsverlag, Wien, Austria, 1998.

[8] A. Hugill, Introductory Dedicational Metaphor, in *Sugar and all That. A History of Tate and Lyle*, Gentry Books, London, 1978.

[9] World sugar production 1995/96–1997/98. *Zuckerind. (Berlin)*, 123 (1998) 473.

[10] F.W. Lichtenthaler, P. Pokinskyj, and S. Immel, *Zuckerind. (Berlin)*, 121 (1996) 174–190.

[11] H. Hustede, H.-J. Haberstroh, and E. Schinzig, *Ullmann's Encyclop. Ind. Chem.*, 5th ed., Vol. A12, 1996, pp 449–456.

[12] B. Oster and U. Fechtel, *Ullmann's Encyclop. Ind. Chem.*, 5th ed., Vol. A27, 1996, 547–559.

[13] (a) K. Hill, W. von Rybinski, and G. Stoll, *Alkyl Polyglycosides: Technology, Properties, and Applications*, VCH Publ., Weinheim/New York, 1997; (b) W. von Rybinski and K. Hill, *Angew. Chem.*, 110 (1998) 1394–1412; *Angew. Chem. Int. Ed.*, 37 (1998) 1328–1345.

[14] K. Heyns, *Starch/Stärke*, 30 (1978) 345–351.

[15] C.P. Barry and J. Honeyman, *Adv. Carbohydr. Chem.*, 7 (1952) 53–98.

[16] J.V. Karabinos, *Adv. Carbohydr. Chem.*, 7 (1952) 99–136.

[17] J.A. Kanters, G. Roelofsen, B.P. Alblas, and I. Meinders, *Acta Crystallogr., Sect. B.*, 33 (1977) 665–672.

[18] S.J. Angyal, *Adv. Carbohydr. Chem. Biochem.*, 42 (1984) 37–68.

[19] B. Schneider, F.W. Lichtenthaler, G. Steinle, and H. Schiweck, *Liebigs Ann. Chem.*, (1985) 2443–2453.

[20] R.S. Shallenberger, C.Y. Lee, T.E. Acree, J. Barnard, and M.G. Lindley, *Carbohydr. Res.*, 58 (1977) 209–211; R.S. Shallenberger, *Pure Appl. Chem.*, 50 (1978) 1412.

[21] F.W. Lichtenthaler and S. Rönninger, *J. Chem. Soc., Perkin Trans. 2*, (1990) 1489–1497.

[22] A.S. Perlin, P. Herve du Penhoat, and H.S. Isbell, *Am. Chem. Soc. Symp. Ser.*, 117 (1973) 39–50; P. Dais and A.S. Perlin, *Carbohydr. Res.*, 136 (1985) 215–223.

[23] P. Brigl and R. Schinle, *Ber. Dtsch. Chem. Ges.*, 66 (1933) 325–330.

[24] F.W. Lichtenthaler, J. Klotz, and F.-J. Flath, *Liebigs Ann. Chem.*, (1995) 2069–2080.

[25] P. Brigl and R. Schinle, *Ber. Dtsch. Chem. Ges.*, 67 (1934) 127–130; J.W. van Cleve, *Methods Carbohydr. Chem.*, 2 (1963) 237–238.

[26] A. Bouali, G. Descotes, D.F. Ewing, A. Grouiller, J. Lefkidou, A.-D. Lespinasse, and G. Mackenzie, *J. Carbohydr. Chem.*, 11 (1992) 159–169.

[27] G.S. Bethell and R.J. Ferrier, *Carbohydr. Res.*, 31 (1973) 69–80.

[28] P. Voß, *Starch/Stärke*, 32 (1980) 24–27.

[29] L. Johnson, D.L. Verraest, J. van Haveren, K. Hakala, J.A. Peters, and H. van Bekkum, *Tetrahedron: Asymmetry*, 5 (1994) 2475–2484.

[30] C.G.J. Verhart, C.T.M. Fransen, B. Zwanenburg, and G.J.F. Chittenden, *Recl. Trav. Chim. Pays-Bas*, 115 (1996) 133–139.

[31] K. Noda, A. Nakagawa, Y. Haraguchi, K. Ueda, M. Hirano, I. Nishioka, and A. Yagi (Hisamitsu Pharmac. Co.), *Ger. Offen.* DE 3.019.221 (appl. 1979); *Chem. Abstr.* 95 (1981) 25551e.

