# Some Disaccharide-derived Building Blocks of Potential Industrial Utility

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The utilization of inexpensive, bulk-scale accessible, renewable disaccharides as organic raw materials necessitates their practice-oriented conversion into products with different functional groups and, hence, broader application profiles. The backlog for the development of practical reaction channels to versatile building blocks from disaccharides being particularly obvious. Correspondingly, this account describes a series of examples by which the reaction potential inherent in disaccharides such as sucrose, lactose, maltose and isomaltulose is utilized towards the acquisition of versatile building blocks without cleaving the intersaccharidic linkage. – The glucose portion of sucrose, e.g. can be converted into dihydropyranones with the carbonyl function at C-2 or C-4, the reducing glucose parts of maltose and lactose may be transformed into enediolone, enelactone, or enollactone structures, whilst the fructose moiety of isomaltulose elaborates a furan ring by threefold, acid-induced elimination of water to yield the terminally *O*-glucosylated HMF, i.e. glucosyloxymethyl-furan-2-carboxaldehyde. – All reaction sequences comply with criteria of practicallity and therefore being transformable to large scale without major changes. Another novel entry reaction into *O*-functionalized disaccharide derivatives, the cathodic deprotonation and subsequent trapping of the mono-anion with suitable reagents according to *Hamann*, was evaluated in terms of understanding the regioselectivity attainable through computer simulations of relevant conformers of sucrose in solution, and the corresponding molecular electrostatic potential (MEP) profiles.

**Von Disacchariden abgeleitete Synthesebausteine mit potentiellem industriellem Verwendungsprofil.** Die Verwendung von billigen, in großem Maßstab verfügbaren Disacchariden als nachwachsende organische Rohstoffe erfordert ihre praxisorientierte Umwandlung in Synthesebausteine mit verschiedenen funktionellen Gruppen und folglich breiteren Anwendungsprofilen. Dabei ist der Nachholbedarf zur Entwicklung praktischer „Reaktionskanäle" zu vielseitig verwendbaren Folgeprodukten gerade bei Disacchariden besonders hoch. Entsprechend beschreibt dieser Beitrag eine Reihe von Beispielen für die effiziente Nutzung des Synthesepotentials von Saccharose, Lactose, Maltose und Isomaltulose unter Erhalt der glycosidischen Bindung. – So kann z. B. der Glucose-Teil der Saccharose selektiv in Dihydropyranone mit der Carbonylfunktion entweder an C-2 oder C-4 umgewandelt werden, während von Maltose und Lactose durch Modifikation des reduzierenden Glucose-Restes Endiolon-, Enlacton- oder Enollacton-Bausteine darstellbar sind. Weiterhin eröffnet die säurekatalysierte, dreifache Dehydratisierung der Fructose-Einheit von Isomaltulose einen wertvollen Zugang zu terminal *O*-glucosylierten Hydroxymethyl-furan-Derivaten, wie z. B. zum 5-Glucosyloxymethyl-furan-2-carboxaldehyd. Alle beschriebenen Reaktionen erfüllen die Voraussetzungen industrieller Anwendbarkeit und sind ohne wesentliche Änderungen auf größere Reaktionsmaßstäbe übertragbar. – Ein weiterer Zugang zu mono-*O*-funktionalisierten Disaccharid-Derivaten wird durch die elektrochemische Deprotonierung von Kohlenhydraten nach *Hamann* und anschließendes Abfangen der Mono-anionen mit geeigneten Reagenzien eröffnet. Im Fall der Saccharose wird demonstriert, daß die in Abfangreaktionen beobachteten Regioselektivitäten durch Computersimulation der in Lösung vorliegenden Konformere und ihrer molekularen elektrostatischen Potentiale (MEP) verständlich werden.

## 1 Introduction

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

The systematic industrial utilization of this vast, mostly unexploited potential of carbohydrates as organic raw materials is in the beginning. The present situation is characterized by the fact, that, on one hand, there are world-wide major efforts for opening up new application fields for carbohydrates in general, and for low molecular weight saccharides in particular, and that, on the other hand, chemical industry adopts a wait-and-see-attitude due to lack of marketable products and leaves the basic research required on a broad scale to academic institutions and state research funding.

The challenges posed by this situation are obvious: in view of the comparatively few reaction sequences meeting process chemistry demands, there is an urgent necessity to further develop practical, large scale-adaptable *reaction channels from sugars to versatile building blocks with potential industrial application profiles* – a task that can successfully be achieved only if the present chemical and biotechnological methodology is utilized to its fullest.

Within this scenario, this account presents a series of examples, by which the reaction potential inherent in the bulk-scale accessible disaccharides sucrose, lactose, maltose, and isomaltulose (cf. Table 1) is moulded towards the practical acquisition of versatile building blocks, which are devoid of the standard shortcomings of sugars, i.e. overfunctionalization with hydroxyl groups and lack of suitable olefinic unsaturation.

## 2 Selective *O*-Functionalization of Sucrose Towards Some Novel Building Blocks

Sucrose occupies a key position amongst the readily accessible disaccharides. It is the major product of photosynthesis and mobile source of energy in plants. With an annual production of over a 100 million t it clearly is the world's most abundantly produced organic compound (cf. Table 1), and this in unparalleled purity. But in spite of the chemistry of sucrose has being fairly well developed [1, 2], still by far the major portion of the total production is utilized as a sweetener of processed or directly consumed foods, whereas less than 5% are directed to non-food uses.

The reasons for this lie in the chemical limitations imposed by the instability of the glycosidic linkage under even slightly acidic conditions, which causes hydrolysis to occur either before or

Table 1.
Accessibility and World Market Prices of Low Molecular Weight Carbohydrates.

| | World production (t/year)* | Price (DM/kg)** | Source (Supplier) |
|---|---|---|---|
| **D-Sucrose** | 113 614 000 | 0.60 | World Market |
| D-Glucose | 5 000 000 | 1.15 | Cerestar |
| D-Sorbitol | 650 000 | 1.20 | Cerestar |
| **D-Lactose** | 180 000 | 1.20 | Meggle |
| D-Fructose | 50 000 | 2.50 | Südzucker |
| D-Mannitol | 8 000 | 5.– | Cerestar |
| **D-Maltose** | 3 000 | 5.– | Cerestar |
| **D-Isomaltulose** | 20 000 | 5.– | Südzucker |
| D-Gluconic acid | 40 000 | 7.– | Fluka |
| D-Xylose | 1 000 | 12.– | Cerestar |
| Dianhydrosorbitol | 1 000 | 12.– | Cerestar |
| Xylitol | 3 000 | 14.– | Cerestar |
| L-Sorbose | 25 000 | 35.– | Merck |
| D-Galactose | ? | 85.– | Fluka |

* The quantities given are estimations based on information from producers and/or suppliers, except for sucrose, for which exact data for its annual world production are available.

