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Perspectives in the use of low molecular weight carbohydrates as organic raw materials[1]

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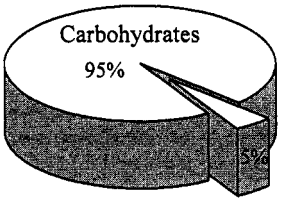
Abstract: Carbohydrates represent 95% of the annually renewable biomass, yet their vast potential as organic raw materials for chemical industry is mostly unexploited. The challenge posed by the necessity to increasingly replace fossile raw materials by those annually regrowing is obvious: systematic basic and applied research for opening up new, non-food application fields for carbohydrates in general and for mono- and disaccharides in particular, as these are more suited for straightforward chemical transformations. – This account gives an overview on recent efforts towards the conversion of inexpensive, bulk-scale accessible mono- and disaccharides – most notably glucose, fructose, sucrose, and isomaltulose – into products with potential industrial application profiles. Thereby, the practicality of the conversion methodologies is emphasized such as the use of simple reactions, of inexpensive reagents, and, if not avoidable altogether, of simple protecting groups in the "reaction channels" leading from sugars to industrially relevant products, in addition to aiming for stable, readily purificable compounds and useful overall yields. Also discussed are the perspectives towards the desired substitution of petrochemicals by those derived from carbohydrates, by "glycochemicals", so to say. Prospects are bright, yet, in their outcome, strongly depend on the actions taken – by academic groups, by funding institutions, and, most importantly, by chemical industry – for the further systematic, broad scale exploitation of high and low molecular carbohydrates towards products with industrially viable property profiles.

INTRODUCTION

Carbohydrates are the world's most important class of organic compounds in terms of volume produced as they represent roughly 95% of the annually regrowing biomass of about 200 billion tons; of these only 3% are used by man, the rest decays and recycles along natural pathways.

Renewable Biomass:
(200 bill. tons/year)



Non-Carbohydrates
(Fats, Proteins, Terpenoids, etc.)

Polysaccharides – cellulose and starch, majorily – are by far the largest bulk of the annually renewable carbohydrate-biomass yet their non-food utilization is confined to textile, paper and coating industries, either as such or in the form of simple esters. In terms of their use as basic organic raw materials for chemical industry, however, the constituent sugars of the large-scale accessible 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. Accordingly, developmental efforts in the area of mono- and disaccharides are more promising to furnish products with which to replace those derived from petrochemical raw materials than those derived from polysaccharides. On account of this, the following account is confined to the exploitation of low molecular weight carbohydrates towards products with industrial application profiles.

The attractiveness of mono- and disaccharides as organic raw materials becomes particularly evident when comparing the bulk quantity prices of the 10 least expensive sugars – all with kg prices well below

DM 100.--, and, hence, ideal starting materials for organic synthesis – with those of other enantiopure compounds of natural origin and with basic organic chemicals from petrochemical sources (Table 1): the six least expensive sugars, some sugar alcohols and sugar-derived acids, are not only cheaper than any other enantiopure product, such as any of the amino acids or terpenoid natural products, but they compare favourably with such basic organic bulk chemicals 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.

Table 1. Availability and price of low molecular carbohydrates in comparison to basic organic compounds and solvents from petrochemical sources

		World Production* (t / year)	Price** (DM / kg)	Source (Supplier)
Sugars	Sucrose	123.000.000	0.75	World Market
	D-Glucose	5.000.000	1.15	Cerestar
	D-Lactose	295.000	1.20	Borculo Whey
	D-Fructose	60.000	2.50	Südzucker
	D-Maltose	3.000	5.–	Cerestar
	D-Isomaltulose	30.000	5.–	Südzucker
	D-Lactulose	9.000	9.–	Borculo Whey
	D-Xylose	16.000	12.–	Xyrofin
	L-Sorbose	25.000	35.–	Merck
	D-Galactose	?	85.–	Fluka
Sugar Alcohols	D-Sorbitol	650.000	2.–	Merck
	D-Mannitol	20.000	6.–	Cerestar
	D-Xylitol	15.000	12.–	Xyrofin
Sugar-derived Acids	D-Gluconic Acid	60.000	7.–	Fluka
	L-Tartaric Acid	?	10.–	Merck
	L-Ascorbic Acid	60.000	10.–	Merck
Amino Acids	L-Glutamic Acid	250.000	15.–	
	L-Lysine	40.000	20.–	
Industrial Organic Chemicals	Acetaldehyd	900.000†	1.–	
	Aniline	1.320.000	1.50	
	Benzaldehyde	50.000	3.60	
Solvents	Methanol	26.500.000†	0.30	
	Toluene	6.500.000†	0.50	
	Acetone	3.200.000	0.75	

* Reasonably exact data are available for the 1995 world production of sucrose[3]; all other data are average values based on more or less comprehensive estimations from producers and/or suppliers.

** Prices given are those attainable in mid-1996 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.

† Data from "*The Chemical Industry in 1994*", UN Annual Review, New York/Geneva 1995.