[32] A.T.J.W. de Goede, M.P.J. van Deurzen, I.G. van der Leij, A.M. van der Heijden, J.M.A. Baas, F. van Rantwijk, and H. van Bekkum, *J. Carbohydr. Chem.*, 15 (1996) 331–349.

[33] C.B. Purves and C.S. Hudson, *J. Am. Chem. Soc.*, 59 (1937) 1170–1174.

[34] (a) F.W. Lichtenthaler and H.K. Yahya, *Chem. Ber.*, 100 (1967) 2389–2400; (b) F.W. Lichtenthaler, A. Pashalidis, and H.J. Lindner, *Carbohydr. Res.*, 164 (1987) 357–372.

[35] H.W.C. Raaijmakers, E.G. Arnouts, B. Zwanenburg, and G.J.F. Chittenden, *Carbohydr. Res.*, 257 (1994) 293–297.

[36] J.Y.C. Chan, P.P.L. Cheong, L. Hough, and A.C. Richardson, *J. Chem. Soc., Perkin Trans. 1*, (1985) 1445–1455.

[37] F.W. Lichtenthaler, *Enantiopure Building Blocks from Sugars and their Utilization in Natural Product Synthesis,* in R. Scheffold (Ed.), *Modern Synthetic Methods*, Vol. 6, VCH Publ., Weinheim/New York, 1992, pp 273–376.

[38] F.W. Lichtenthaler and F. Hoyer, *Carbohydr. Res.*, 253 (1994) 141–150.

[39] R.K. Ness and H.G. Fletcher Jr., *J. Org. Chem.*, 33 (1968) 181–184.

[40] F.W. Lichtenthaler, S. Hahn, and F.-J. Flath, *Liebigs Ann. Chem.*, (1995) 2081–2088.

[41] A. Boettcher, Dissertation, Techn. Hochschule Darmstadt, 1995.

[42] R.F. Brady Jr., *Carbohydr. Res.*, 15 (1970) 35–40.

[43] G. Koßmehl and J. Volkheiner, *Liebigs Ann. Chem.*, (1989) 1127–1130.

[44] J. Kang, G.J. Lim, S.K. Yoon, and M.Y. Kim, *J. Org. Chem.*, 60 (1995) 564–577.

[45] B.E. Maryanoff, S.O. Nortey, J.F. Gardocki, R.P. Shank, and S.P. Dodgson, *J. Med. Chem.*, 30 (1987) 880–887.

[46] (a) R. Weidenhagen, R. Herrmann, and H. Wegner, *Ber. Dtsch. Chem. Ges.*, 70 (1937) 570–583; (b) J.R. Totter and W.J. Darby, *Org. Synth., Coll. Vol. III*, (1964) 460–462.

[47] J. Streith, A. Boiron, A. Frankowski, D. Le Nouen, H. Rudyk, and T. Tschamber, *Synthesis*, (1995) 944–946.

[48] F.B. Cramer and E. Pacsu, *J. Am. Chem. Soc.*, 59 (1937) 1148; M.L. Wolfrom and A. Thompson, *Methods Carbohydr. Chem.*, 2 (1963) 213.

[49] (a) E. Pacsu and F.V. Rich, *J. Am. Chem. Soc.*, 55 (1933) 3018–3024; (b) B. Helferich and R. Steinpreis, *Chem. Ber.*, 91 (1958) 1794–1798.

[50] D.H. Brauns, *J. Am. Chem. Soc.*, 42 (1980) 1846–1854; E. Pacsu and F.V. Rich, *J. Am. Chem. Soc.*, 54 (1932) 1697.

[51] F.W. Lichtenthaler, E. Cuny, D. Martin, S. Rönninger, and T. Weber, *Practical Routes from Mono- and Disaccharides to Building Blocks with Industrial Application Profiles,* in F.W. Lichtenthaler (Ed.), *Carbohydrates as Organic Raw Materials*, VCH Publ., Weinheim/New York, 1991, p 213.