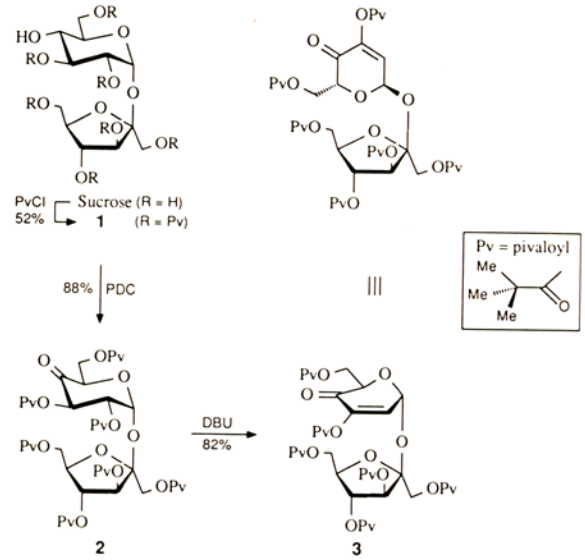
** Prices listed are based on bulk delivery (ton range) of the crystalline product, except for those supplied by Fluka and Merck, which refer to 100 kg batches.

during the reaction, and its "overfunctionalization" with hydroxyl groups of similar or identical reactivity, such that regioselective functionalizations are difficult to achieve. Like most disaccharides, sucrose features eight hydroxyl groups, thus, the accessibility of any given sucrose derivative depends on the efficiency with which a selective *mono*-functionalization may be achieved, either directly, or by chemically blocking seven of the eight OH-groups leaving one free for further manipulation.

There are numerous procedures in the literature for chemically effecting mono-*O*-acylations [3–7], yet the most readily accessible derivatives are invariably those carrying the acyl function at the primary OH-groups, *i.e.* the 6-*O*-, 6′-*O*-, and 1′-*O*-positions – a type of mono-functionalization that is not of much use for performing chemical modifications at the pyranoid or furanoid ring carbons of sucrose. The same holds true for enzyme-mediated transesterifications [8, 9]. Only recently a number of selective mono-acylations at the glucosyl-2-OH have been achieved by deprotonation of sucrose with sodium hydride in pyridine solution and subsequent reaction with a mild heterocyclic acylating agent [10]. The same preference for the glucosyl-2-OH has been observed for the benzylation of sucrose with one mole of benzyl bromide under Kuhn conditions ($Ag_2O$ in DMF), giving in a yield of 40% a mixture of four monobenzyl ethers in the ratio of 86 : 10 : 3 : 1, of which the major product proved to be the 2-*O*-benzylated derivative **4** [11] (cf. below).

Hepta-*O*-functionalized derivatives of sucrose are accessible by selective mono-deacylation of sucrose octaacetate by either enzymatic [12] or chemical means [13], yet the yields are moderate to low. The easiest and preparatively undoubtedly most convenient entry to hepta-*O*-acylated sucrose is *via* direct reaction, the sterically demanding pivaloyl chloride yielding 52% of crystalline **1** [14].

The unusually easy acquisition of the heptapivaloylate **1** from sucrose makes it an unique starting material, due to its free 4-OH providing an entry to C-4-modified sucroses. Accordingly, the 4-keto-sucrose derivative **2** is readily made by oxidation [15], as well as – in a lengthy procedure though [16] – 4-amino-sucrose. It was obvious to also effect elimination of

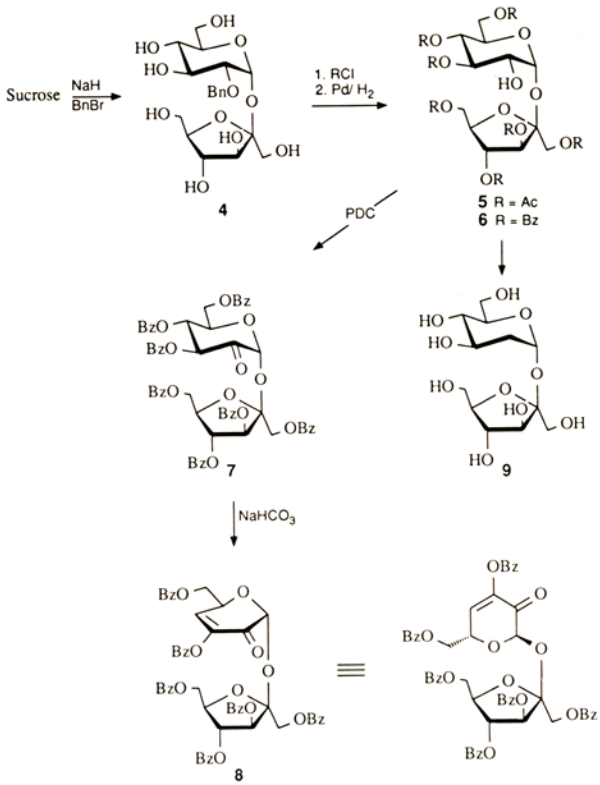



pivaloic acid in **2**, which required rather forcing basic conditions (DBU in dichloromethane), yet gave the unsaturated disaccharide-ulose **3** in high yield [17]. Thus, a most versatile, enantiopure building block, featuring functionality in one of the two sugar portions, and an acid-sensitive blocking group in the other (i.e. the fructofuranosyl moiety), is accessible from sucrose in an overall yield of 38% for the three steps.

An entry into C-2-modified sucrose derivatives is offered by the 2-*O*-benzyl-sucrose **4** already mentioned, generated by direct benzylation [11]. However, **4** had not been obtained in an analytically pure state due to separation difficulties, and the use of silver oxide for deprotonation appeared not very practical. However, if this procedure could be improved, a variety of hitherto elusive 2-derivatized sucroses would become accessible, e.g. 2-keto-sucrose, which has been reported to be part of a mixture resulting from bromine oxidation of sucrose [18], or 2-amino-sucrose, that has only been obtained by fructosylation of glucosamine [19], or, most notably, 2-deoxy-sucrose **9**. This simple sucrose derivative, made by an undisclosed mode of preparation, is being sold at a price of £ 400 for 100 mg [20], and a reaction sequence incidentally outlined for its acquisition is quite lenghty: conversion of sucrose into its 1′,2:4,6-di-*O*-isopropylidene-3,3′,4′,6′-tetra-*O*-acetyl derivative, acetal deprotection, partial acetylation of C-4, C-6 and C-1′ alcohols, and classical reduction of the residual C-2-hydroxyl group [21].