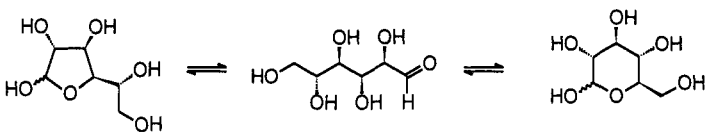
The uniqueness of this situation becomes even more imposing when looking at the availability of these sugars. *Sucrose*, affectionately designated "the royal carbohydrate"[2], has for centuries been the worlds most abundantly produced organic compound of low molecular weight, and this in unparalleled purity. Of the annual world production of 120 million tons – the record level in 1995 amounted to 123 million[3] – only about 90% are required for food purposes, thus setting free around 10 million t for non-food use, i.e. as an organic raw material. A similar potential lies in the bulk scale-accessible component sugars of sucrose, *D-glucose* and *D-fructose*, which today are produced by hydrolysis of starch[4] and inulin[5], respectively, rather than from sucrose. –Two isomers of sucrose, the $\alpha(1\rightarrow6)$- and $\alpha(1\rightarrow5)$-linked glucosyl-fructoses *isomaltulose* and *leucrose*, have recently become accessible through biotechnological processes involving *Protaminobacter rubrum*-[6] and *Leuconostoc mesenteroides*-induced[7]

transglucosylations. However, only isomaltulose is produced on an industrial scale (cf. Table 1), and, hence, is deemed to be a most useful starting material for exploitation towards products with industrial application profiles, particularly as its ensuing chemistry is expected to proceed in a more uniform fashion than that of fructose due to the fixation of its fructose portion in furanoid form[8].

D-Lactose and *D-maltose*, readily available in large quantities from whey[9] and starch[10], respectively, have some applications in the form of their reduction products maltitol and lactitol (as sweetening agents), and of lactulose, a lactose isomerization product; however, despite of their basic chemistry being fairly well developed[9b,10b], there, at present, does not seem to be a qualified chemical use on an industrial scale for these disaccharides. – *D-Xylose* is the cheapest pentose, readily accessible from wood- or straw-derived-xylans[11]; *L-sorbose* is the most readily, large-scale available L-sugar due to its technical production from D-sorbitol in the Vitamin C fabrication process[12]. The sugar alcohols *D-xylitol*[11] and *D-sorbitol*[13], both of comparatively high yearly production, are mostly used as food ingredients due to their sweetening properties, yet their utilization as a raw material for broad-scale organic preparative purposes is essentially non-existent. The same holds for *D-gluconic acid*[14], the sizeable annual production going into its use as a chelating agent and a catalyst for textile printing.

In view of the large-scale accessibility of these mono- and disaccharides it must – at one hand – appear surprising that chemical industry does not utilize them on a much larger scale than now as a organic raw material. On the other hand, there are obvious reasons for this, of course. Sucrose, lactose, and maltose, for example, provide an interesting chemistry[9,10,15], yet are unsuited for many synthetic transformations due to their acid-sensitive intersaccharidic linkage. Their component monosaccharides are devoid of this deficiency, yet *direct* utilization of their vast synthetic potential is impeded by a number of obstacles: they are overfunctionalized with hydroxyl

Sugars as Enantiopure Raw Materials



D-Glucose

Shortcomings: overfunctionalized with hydroxyl groups
too many chirality centers
lack of C=C and C=O functionalities

groups of similar or identical reactivities, they have considerably more chiral centers than required for non-sugar target molecules, and they lack suitable functional groups such as olefinic or carbonyl unsaturation to which modern preparative organic methodology can directly be applied.

These adverse conditions have elicited considerable efforts to reduce the number of chiral centers as well as hydroxyl groups with the simultaneous introduction of useful functionality. One approach involves the shortening of the aldose carbon chain, or, more simply, its bisection, as exemplified by the use of D-mannitol-derived 2,3-*O*-isopropyliden-D-glyceraldehyde[16]. Whilst this product and its L-ascorbic acid-derived enantiomer have developed into the presently most popular enantiopure three-carbon synthons, it must be objected that nature graciously provides us – via photosynthesis – with six-carbon compounds, and if their synthetic potential is to be used efficiently, elaboration of building blocks from sugars or of industrially relevant products should retain the carbon chain.

Indeed, the most frequently used alternative is the gradual step-by-step carving out of a target molecule or a segment thereof. The number of complex, non-carbohydrate natural products synthesized via this approach is enormous[17], yet the fact cannot be concealed that the large majority of these total syntheses are exceptionally long, and that their transferability to large scale is essentially impossible with respect to the reagents used, the number of steps required, the expenditure of work involved, and the overall yields attainable.

Accordingly, reaction sequences – *reaction channels*, so to say – have to be newly developed with which mono- and disaccharides can efficiently be converted into products with economically sound

industrial application profiles, which in turn necessitates the adoption of and strong adherence to *practical criteria*, such as:

- retention of the carbon chain of the sugar
- selection of reactions that allow for simple reagents and uncomplicated, non-chromatographic workup
- high selectivity with minimal use of protecting groups
- aiming for stable, crystalline, readily purifiable products
- minimal waste production (catalytic methods and/or potential for reagent recycling)
- reasonably high overall yields (75% per step on the average)
- overall reaction sequences transposable to the hectogram scale

Strict adherence to most, if not all of these criteria of practicality is an irrevocable necessity, if the resulting products are to be of potential industrial utility. This imposition of practical norms for the acquisition of furanoid, open-chain, and pyranoid building blocks from simple sugars reduces the number of possible reactions quite substantially, leaving comparatively few efficient, large scale-adaptable *reaction channels*, which happen to be genuine for each specific mono- and disaccharide. To be presented in the sequel are a series of practicality-oriented reaction channels leading from simple, tautomerically fixed mono- and disaccharides to versatile intermediates with suitable functionalities, i.e. olefinic or carbonyl unsaturation, or preferably both.

NON-FOOD VALORIZATION OF SUCROSE

Whilst the synthetically prepared octa-fatty acid ester of sucrose has recently been approved in the U.S. as a "fat-free fat"[18], its foreseeable global introduction will contribute to the further food use of sucrose, rather than to its use as a raw material for chemical industry. Indeed the non-food applications of sucrose, as of now, are modest. Monoesters of sucrose with long chain fatty acids with a random *O*-substitution pattern have found some application as non-ionic surfactants[15c], whereas the cross-linked hydrophilic gels resulting from radical polymerization of sucrose-mono-, di- or higher *O*-substituted methacrylates have, despite extensive exploitation[19], not materialized industrially.