[52] H. Schiweck, M. Munir, K.M. Rapp, B. Schneider, and M. Vogel, *New Developments in the Use of Sucrose as an Industrial Bulk Chemical,* in F.W. Lichtenthaler (Ed.), *Carbohydrates as Organic Raw Materials*, VCH Publ., Weinheim/New York, 1991, pp 78–82.

[53] B.F.M. Kuster, *Starch/Stärke*, 42 (1990) 314–321.

[54] K. Hamada, H. Yoshihara, and G. Suzukamo, *Chem. Lett.*, (1982) 617–618.

[55] L. Zervas and P. Sessler, *Ber. Dtsch. Chem. Ges.*, 66 (1933) 1698–1703.

[56] W.T.J. Morgan and T. Reichstein, *Helv. Chim. Acta*, 21 (1938) 1023–1031.

[57] H. Koch, F. Krause, R. Steffen, and H.U. Woelk, *Starch/Stärke*, 35 (1983) 304–313; H. Koch and J. Pein, *Polym. Bull. (Berlin)*, 13 (1985) 525–532.

[58] V. Schiavo, G. Descotes, and J. Mentech, *Bull. Soc. Chim. Fr.*, 128 (1991) 704–711.

[59] T. El Hajj, A. Masroua, J.-C. Martin, and G. Descotes, *Bull. Chem. Soc. Chim. Fr.*, (1987) 855–860.

[60] E.I. Leupold, M. Wiesner, M. Schlingmann, and K. Rapp, *Ger. Offen.* DE 3.826.073 (appl. 1988); *Chem. Abstr.*, 113 (1990) 23678t.

[61] L. Cottier, G. Descotes, J. Lewkowski, R. Skowroñski, and E. Viollet, *J. Heterocycl. Chem.*, 32 (1995) 927–929.

[62] N. Elming and N. Clauson-Kaas, *Acta Chem. Scand.*, 10 (1956) 1603–1605.

[63] C. Müller, V. Diehl, and F.W. Lichtenthaler, *Tetrahedron*, 54 (1998) 10703–10712.

[64] G.C.A. Luijkx, F. van Rantwijk, and H. van Bekkum, *Carbohydr. Res.*, 242 (1993) 131–139.

[65] J.A. Moore and J.E. Kelly, *Macromolecules*, 11 (1978) 568–573; *Polymer*, 20 (1979) 627–628; *J. Polym. Sci. Polym. Chem. Ed.*, 22 (1984) 863–864; J.A. Moore and W.W. Bunting, *Polym. Sci. Technol. (Plenum), Adv. Polym. Synth.*, 31 (1985) 51–91.

[66] H. Hirai, *J. Macromol. Sci. Chem.*, A21 (1984) 1165–1169.

[67] H. Hopff and A. Krieger, *Makromol. Chem.*, 47 (1961) 93–113.

[68] M.G. Grishkova, V. Trosnitskaya, K.A. Malyshevskaya, and N.A. Tyakaykina, *Fiz. Khim. Tekhnol.*, (1969) 240–244; *Chem. Abstr.*, 75 (1971) 99835x.

[69] A. Mitiakoudis, A. Gandini, and H. Cheradame, *Polym. Commun.*, 26 (1985) 246–249.

[70] A. Mitiakoudis and A. Gandini, *Macromolecules*, 24 (1991) 830–835.

[71] M. Kunz, in A. Fuchs (Ed.), *Inulin and Inulin-containing Crops*, Elsevier, Amsterdam, 1993, pp 149–160.

[72] B.J. Price, J.W. Clitherow, and J. Bradshaw (Allen and Hanburys Lts.), *Swiss Patent* 640.846 (appl. 1978); *Chem. Abstr.*, 101 (1984) 23317b; J.W. Clitherow (Glaxo Group Ltd.), *US Patent* 4,497,961 (appl. 1980); *Chem. Abstr.*, 102 (1985) 166604z.

[73] J. Bradshaw, R.T. Brittain, J.W. Clitherow, M.J. Daly, D. Jack, B.J. Price, and R. Stables, *Brit. J. Pharmacol.*, 66 (1979) 464P.

[74] E. Fischer, *Ber. Dtsch. Chem. Ges.*, 28 (1895) 1145–1167; (b) G. Arragon, *Compt. Rend. Acad. Sci. Fr.*, 199 (1934) 1231–1233; *Bull. Soc. Chim. Biol.*, 17 (1935) 831–837.