Reinvestigation of the equimolar benzylation of sucrose in DMF using sodium hydride as the base [17] resulted in mixtures of monobenzyl ethers similar to those obtained previously, **4** invariably being the major product (> 80% based on $^1$H-NMR). At room temperature for 12–15 h, the benzylation proceeds only to the extent of 50%, yet is not forced any further to keep introduction of more than one benzyl group at a minimum. Separation of **4** from sucrose is simple, its isolation from the resulting mixture of monobenzyl ethers, however, exceedingly difficult. Thus, it is advantageous to further derivatize by acetylation and hydrogenolysis, which allows the crystallization of the 3,4,6,1′,3′4′,6′-hepta-*O*-acetyl-sucrose **5**, of m.p. 116°C and $[\alpha]_D^{20} = +68°$ (c = 1, $CHCl_3$) [22], in a yield of 21% based on sucrose [17]. When taking into consideration though, that only about half of the sucrose undergoes the initial reaction, the yield of **5** is well over 40%, thus providing an ideal starting material for further modifications.

Thiocarbonylation of **5** with thiocarbonyldiimidazol and subsequent reduction by tributyltin hydride in toluene according to standard procedures [23] gives after deacetylation



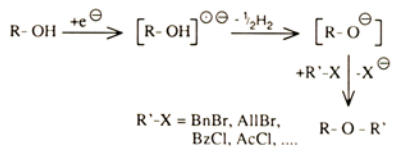

2-deoxy-sucrose **9** in the useful overall yield of 51% for the three step-sequence [17].

In analogous fashion to **5**, the corresponding heptabenzoate **6** can also be generated, which on oxidation with pyridinium dichromate (PDC) smoothly affords the respective 2-keto-sucrose derivative **7**. Slightly basic conditions, such as stirring in acetonitril with solid sodium hydrogen carbonate induce quantitative elimination of benzoic acid from the 3,4-positions to yield **8**, a fructosylated dihydropyranone, and as such a most versatile enantiopure building block.

## 3 Is there an Electrochemical Entry to Selective O-Functionalization?

As outlined above, the methodologies for generation of sucrose derivatives with *one* free ring-OH are quite limited, and therefore it is an enticing idea to evaluate unconventional methods for their utility in yielding more practicable entries into suitably functionalized products. One such possibility was recently developed from electrochemical investigations, most notably the electroreductive deprotonation of polyols.

The cathodic deprotonation [24] of alcohols within an electrolysis cell is a process, which is initiated by a **s**ingle **e**lectron **t**ransfer (**SET**) from the electrode to the alcohol molecule forming a radical anion, which after elimination of a hydrogen atom ($\rightarrow H_2$) [25] generates the respective alkoxide:




The subsequent trapping of the alkoxide by a suitable reagent such as an alkyl or acyl halide – carried out either *in situ* or *ex situ* depending on the stability of the compounds under electrochemical conditions – then provides the corresponding ethers or esters. This mode of deprotonation should conceivably be applicable to polyols, the crucial questions being:

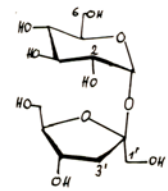
Can specific OH-groups in mono- or disaccharides **selectively** be deprotonated?

and, if so,

can this method be used for **selective *O*-acylation, *O*-alkylation**, and, possibly, for ***O*-glycosidation**?

As demonstrated by recent, quite fundamental work of *Hamann* et al., [26–28] electrolysis of sucrose and some other simple sugars at platinum electrodes in aprotic polar solvents like DMF in the presence of $LiClO_4$, indeed generates the stable sugar anions, Subsequent chemical trapping with suitable reagents provides remarkably high selectivities; the ones obtained in the case of sucrose are summarized in Table 2.

Table 2.
Product Distribution of the Etherification and Esterification of the Electrochemically Generated Sucrose Mono-anions with Various Trapping Reagents [26–28] (main products are marked in bold).



| Reagent* | Product distribution (%) *O*-2 | *O*-6 | *O*-1′ | *O*-3′ | Reaction conditions |
|---|---|---|---|---|---|
| BnCl | **49** | – | 41 | 10 | *ex situ* |
| BnBr | **48** | – | 39 | 13 | *ex situ* |
| MeI | **54** | – | 27 | 19 | *ex situ* |
| BzCl | – | – | **100** | – | *ex situ* |
| BzOMe | – | **50** | **50** | – | *in situ* |

* Bn = $C_6H_5CH_2$; Me = $CH_3$; Bz = $C_6H_5CO$.

From this data it is clearly evident, that alkylation of electrochemically generated sucrose anions yields 2-*O*-alkyl derivatives with high selectivity, while benzoylation preferentially either leads to 1′-*O*-substituted products exclusively, or, when employing transesterification with methyl benzoate, to a 1:1 mixture of the 6-*O*- and 1′-*O*-benzoates (cf. Table 2) [27, 28]. These selectivity patterns emphasize the high potential of this approach for the preparation of disaccharide-derived building blocks with potential industrial utility.

In order to understand the selectivities observed, i.e. to get an insight into which of the eight OH-groups is the one preferentially deprotonated, it is of course a prerequisite to know the solution behaviour of sucrose, i.e. the conformations adopted in any given solvent, and the electrostatic properties of the individual OH-groups.

### Conformational properties of sucrose in solution

The common sucrose formula (Fig. 1A) does neither give any three-dimensional information about the actually predominating conformation [29], nor does it give any hint what selectivity of deprotonation is to be expected. A more "realistic" molecu-

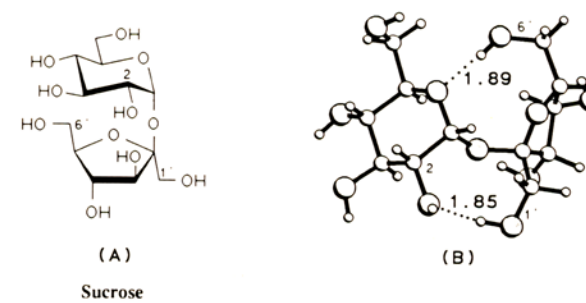



Fig. 1. Representation of the common chemical formula of sucrose (A) *versus* a ball-stick model of the solid state conformation (B) derived from neutron diffraction data [33], giving a more "realistic" molecular picture (oxygen atoms are shaded).

lar picture is obtained from the Cambridge Crystallographic Database [30, 31] from neutron diffraction [32, 33], and from X-ray analysis [34] of the solid-state conformation (Fig. 1B), showing the glucose and fructose moiety fixed in their relative orientation by two strong interresidue hydrogen bonds between 5-O$^g$··· HO-6$^f$ and 2-O$^g$ ··· HO-1$^f$ of 1.89 and 1.85 Å length, respectively.