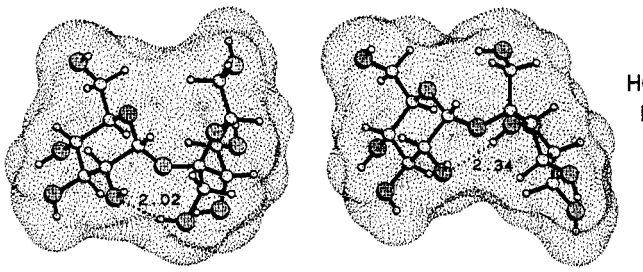
Rather than generating mixtures of randomly *O*-substituted sucrose derivatives, it is considered of more relevance in this context, to develop novel, high regioselective, *O*-protection-free "entry reactions", i.e. practical, technical scale-adaptable modifications at only one of the eight sucrose-hydroxyls, whereafter ensuing reactions can be exploited systematically at the selectively modified (or free) site.

Prototype of such an "entry reaction" is the essentially regiospecific oxidation of sucrose by *Agrobacterium tumefaciens*, whose dehydrogenase generates 3*g*-ketosucrose* exclusively, which then is open to manifold modifications at the 3*g*-carbonyl function[20]. Other enzymes with which sucrose can be selectively esterified, are lipases and proteases, e.g. the commercially available subtilisin acylates the 1*f*-OH with high selectivity[21].

Chemical reactions with sucrose proceed considerably less regioselective[15] – expectedly, because the substantial "selectivity expenditure" inherent to enzymatic binding sites (incorporation of the substrate into enzyme pockets in a lock-and-key type manner) cannot be provided by simple chemical reagents. There are, however, subtle reactivity differences between primary and secondary hydroxyl groups, such that the three primary ones are preferentially alkylated, acylated, oxidized and displaced by halogen in the order 6*g*-OH ≈ 6*f*-OH >> 1*f*-OH[15].

The high preference for reactions at the 6*g*- and 6*f*-positions – rather than at the equally primary 1*f*-OH – is readily understood on the basis of the solution conformations of sucrose that recently evolved from NMR data[22] and, more transparently, from molecular modelling[23]. In aprotic solvents such as DMSO, DMF or pyridine) the major conformer S1 (cf. Fig. 1) is characterized by a strong intramolecular hydrogen bond of the 2*g*-O ···· H-1*f* type, whereas the hydrogen bond of the 6*g*-OH and 6*f*-OH groups are freely exposed to potential reagents. Accordingly, the highly selective displacement of the 6*g*- and 6*f*-OH

* For ready differentiation of the oxygens in the fructose (primed numbers usually) and the glucose portions, they are denoted with "*f*" and "*g*" superscripts, respectively.



S1 S2

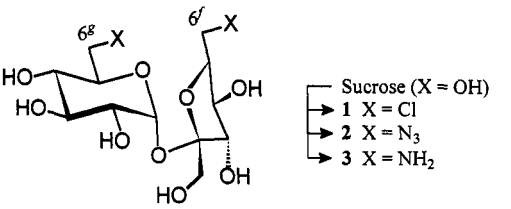
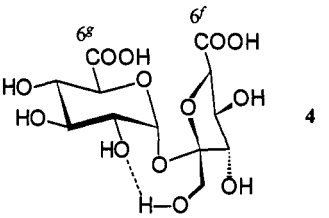


Fig. 1. Ball-and-stick model representations of the favoured conformations S1 and S2 of sucrose in aprotic solvents (DMSO, DMF, or pyridine) and, in dotted form, the corresponding contact surfaces, roughly equivalent to the solvent accessible surfaces[23d].



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groups by chlorine (i.e. →**1**)[24] in an aprotic solvent (pyridine) may be rationalized on the basis of their substantially better accessibility, for the reagent complex generated in situ form triphenylphosphine and carbon tetrachloride is sterically quite demanding. The resulting 6*g*,6*f*-dichloro-sucrose (**1**) then allows further modification at the chlorinated positions, as, for example, to the sucrose-6*g*,6*f*-diamine **3** via azidolysis (**1**→**2**)[24b] and hydrogenation[24c].

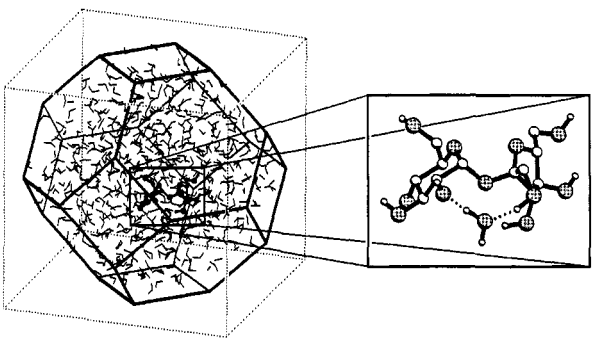


Fig. 2. Molecular dynamics simulation of sucrose in an octahedron with truncated corners, "filled" with 571 water molecules: a 500 picoseconds simulation followed by the analysis of the radial pair distribution function of water protons and oxygens of the first hydration sphere reveals the outlined sucrose geometry, characterized by a water molecule inserted between glucose-2-O and fructose-1-OH via hydrogen bonds[23e].