[75] M.C. Teglia and R.A. Cadenas, *Carbohydr. Res.*, 19 (1971) 223–230.

[76] H.H. Schlubach and G. Graefe, *Liebigs Ann. Chem.*, 532 (1937) 211–227.

[77] H. Paulsen, H. Köster, and K. Heyns, *Chem. Ber.*, 100 (1967) 2669–2680.

[78] T.C. Crawford and S.A. Crawford, *Adv. Carbohydr. Chem. Biochem.*, 37 (1980) 92–96.

[79] T. Reichstein and A. Grüssner, *Helv. Chim. Acta*, 17 (1980) 311–328.

[80] (a) H.H. Schlubach and J. Vorwerk, *Ber. Dtsch. Chem. Ges.*, 66 (1933) 1251–1253; (b) F.B. Cramer and E. Pacsu, *J. Am. Chem. Soc.*, 59 (1937) 1467–1469; (c) H. Zinner and U. Schneider, *Chem. Ber.*, 96 (1963) 2159–2164.

[81] R. Weidenhagen and S. Lorenz, *Angew. Chem.*, 69 (1954) 641; *Z. Zuckerind.*, 7 (1954) 533–534; *Chem. Abstr.*, 52 (1958) 6823h.

[82] H. Schiweck, M. Munir, K.M. Rapp, B. Schneider, and M. Vogel, *Zuckerind. (Berlin)*, 115 (1990) 555–565.

[83] M. Kunz, *Ullmann's Encyclop. Ind. Chem.*, 5th ed., A25 (1994) 426–429.

[84] S. Immel and F.W. Lichtenthaler, *Liebigs Ann. Chem.*, (1995) 1925–1937.

[85] W. Mauch and S. Schmidt-Berg-Lorenz, *Z. Zuckerind.*, 14 (1964) 375–383; *Chem. Abstr.*, 61 (1964) 14877h.

[86] W. Mauch and F. El Aama, *Zuckerind. (Berlin)*, 26 (1976) 21–25; 711-713; *Chem. Abstr.*, 84 (1976) 166575a; 86 (1977) 102209t.

[87] M. Munir (Südzucker AG), *German Patent* 3.241.788 (appl. 1982); *Chem. Abstr.*, 101 (1984) 88842p.

[88] M. Munir, B. Schneider, and H. Schiweck, *Carbohydr. Res.*, 164 (1987) 477–485.

[89] T. Sugitani, K. Tsuyuki, Y. Miyata, T. Ebashi, H. Okui, Y. Nakajima, and K. Sawada (Mitsui Sugar Co., Südzucker AG), *European Patent* EP 483.755 (appl. 1990); *Chem. Abstr.*, 117 (1992) 110105e.

[90] W. Dreißig and P. Luger, *Acta Crystallogr., Sect. B*, 29 (1973) 514–521.

[91] J. Klein, W. Behrens, and M. Kunz (Südzucker AG), *German Offen.* DE 3.625.931 (appl. 1986); *Chem. Abstr.*, 110 (1989) 95711i; M. Kunz, L. Guderjahn, M. Schüttenhelm, and J. Kowalczyk (Südzucker AG), *German Offen.* DE 4.310.032 (appl. 1993); *Chem. Abstr.* 122 (1995) 191050m.

[92] F.W. Lichtenthaler, R. Klimesch, V. Müller, and M. Kunz, *Liebigs Ann. Chem.*, (1993) 975–980.

[93] V. Diehl, E. Cuny, and F.W. Lichtenthaler, *Heterocycles*, 48 (1998) 1193–1201.

[94] N. Oikawa, C. Müller, M. Kunz, and F.W. Lichtenthaler, *Carbohydr. Res.*, 309 (1998) 269–279.

[95] F.W. Lichtenthaler, D. Martin, T. Weber, and H. Schiweck, *Liebigs Ann. Chem.*, (1993) 967–974.

[96] F.W. Lichtenthaler, D. Martin, T. Weber, and H. Schiweck (Südzucker AG), *German Offen.* DE 3 936 522 (appl. 1989); *Chem. Abstr.*, 115 (1991) 92826t.