In solution, particularly in water, it is unlikely that both intramolecular hydrogen bonds present in the crystalline state are retained; indeed, extensive $^1$H- and $^{13}$C-NMR investigations [35–39] strongly attest to the disintegration of the 5-O$^g$ ··· HO-6$^f$ hydrogen bond by solvation, a most recent NMR-study even questions alltogether the existence of any stable intramolecular hydrogen bond in sucrose in aqueous solutions [40]. Nevertheless, for polar aprotic solvents like dimethyl sulfoxide, a competitive equilibrium between forms A and B (Fig. 2) has been deduced [38] with the former predominating in a 2:1 ratio.

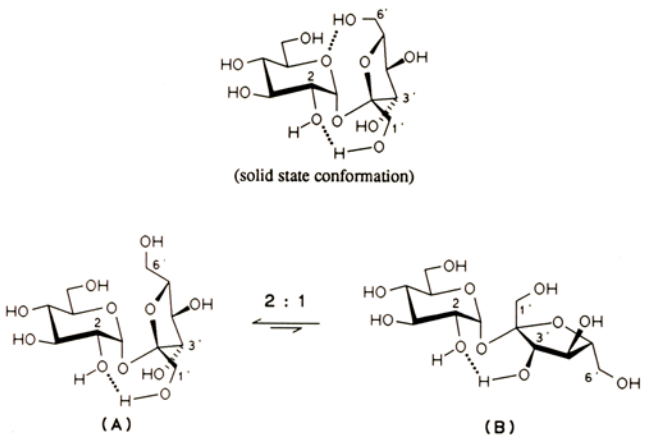



Fig. 2. Sucrose: conformation in the crystal as derived from neutron diffraction data [33] (upper formula) *versus* the situation in solution: in DMSO a competitive equilibrium A B, with A predominating has been proposed [38].

In conformer A, the glucose and the fructose part are being fixed in respect to each other by the intersaccharidic linkage as well as by the same interresidue hydrogen bond as observed in the crystal lattice, thus the solid state conformation and A are very close. Several calculations of the energy potential surface of sucrose [35, 41–45] have provided additional indications as to the relevance of forms A and B. In Fig. 3, a contour plot of the fully relaxed energy contour map of sucrose is given as a function of the two intersaccharidic torsion angles Φ ($O_5$-$C_1$-$O_1$-$C_2'$) and Ψ ($C_1$-$O_1$-$C_2'$-$O_5'$) as calculated by using the PIMM88 [46] force field program for vacuum conditions ($\varepsilon = 1$).

Of the three energy minima observed in Fig. 3, the center and lower one differ mainly in the Ψ-torsion angle, and correspond to conformers A and B in Fig. 2, respectively. A ball-stick model representation including the MOLCAD-generated [47] dotted contact surface [48–50] (roughly equivalent to the solvent-accessible surface [51], i.e. "how water sees the molecule") of A and B as molecular images for the situation in solution is given in Fig. 4; a conformer associated with the upper minimum was not detectable experimentally and is not depicted therefore. In Table 3, the molecular parameters of the calculated conformers are summarized.

The surprisingly close agreement between calculated data and the experimental observations is impressively emphasized by the 3D-plot of the percentage distribution shown in Fig. 5: the calculated ratio of 71:21:8 for the three sucrose conformers is

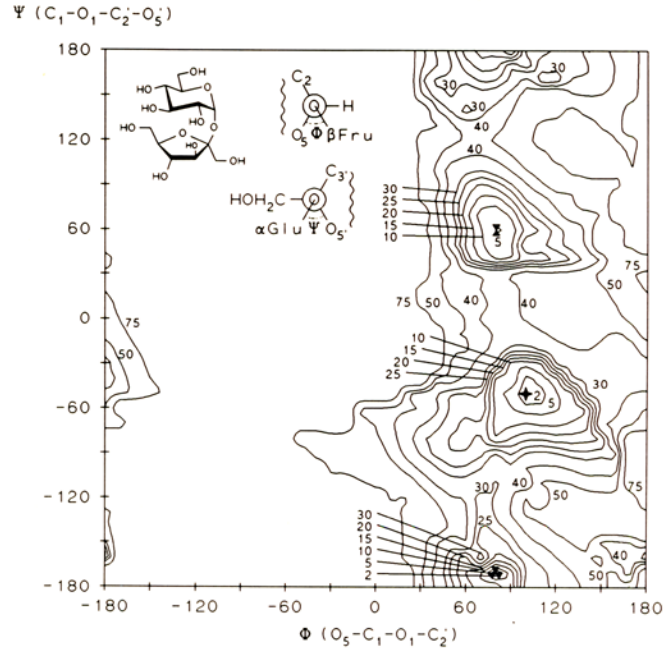



Fig. 3. Fully relaxed energy potential surface of sucrose as a function of the two intersaccharidic torsion angles Φ ($O_5$-$C_1$-$O_1$-$C_2'$) and Ψ ($C_1$-$O_1$-$C_2'$-$O_5'$)*, as generated by the PIMM88 [46] force field program. Energy contours are given in kJ/mol relative to the global minimum. The energy minimum at $\Phi \approx +110°/\Psi \approx -50°$ corresponds closely to the solid state conformation of sucrose.

* The Φ/Ψ-torsion angles were driven in steps of 10° each and fixed, whilst all other molecular parameters were fully optimized in each step. New geometries were generated from conformationally adjacent, already optimized conformers; the self-consistency of the map was counter checked by double calculation of structures on same Φ/Ψ-grid points, generated by different conformational pathways.

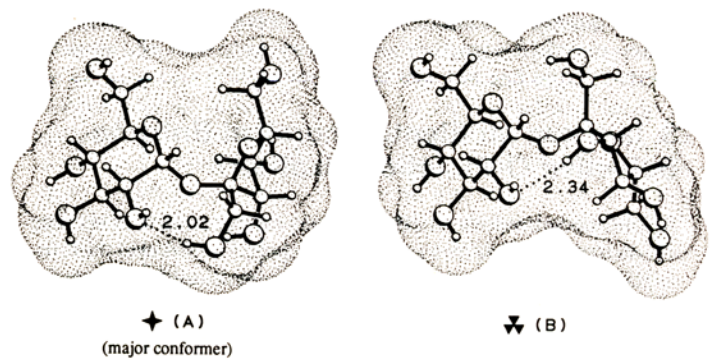



Fig. 4. Ball-stick model representation including the contact surface in dotted form of the low energy conformers of sucrose (cf. Fig. 3) which are likely to represent the conformations populated in solution (oxygen atoms are shaded).