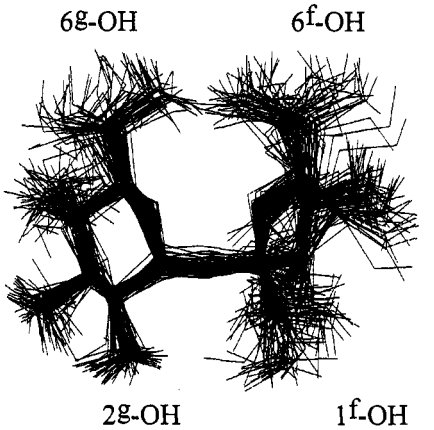
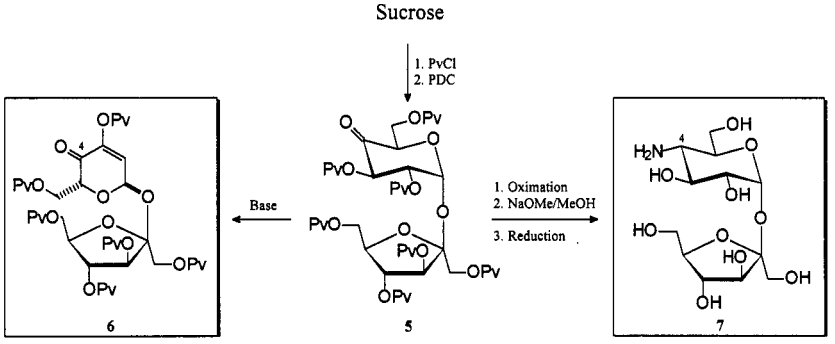


Fig. 3. Superimposition of 100 sucrose snapshot geometries taken in 5 picoseconds intervals during a 500 ps molecular dynamics simulation in water (octahedron in Fig. 2 with 571 water molecules)[23e]. The furanoid fructose part (right) is considerably more flexible than the rigid $^4C_1$-chair conformation of the pyranoid glucose-portion (left).

In water, the orientation of the glucose and fructose portions towards each other is similar to that in aprotic solvents, since a water molecule is interjected into the intramolecular 2*g*-O ···· HO-1*f* hydrogen bond (Fig. 1, S1) to form a *water bridge* of the 2*g*-O ···· H_2O ···· HO-1*f* type (Fig. 2. and 3.). The selectivities on Pt/O_2-oxidation of sucrose may be rationalized on the basis of this molecular geometry: a 9:9:1 ratio of the 6*g*-, 6*f*-, and 1*f*-saccharonic acids was obtained by continuous oxidation with air at pH 6.5-7.0 and 35 °C in the presence of 0.5% Pt/C[25a]. On further oxidation, particularly when using large amounts of the Pt catalyst and higher temperature (80-100 °C), the preferred formation of the 6*g*,6*f*-dicarboxylic acid **4** has been observed[25b], yet a preparatively useful procedure for the acquisition of **4** was developed only recently[25c] by combination of continuous Pt/air-oxidation with continuous electrodialytic

removal of **4**, thereby protecting it from further oxidation. Both, the sucrose-6*g*,6*f*-diamine **3** as well as the 6*g*,6*f*-dicarboxylic acid **4** wait for exploitation of their sizable industrial potential.

An alternative approach for selective chemical modification of sucrose is the derivatization of its hydroxyl groups by alkylation or acylation in such a way, that only the least reactive OH group remains untouched, which is then open to a straightforward ensuing chemistry, e.g. to oxidation or configurational inversion. One of the few reactions of this type that fulfils preparative criteria, is the acylation of sucrose with the sterically bulky pivaloyl chloride in pyridine at -40 °C, seizing only seven of the eight hydroxyl

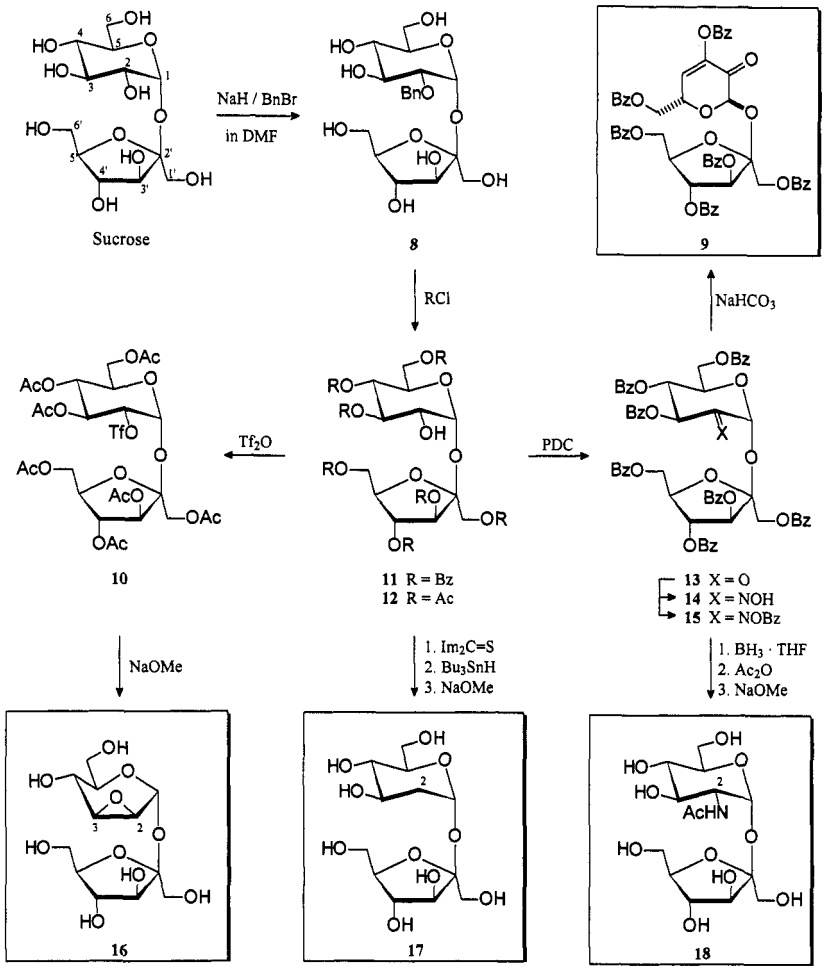


groups to afford the 4*g*-OH-free heptapivaloate in yields of up to 50%[26a]. Adaptation to large scale and optimization of this entry reaction made C-4*g*-modified sucrose derivatives readily accessible[26b]: the 4-ketosucrose **5** (in protected form) by PDC-oxidation, the dihydropyranone building block **6** through base-induced elimination of pivaloic acid, and the 4-amino-sucrose **7**.