[97] M. Kunz, *Disaccharide Derivatives as Intermediates for Surfactants, Polymers, and Polymeric Surfactants*, in G. Descotes (Ed.), *Carbohydrates as Organic Raw Materials II*, VCH Publ., Weinheim/New York, 1993, pp 135–161.

[98] T. Hanemann, E. Schumacher, W. Haase, and F.W. Lichtenthaler, *Liquid Cryst.*, 27 (1997) 47–50.

[99] H. Pluim and M. Verhage, *Ullmann's Encyclop. Ind. Chem.*, 5th ed., A15 (1990) 111–114.

[100] (a) K.B. Hicks and F.W. Parrish, *Carbohydr. Res.*, 82 (1980) 393–397; (b) M. Dorscheid and R. Krumbholz (Duphar Internat. Res. B.V.),

European Patent EP 375 046 (appl. 1988); *Chem. Abstr.*, 113 (1990) 231930w; (c) M. Kozempel and M. Kurantz, *J. Chem. Technol. Biotechnol.*, 59 (1994) 25–29.

[101] H.O. Conn, *Gastroenterology*, 74 (1978) 624-626; H.O. Conn and M.M. Lieberthal (Eds.), *The Hepatic Coma Syndromes and Lactulose*, Williams and Wilkins Co., Baltimore, MD, 1979.

[102] A. Dahlquist and J.D. Gryboski, *Biochim. Biophys. Acta*, 110 (1965) 635–636.

[103] G.A. Jeffrey, R.A. Wood, P.E. Pfeffer, and K.B. Hicks, *J. Am. Chem. Soc.*, 105 (1983) 2128–2133.

[104] G.A. Jeffrey, D. Huang, P.E. Pfeffer, R.L. Dudley, K.B. Hicks, and E. Nitsch, *Carbohydr. Res.*, 226 (1992) 29–42.

[105] P.E. Pfeffer and K.B. Hicks, *Carbohydr. Res.*, 102 (1982) 11–22.

[106] P.E. Pfeffer, K.B. Hicks, and W.L. Earl, *Carbohydr. Res.*, 111 (1983) 181–194; M. Jaseja, A.S. Perlin, and P. Dais, *Org. Magn. Reson.*, 28 (1990) 283–289.

[107] H.L. Frush and H.S. Isbell, *J. Res. Natl. Bur. Standards*, 35 (1945) 122–130; E.M. Montgomery, *Methods Carbohydr. Chem.*, 1 (1962) 325–328.

[108] (a) I. Machida, J. Kanaeda, H. Miki, S. Kubomura, H. Toda, and T. Shiroishi (Niken Chemicals), *Jpn. Kokai* 73–49938 (appl. 1971); *Chem. Abstr.*, 79 (1973) 126744v; (b) J.A. Rendleman Jr. and J.E. Hodge, *Carbohydr. Res.*, 75 (1979) 83–99; (c) K.B. Hicks, E.V. Symanski, and P.E. Pfeffer, *Carbohydr. Res.*, 112 (1983) 37–50.

[109] (a) D. Schwengers and H. Benecke (Pfeifer & Langen), *German Offen.* DE 3.446.380 (appl. 1984); *Chem. Abstr.*, 105 (1986) 77815p; (b) D. Schwengers, *Leucrose, a Ketodisaccharide of Industrial Design,* in F.W. Lichtenthaler (Ed.), *Carbohydrates as Organic Raw Materials*, VCH Publ., Weinheim/New York, 1991, pp 183–195; (c) M. Böker, H.-J. Jördening, and K. Buchholz, *Biotechnol. Bioengineering*, 43 (1994) 856–864. (d) K. Buchholz, M. Noll-Borchers, and D. Schwengers, *Starch/Stärke*, 50 (1998) 164–172.

[110] J.A. Kanters, W.P.J. Gaykema, and G. Roelofsen, *Acta Crystallogr., Sect. A*, 34 (1978) s295; J. Thiem, M. Kleeberg, and K.H. Klaska, *Carbohydr. Res.*, 189 (1989) 65–77.

[111] F.W. Lichtenthaler, U. Kreis, and S. Immel, *Starch/Stärke*, 43 (1991) 121–132.

[112] J. Thiem and M. Kleeberg, *Carbohydr. Res.*, 205 (1990) 333–345.