Table 3.
Molecular Parameters and Percentage Distribution of Sucrose Conformers as Obtained from Fig. 2 und 3.

| Conformer | (**A**)[a] | (**B**)[b] | (**C**) |
|---|---|---|---|
| $\Delta H_F^{298}$ [kJ/mol] | −1741.8 | −1742.2 | −1737.3 |
| H-Bonds | 2-O$^g$ ··· HO-1$^f$ | 2-O$^g$ ··· HO-3$^f$ | 5-O$^g$ ··· HO-3$^f$ |
| d(O ··· H) [Å] | 2.02 | 2.34 | 1.79 |
| calc. distribution [%] | 71 | 21 | 8 |
| exp. (DMSO)[38] | 67 | 33 | (−) |

a) corresponding to conformer **A** in Fig. 2. b) conformer **B** (Fig. 2).

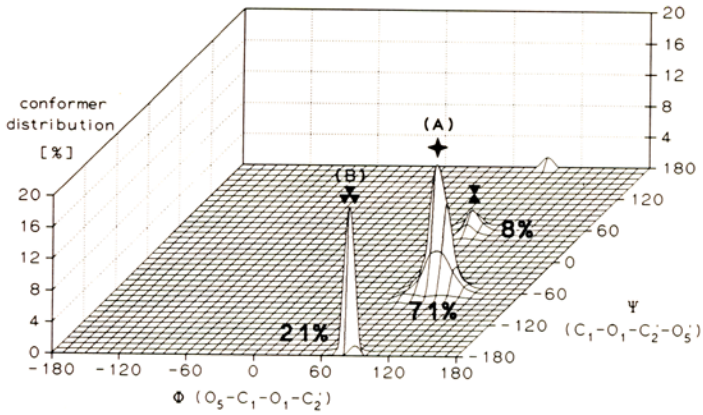



Fig. 5. 3D-Pot of the percentage distribution of sucrose conformers as a function of the Φ/Ψ-torsion angles, calculated from the energy potential surface (Fig. 3). $^1$H-NMR measurements in DMSO [38] indicate a 67:33 ratio of conformers A and B, without detecting a third one.

close to the experimentally observed proportions of 67:33:0 in DMSO-solutions [38].

## Electrochemical properties of sucrose

For predicting the electrochemical properties of sucrose from its solution behaviour, i.e. how the sucrose molecule is oriented in an electric field and, hence, arrives at the cathode, the **m**olecular **e**lectrostatic **p**otential (**MEP**) profiles [52] of the two relevant conformers in solution were calculated, using the corresponding MOPAC [53] program-generated AM**1** [54] atomic charges. In Fig. 6 the MEP patterns are represented on a solid surface model in a 16-color code ranging from violet (most positive electrostatic potential) to red (area of highest electronegative potential).

Each of these sucrose conformers has the violet, i.e. most electropositive area, centered around the glucosyl-2-OH. The major cause for this is clearly to be found in the cooperativity [55, 56] of the hydrogen bond directed towards the oxygen of this hydroxyl group; the electron-withdrawing effect of the adjacent anomeric center can contribute thereto only to a minor extent, since this would also have to be observed for the 1′- and 3′-OH groups in the fructose moiety.

The data presented, most impressively the MEP distribution patterns of Fig. 6, necessarily entail the notion, that the sucrose-2-OH exhibits an enhanced reactivity for deprotonation by electrochemical means: orientation of the molecule in the electric field in such a way that the glucosyl-2-OH side is directed towards the cathode, arrives there this way, induces the single electron transfer at that very position, and hence, converts the 2-OH into the alkoxide.

However, the SET-initiated deprotonation may not be the decisive regioselective step, since the resulting sucrose anion can undergo fast equilibration via very fast intramolecular proton shifts between the various hydroxyl groups, thus elaborating the thermodynamically most stable mono-anion. The time scales for the formation of the radical anion, for releasing a hydrogen atom, equilibration, and the subsequent trapping reactions of the anions (even when carried out *in situ*) differ by several orders of magnitude, and therefore, the observed product distribution upon trapping the anions by alkylation or acylation may, but does not necessarily have to be the result of the regioselectivity in the initial electrochemically induced deprotonation.

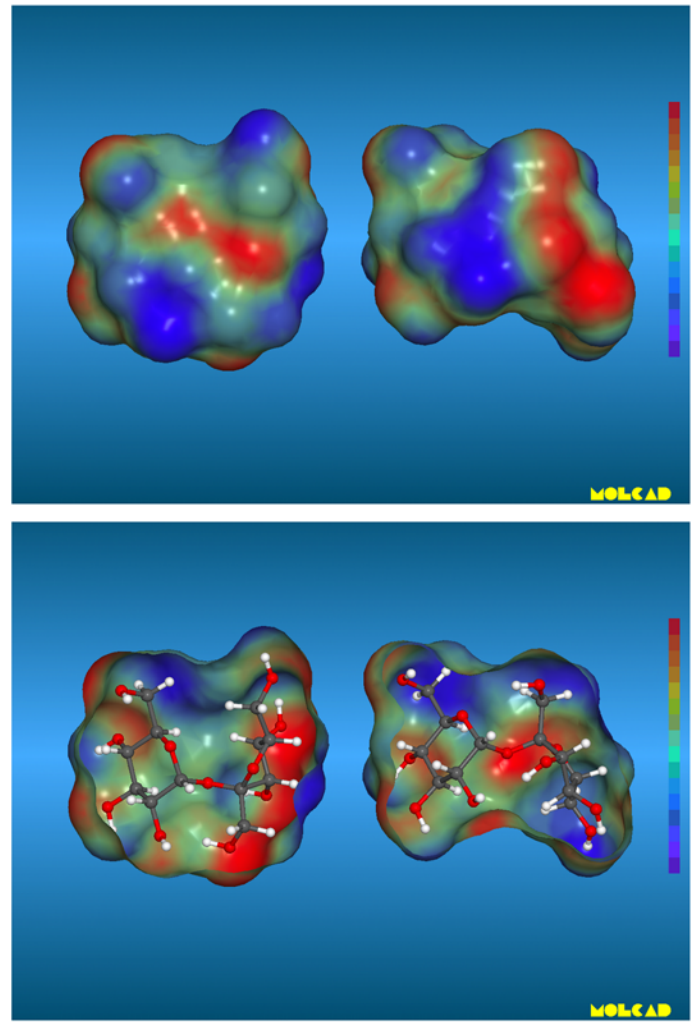



Fig. 6. **M**olecular **e**lectrostatic **p**otential (**MEP**) profiles of sucrose conformers A and B of Fig. 4, depicted on the corresponding contact surfaces in a 16-color code ranging from violet (most positive potential) to red (most electronegative potential) in relative terms. To facilitate visualization, the front side opened forms of the two conformers are also provided with a ball-stick model insert. In either case, it is evident that the proton of the 2-OH group of the glucose part is characterized by high positive electrostatic potential (violet), indicating its enhanced acidity over other protons.