The impulse to exploit towards C-2*g*-modified derivatives derived from molecular modelling, most notably from the molecular electrostatic potential (MEP) patterns[23a-d] projected onto the contact surfaces (dots in Fig. 1.) of the solution conformations, which convincingly showed the area around the glucosyl-2-OH to be the most electropositive, i.e. the 2-OH to be deprotonated most easily. Indeed, exposure of a DMF solution of sucrose to nearly one equivalent of NaH (1 h, 0 °C), followed by addition of benzyl bromide, resulted in an 11:2:1 mixture of three monobenzyl ethers, in which the 2*g*-*O*-benzyl-sucrose (**8**) was the major product (>80% based on ^{1}H NMR)[23d]. This entry reaction, in principle transferable into technical scale, was used to prepare the 2-ketosucrose **13** (in blocked form), the versatile dihydropyran building block **9**, in which the fructose residue formally functions as an acid-labile blocking group. 2-Deoxysucrose (**17**) and *N*-acetyl-sucrosamine (**18**), both potential enzyme inhibitors, are also well accessible through deoxygenation of the heptaacetate **12**, or by borane reduction of the oxime **15**[23d]. The synthetic route elaborated for *N*-acetyl-sucrosamine should readily be applicable to the preparation of products with interesting tenside and liquid crystal properties, e.g. by using fatty acid halides instead of acetic anhydride in the *N*-acylation step. Similarly high potential as industrially interesting intermediates has the epoxide **16**, well accessible from **12** via **10** in 74% yield for the two steps involved[27]; its oxirane ring-opening with long-chain alcohols or amines is apt to lead to new, hydrophilically modified softening agents with the performance profile of epoxidized linseed oil.

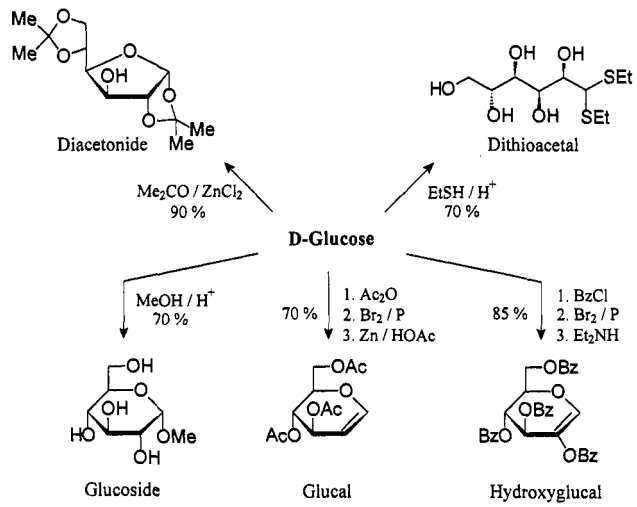
NON-FOOD UTILIZATION OF GLUCOSE AND FRUCTOSE

The sizable amounts of D-glucose and D-fructose produced annually (cf. Table 1), interestingly, are not made by hydrolysis of sucrose, as the resulting 1:1-mixture would have to be separated; the hydrolysis of starch to its component sugar is much more economic[4], as is the acquisition of fructose via base-catalyzed isomerization of glucose or by hydrolysis of inulin[5]. As of now – and this is to be outlined in the sequel – price and large scale accessibility of these two monosaccharides are in a notoriously inverse relationship to their use as an inexpensive organic raw material.

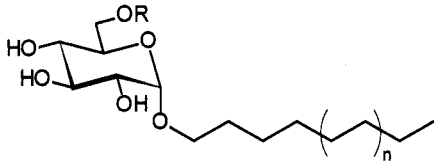


D-Glucose

The principal, preparatively useful derivatizations of D-glucose – entry reactions, with which the tautomeric forms are fixed – have already been elaborated before the turn of the century: mercaptalization to the *acyclic* dithio acetals, isopropylidenation to *furanoid* systems, or the generation of *pyranoid* structures, such as glucosides, glucals, and hydroxyglucalesters[28]:



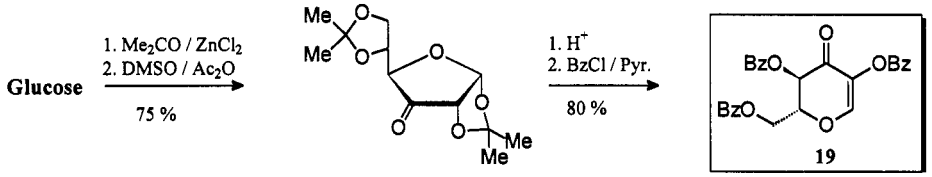
Despite of the ready accessibility of these "entry products", and their fairly well developed ensuing chemistry, their exploitation towards industrial intermediates is small. A notable exception though are **alkyl polyglucosides** (APG's), which combine high performance as non-ionic surfactants with non-toxicity, low-skin irritation, and biodegradability[29]:

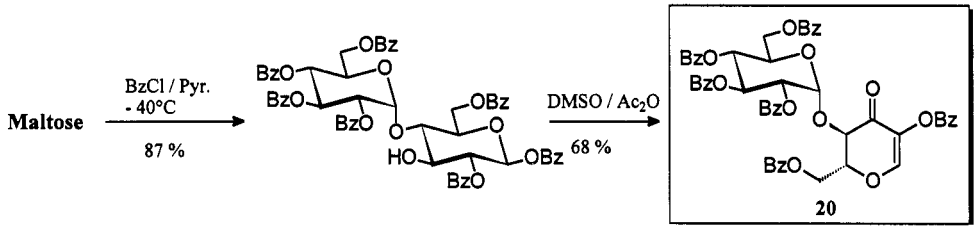


APG's
(R = H, glucosyl, isomaltosyl; n = 0-4)

They are technically produced – on an estimated 46.000 t scale worldwide in 1995 – either through acid-induced glycosidation of glucose with a long chain fat alcohol or by transglycosylation of a short-chain alkyl glucoside with the appropriate long-chain alkanol. The resulting mixtures contain the α-D-glucosides majorily, as designated by the above formula, and are marketed as such.

Other non-food applications of D-glucose comprise its oxidation (D-gluconic acid → chelating agent, textile printing additive)[14] and reduction product (sorbitol → Vitamin C)[13]. In contrast thereto, the use of the ton-scale available[30] diacetone-glucose and its use for the preparation of amiprilose, a non-steroidal, anti-inflammatory drug[31] is a small-scale, high value-added application. The same holds for the use of dihydropyranones of type **19**[32] as enantiopure building blocks, which combine chirality on one side of the ring with versatile functionality at the other:





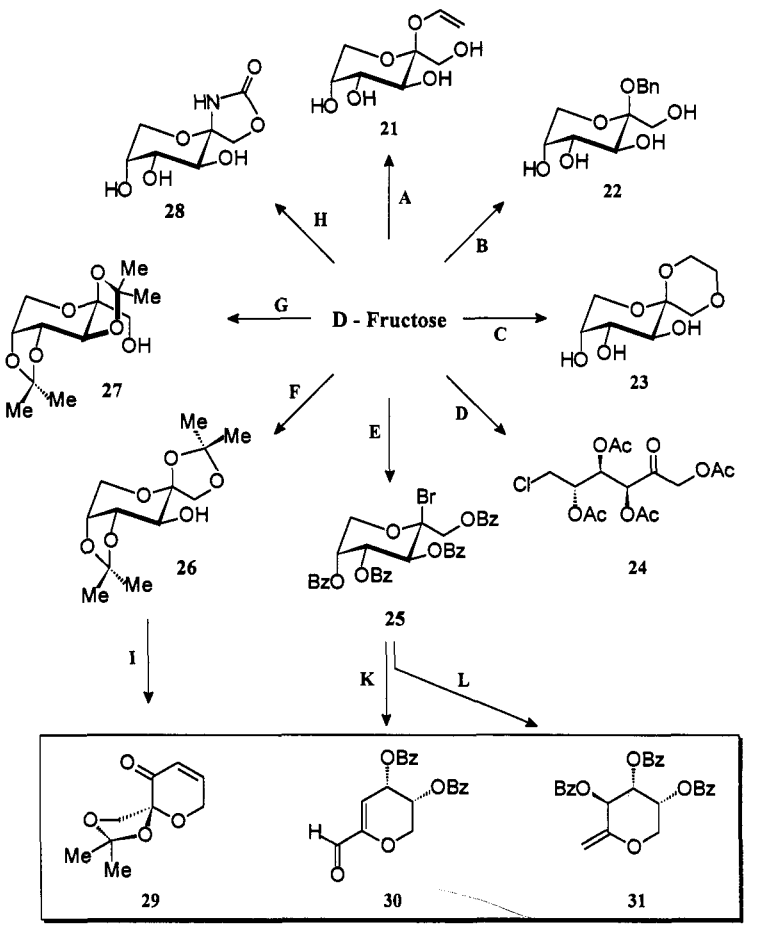
If one is prepared to accept a tetrabenzoylglucosyl residue as an acid-sensitive, alkali-stable blocking group – and a cheap one at that – the disaccharide-derived dihydropyranone **20** is even more directly accessible: low temperature benzoylation of maltose to the heptabenzoate and subsequent oxidation, which entails elimination of benzoic acid[32].

Substantial efforts by several academic research groups have gone into the generation of hydrophilic polyamide analogues of nylon-6,6 and perlon from glucose[33], based on the enticing concept to substitute adipic acid, hexamethylene diamine, and ε-amino-caprolactam by glucaric acid, 2,5-diamino-dianhydrosorbitol, and 6-amino-glucono-lactame, respectively. Despite of the huge industrial potential of such polyamides, which would have the additional advantage of high biodegradability, chemical industry has not materialized on these possibilities, presumably due to the fact, that the generation of the monomers, as of now, do not meet process chemistry demands, and that petrochemically derived monomers are still more economic to produce.

D-Fructose

The substantial amounts of this ketohexose produced technically (cf. Table 1) is mainly used as a sweetener for beverages ("high fructose syrup"). Its non-food utilization is modest – not surprisingly since its basic chemistry is more capricious and considerably less developed than that of glucose. The "entry reactions" compiled in the following scheme, of which some have only recently been elaborated, provide with the fructose derivatives **21** - **28** a multifaceted array of functionalities with which to embark on exploitation of their application potential. The enantiopure building blocks **29** and **30** are such examples, or the rich chemistry to be derived from the *exo*-D-fructal **31**[34]. The diacetone-fructose **27** similarly is the starting material for drugs – e.g. the anticonvulsant Topiramate® [35] – or, after introducing polymerizable vinyl groups at C-1, for polyvinylsugars that have interesting polymer properties[36].