## Hydrogen bonding effects in sucrose

In order to get an anticipation of the thermodynamically most stable sucrose mono-anion, that emerges – after either electrochemical or chemical deprotonation – from an interplay of intramolecular proton shifts and hydrogen bond stabilizations, some uncharged cyclopentanoid and cyclohexanoid model compounds were subjected to calculations using the PIMM88 force field program [46, 57].

The results summarized in Fig. 7, despite of being approximations due to not considering various hydrogen bond directionalities, allow clear conclusions:

- Intramolecular H-bonds between vicinal hydroxyl groups cannot contribute effectively to stabilization of anions due to their rather long O ⋯ H distances [58] of 2.6–2.8 Å and the small O ⋯HO angles [58] of $\varphi \approx 90-100°$.
- Interactions between hydroxyl and exocyclic hydroxymethyl groups [58], despite their shorter distances and larger angles ($d(O \cdots H) \approx 2.0-2.6$ Å, $\varphi(O \cdots HO) \approx 110-130°$), are unfavorable in solution [59–61], due to 1,3-diaxial like repulsions between the negatively charged oxygen atoms [62, 63].

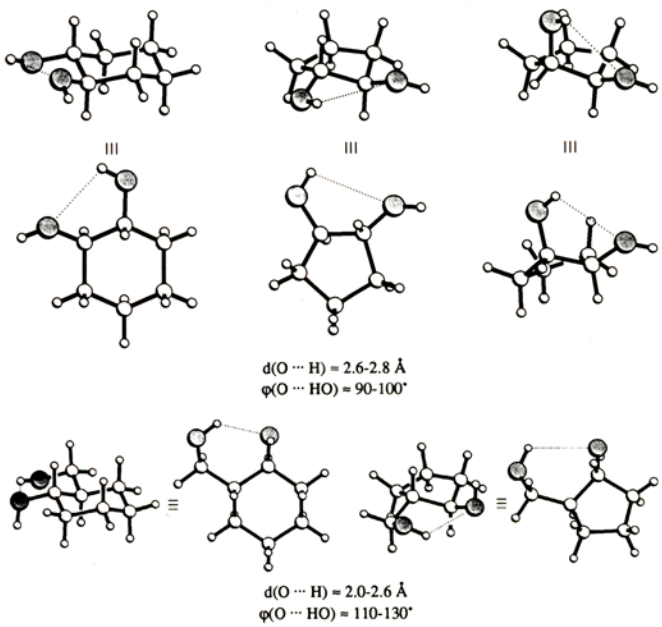
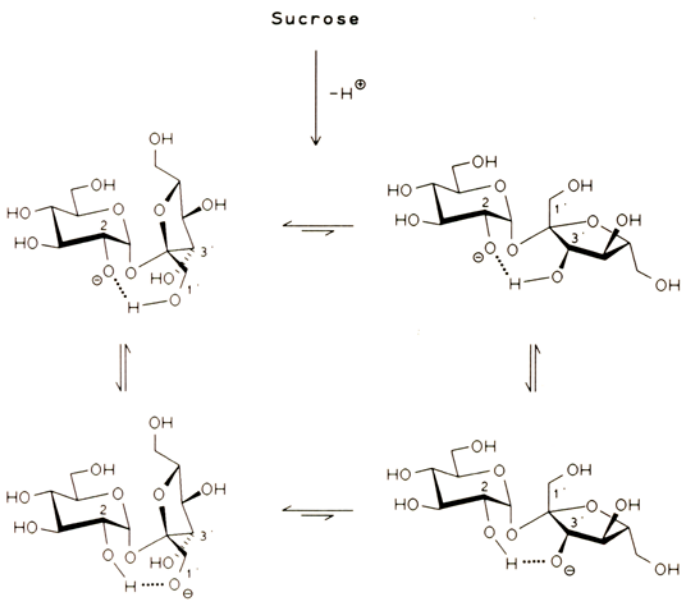



Fig. 7. A selection of typical hydrogen bond geometries (PIMM88 [46]) between vicinal hydroxyl groups (top row) and hydroxyl- and $CH_2OH$-groups (lower row) in cyclohexane- and cyclopentane-type model compounds; the approximate O ··· H distances and O ··· HO angles are given (in all cases, a projection of the molecule perpendicular to the O ··· HO-plane is depicted in addition; oxygen atoms are shaded).

In disaccharides, hydrogen bonds between the two sugar residues [58] are less stereochemically restricted and much more favorable, and therefore will contribute to a large extend to anion stabilization, in sucrose most pronouncedly the H-bonds between 1′-OH and 2-O (conformer A in Fig. 2 with $\varphi \approx 145°$) and 3′-OH ··· 2-O (conformer B, $\varphi \approx 165°$), both being comparatively short (2.0–2.3 Å). It is these interresidue hydrogen bonds, that obviously not only determine the MEP profile, i.e. the electropositive 2-OH proton, but are also responsible for the stabilization of the anion at these positions:




Thus, the glucosyl-2-OH of sucrose is not only the one to be most likely deprotonated by electrochemical (and, conceivably, also by chemical) means, but the respective anion is also the one best stabilized. Assuming, that the equilibrium between the two conformers A and B (2:1 in DMSO solution[38]) is the same, or at least very similar for the anion, chemical trapping by suitable reagents should lead to the 2-, 1′- and 3′-substituted products in an approximate ratio of 3:2:1.

### Correlation with experimental results

These rather detailed theoretical considerations and the predictions derived therefrom have a high degree of probability in such, as the pioneering electrochemical investigations of *Hamann* and his co-workers [26–28] agree with the conceptions exceedingly well: the product distribution upon quenching electrolyzed DMF-solutions of sucrose with alkylating agents such as benzyl chloride, benzyl bromide, or methyl iodide (cf. Table 2) invariably give the 2-*O*-alkylated compounds as the major products, followed by the 1′-*O*- and 3′-*O*-derivatives. Benzoylation of the electrochemically generated sucrose mono-anion by benzoyl chloride or methyl benzoate gave rather different results, but it is well known, that acyl groups may migrate under basic conditions from the place of the first chemical attack to thermodynamically more stable positions [10, 64].