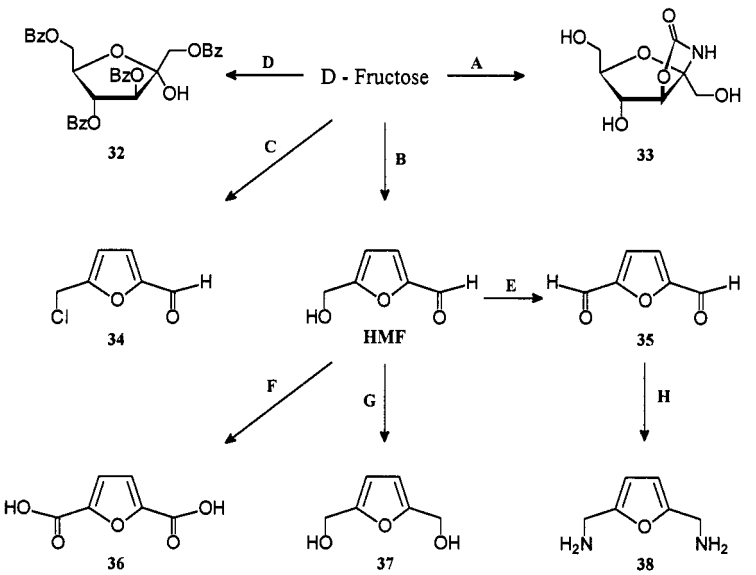
Of the simple furanoid products derived from fructose, the tetrabenzoate **32** and the cyclocarbamate **33** are well accessible, but by far the highest industrial potential demands the hydroxymethyl-furfural (HMF), which has been termed one of the few "petrochemicals" readily accessible from regrowing resources[40] and as a key substance between carbohydrate chemistry and mineral oil-based industrial organic chemistry[41b]. It is readily accessible by acid-induced



A : Allyl alcohol/AcCl, 49%[37a]. – **B** : BnOH/HCl, 25-30%[37b]. – **C** : 2 steps, 74%[37c]. – **D** : AcCl, -10 °C → PCl_5, 61%[38]. – **E** : BzCl, -10 °C → HBr, 63%[38]. – **F** : Me_2CO/cat. H_2SO_4, 58%[37d]. – **G** : Me_2CO/>5% H_2SO_4, 80%[37e]. – **H** : KOCN, 31%[38]. – **I** : 5 steps, 22%[39]. – **K** : DBU → NH_2OH → MeCHO/H^+, 45%[37f]. – **L** : Zn/MIM, 90%[34].

elimination of 3 moles of water[41], and even a pilot plant size process has been elaborated[41b]. As of now, however, it is not produced on an industrial scale, despite of the fact, that the conversions into various ensuing products are well worked out[42]: compounds **34-38**, for example, have high potential as basic industrial intermediates, most notably the dicarboxylic acid **36** and the diamine **38** as conceivable replacements, e.g. for terephthalic acid and hexamethylene diamine, respectively. The main reason, that

HMF or products derived therefrom are not industrially utilized, is that, at present, raw materials from petrochemical sources are still more economical.



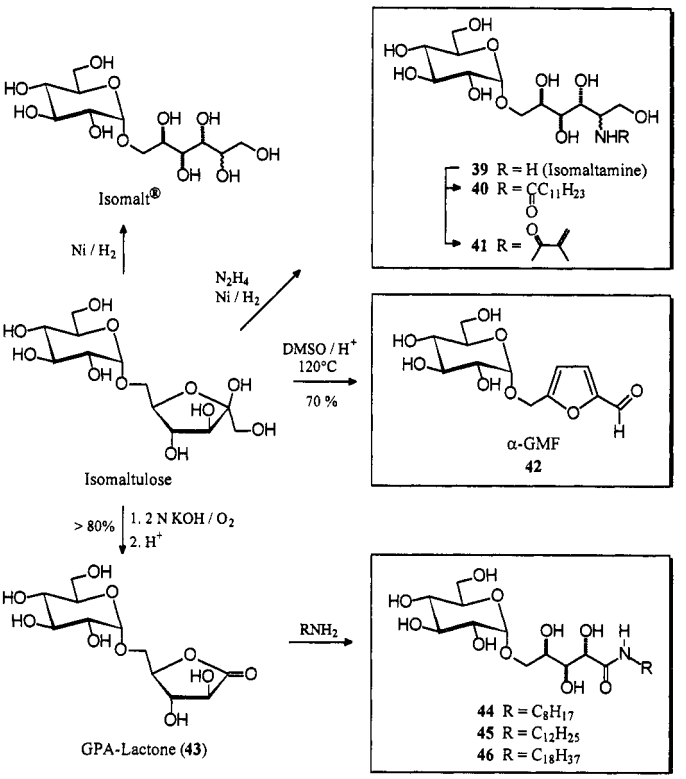
A : $KOCN/KH_2PO_4$, 32%[38]. – **B** : H^+, 90% [41]. – **C** : HCl, 60-85 °C/surfactant, 60-65%[43a]. **D** : BzCl, 60 °C, 60%[43b]. – **E** : $BaMnO_4$/1,1,2-trichloroethane, 93%[43c]. – **F** : $Pb,Pt/O_2$/NaOH, quant.[43d]. – **G** : Pt/H_2, quant.[43e]. – **H** : $NH_2OH/HCl \rightarrow$ Raney-Ni/H_2, 33%[43c].

NON-FOOD VALORIZATION OF ISOMALTULOSE

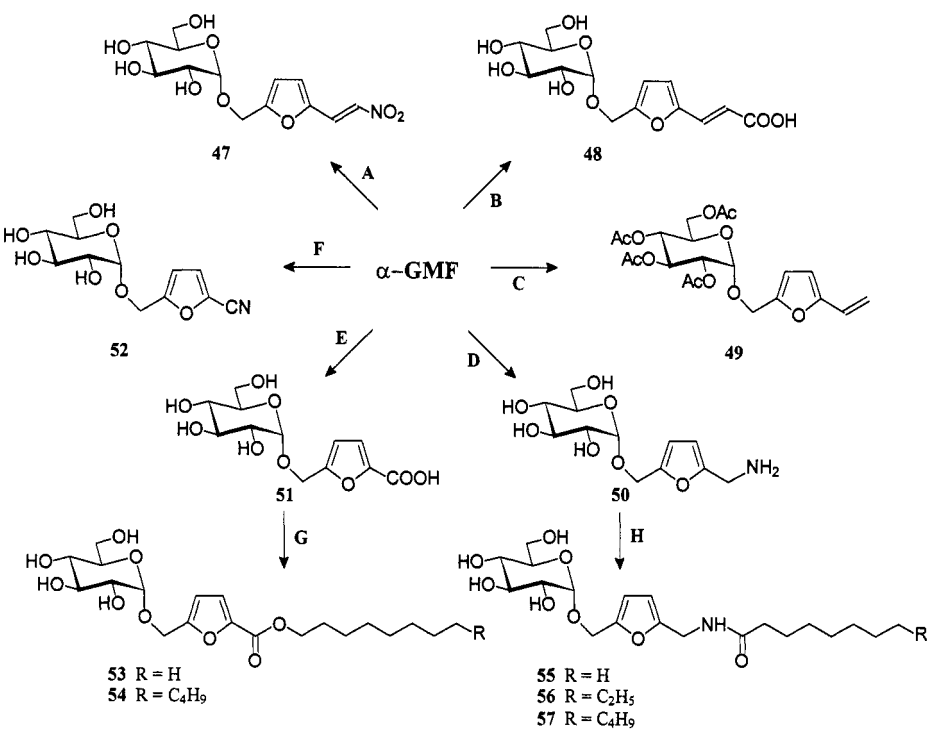
The industrial production of isomaltulose[6] presently on a 30 000 t/a scale for food reasons – as it is hydrogenated to isomalt®, a low calorie sweetener with essentially the same taste profile as sucrose – has made it a lucrative target for generating disaccharide intermediates of potential industrial use. For example, its reductive amination with hydrazine on a nickel catalyst smoothly generates a 1:1-mixture of glucosyl-α(1→6)-2-amino-2-deoxy-D-glucitol and the respective D-mannitol isomer[44], appropriately termed isomaltamine in analogy to isomalt®. As a pronouncedly hydrophilic amine of a disaccharide alcohol, it is a versatile intermediate for further derivatization, e.g. with fatty acid halides to non-ionic, biologically degradable detergents of type **40**[44], or with methacrylic acid derivatives to provide polymerizable acrylamido-disaccharides of type **41**[45].

The air oxidation in strongly alkaline solution (KOH) readily provides the potassium salt of the next lower aldonic acid, i.e. glucosyl-α(1→5)-D-arabinonic acid (GPA), isolable as such, or upon neutralization, as the GPA-lactone **43** in high yields each[46]. Amidation of **43** with long-chain amines, e.g. the C_8-, C_{12}-, and C_{18}-"fat"-amines, provided the GPA-amides **44-46**, which not only exhibit promising detergent profiles but surprising liquid crystalline properties due to S_{Ad}-phases over a broad temperature range[47].

Another, industrially relevant ensuing reaction of isomaltulose comprises its ready conversion into 5-(α-D-glucosyl)-oxymethyl-furfural (α-GMF, **42**) by acidic dehydration of the fructose portion under conditions (acidic resin in DMSO, 120 °C) that retain the intersaccharidic linkage[48]; this process can also be performed in a continuous flow reactor[48b]. As a glucosylated HMF, **42** provides a rich ensuing chemistry towards products with broad application profiles[48]: aldol-type condensations provide derivatives with polymerizable double bonds (routes A and B), most notably the acrylic acid **48** and methylenation product **49**, that are expected to yield novel, hydrophilic polymers with interesting performance profiles; reductive amination smoothly generates the α-GMF-amine **50**, which by *N*-acylation with fatty acids affords compounds of type **55-57**, 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 α-GMF-carboxylic acid **51** and its esters with long-chain alcohols[48].



Key[48]. **A** : CH_3NO_2/NaOH. – **B** : $CH_2(COOH)_2$/quinoline/170 °C. – **C** : $Ac_2O \rightarrow CH_2Br_2/Zn/TiCl_4$. **D** : Ni/H_2 in $MeOH/NH_3$. – **E** : $NaClO_2/H_2O$. – **F** : NH_2OH/HCl/110 °C. – **G** : Fat-alcohol/DCC.– **H** : Acyl chloride.

OUTLOOK

Despite of the new "entry reactions" and "reaction channels" advanced here for bulk-scale accessible mono- and disaccharides, their potential as an organic raw material for the elaboration of industrially useful chemical intermediates and products 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. 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 fossile 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. The prospects are promising, if one is prepared to generously invest into basic research along the criteria outlined in this account by national funding institutions, by supranational bodies such as the European Commission – with hopefully more chemically oriented Agricultural Industrial Research (AIR) programs as to allow chemical industry to profit therefrom rather than majorily the agricultural crop producers – and by chemical industry itself, of course. Research can be planned, results cannot (!). Thus, the only other thing then needed is *patience* – patience until the "fruits" from renewables, in upgraded, value-added form, can be harvested.

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