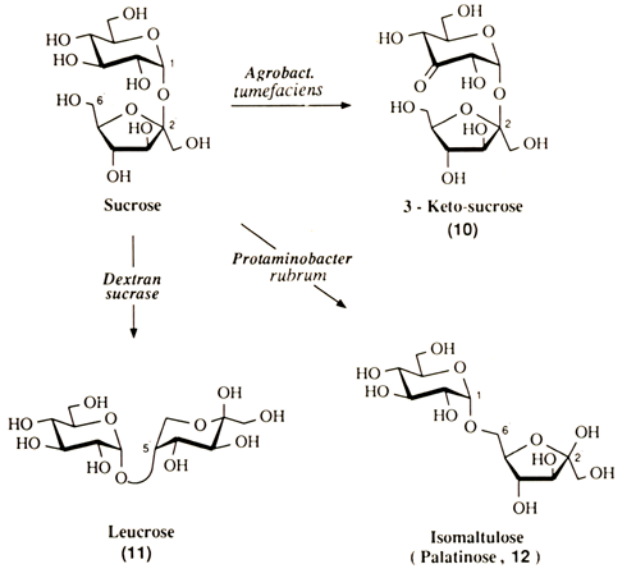
These considerations are also supported by recent results of *Plusquellec* et al. [10]: 2-*O*-acyl and 2-*O*-(N-carbamoyl)-derivatives of sucrose can be obtained in high yields by NaH-deprotonation of sucrose in pyridine and reaction with 3-acylthiazolidinethiones. Other supportive evidence can be derived from *Reinefeld*'s [11] observations on the regioselectivity of the benzylation of sucrose with benzyl bromide / $Ag_2O$ in DMF [11], from the 86:10:3:1-mixture of monobenzyl ethers obtained, he quite appropriately deduced a reactivity of the OH-groups in the order 2-OH > 3′-OH > 1′-OH > 3.OH.

The small differences inherent in the product distributions of the alkylation reactions after electrochemical or standard base-induced deprotonation may be attributed to the different solvents or counter-ions used: deactivation processes of the electrodes require the use of lithium salts, while under the usual standard conditions sodium bases are applied. Despite of this electrochemical approach being highly intriguing, further investigations will have to prove, whether the electrochemical entry into sugar derivatives can compete with standard base induced chemical reactions of sugars in terms of scope and practicability.

## 4 Isomaltulose

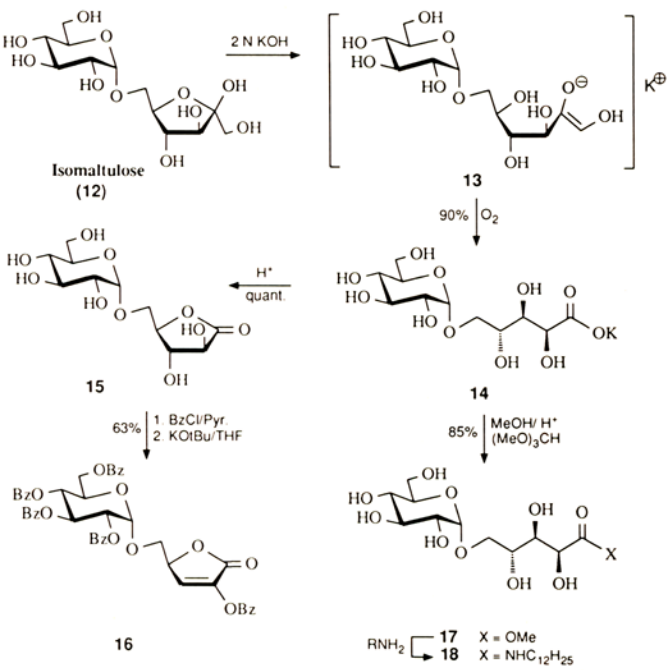
Aside from purely chemical or electrochemically-induced modifications of sucrose there are a number of enzymatic conversions, which – not unexpectedly – are endowed with a high degree of regioselectivity or are essentially regiospecific. Relevant examples are the oxidation of sucrose exclusively at the 3-OH of the glucose part by *Agrobacterium tumefaciens* (→ 3)-keto-sucrose **10**) [65], and its transformation into the α(1→5)-linked leucrose (**11**) under the influence of dextransucrase [66].

Another prototype example of a highly selective bioconversion is the preparation of isomaltulose (palatinose, **12**) from sucrose by means of an immobilized α-glucosyltransferase from *Protaminobacter rubrum*, which by the key development work of Südzucker [67] was brought on an industrial level production of 20 000 t per year (cf. Table 1). Although **12** is considered to be a promising alternative to sucrose as a potential parenteral nutrient [68], it is not being used as such but in the form of its hydrogenation product, a 1:1-mixture of glucosyl-α(1→6)-sorbitol and glucosyl-α(1→1)-mannitol which is marketed under the trade name Isomalt® as a low-caloric, non-cariogenic sweetener [69].



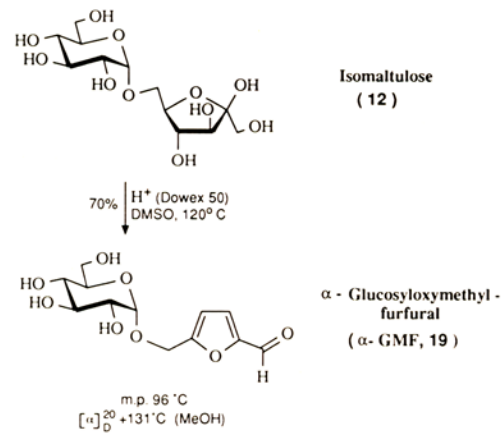

Isomaltulose being thus accessible in bulk scale, it becomes an enticing starting material from which to develop practical reaction channels towards disaccharide-building blocks. Of the many chemical modifications that have been investigated, two high-yielding reaction channels have emerged, free of protecting groups and practical in terms of the criteria outlined in the introduction. The first is the air oxidation of isomaltulose in strongly alkaline (KOH) solution, which – *via* the enediolate intermediate **13** – generates the potassium salt of the next lower aldonic acid, i.e. glucosyl-α(1→5)-D-arabinonate **14** in a surprisingly clean reaction [70, 71]. Unlike the air oxidation of D-fructose under analogous conditions, which is encumbered by many side products such as glycolic, glyceric, lactic and erythronic acids [72], the oxidative degradation of isomaltulose is essentially free of such undesired products, enabling yields of around 80–90% [70, 71].

The ensuing chemistry, feasible with the potassium glucosyl-arabinonate **14** comprises its quantitative conversion into the lactone **15** by treatment with a strongly acidic exchange resin




[70]. Subsequent benzoylation and base-induced elimination elaborates the enelactone **16** [17], a terminally glucosyl-oxymethyl-substituted butenolide. Alternately, on exposure of **14** to methanol/trimethoxymethane in the presence of an acidic exchange resin, the methyl ester **17** is obtained in crystalline form and satisfactory yield, which can either be converted into glucosyl-α(1→5)-D-arabinitol by hydride reduction [70] – a disaccharide-alcohol that has about the same sweetness as its six-carbon alditol analog Palatinit [69] – or, by aminolysis with long-chain alkylamines, to compounds of type **18**, that have a potential utility as non-ionic surfactants [71].

Of the five α-D-glucosyl-D-fructoses isomeric with sucrose, all of which, in solution, have different tautomeric distributions [73], only the α(1→6)-linked isomaltulose (**12**) has the potential of elaborating a furfural structure from its fructose portion. If the intersaccharide linkage survives the acidic conditions required for the threefold dehydratization involved, the product would be α-D-glucopyranosyloxymethyl-furfural (**19**, α-GMF), a glucosylated, and hence, substantially hydrophilic analog of HMF.

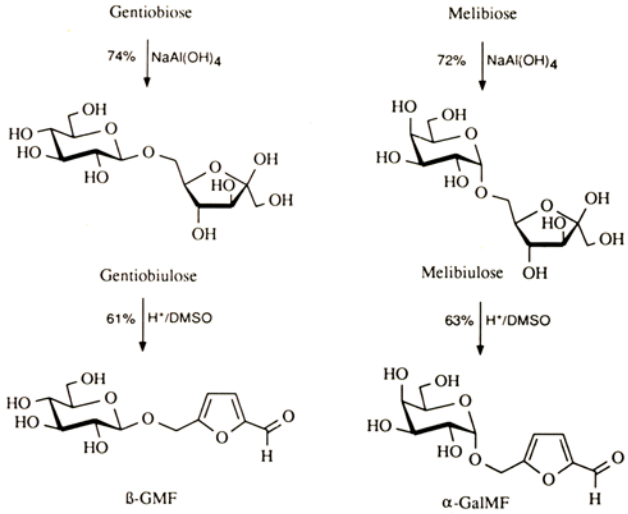



The one-step conversion isomaltulose → α-GMF can indeed be realized in a preparatively satisfactory way. In adaption of work on the conversion of fructose into HMF [74] a series of conditions were evaluated, the best being heating **12** for 4 h in dimethyl sulfoxide solution with a strongly acidic ion exchange resin [75, 76]. From the resulting mixture of α-GMF (**19**, approx. 80%), isomaltulose dimers (≈ 10%), HMF, and glucose, **19** can be isolated in up to 70% yield as well-shaped prisms with a positive rotation (+131° in methanol) [75, 76]. Aside from a batch conversion, a continuous process has also been elaborated using a flow reactor [75] thus making α-GMF a well accessible product of bulk scale, if required.

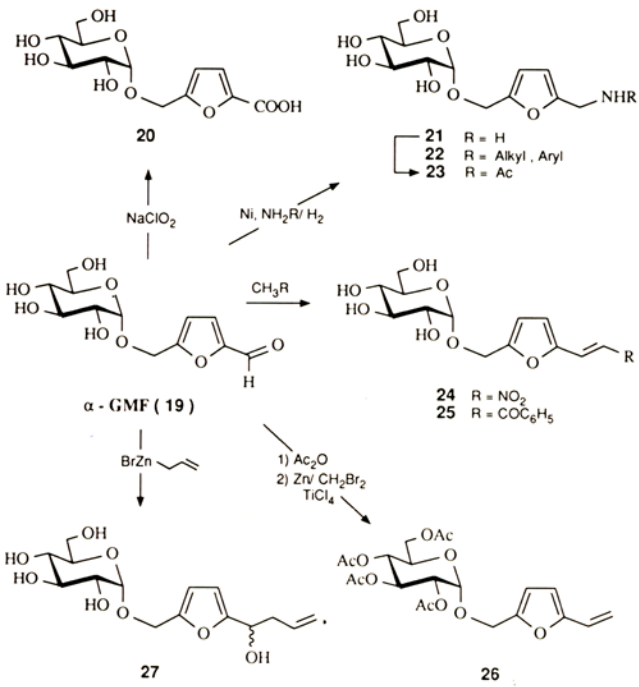
In similar fashion, the also crystalline β-GMF (m.p. 144°C and $[\alpha]_D^{20} = -159°$ in methanol) and α-GalMF (m.p. 143°C, $[\alpha]_D^{20} = +158°$) can be prepared [77] starting from the respective (1→6)-linked β-D-glucosyl- and α-D-galactosyl-fructoses, i.e. from gentiobiulose and melibiulose (planteobiose); these, in turn, are easily obtained from gentiobiose and melibiose, respectively, by sodium aluminate-mediated isomerization in a procedure that had effectively been used for the high-yield conversion of maltose into maltulose [78].

The examples demonstrate the broad applicability of both methods, the isomerization of glycosyl-glucoses on one side, and the selective dehydratization of fructoses, glycosylated at position 6, on the other hand side.

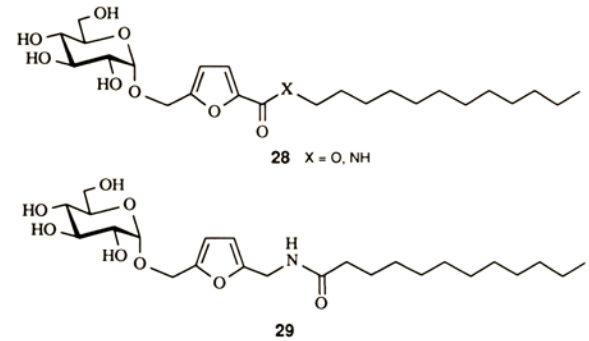
The potential of these glycosylated HMF's for the elaboration of products with industrial application profiles lies in its ensuing reactions, many of which can be executed *without* recourse to *O*-protecting groups. The carboxylic acid **20**, for example,




readily generated from α-GMF on oxidation, is an ideal educt for the preparation – through esterification with long-chain alcohols or by amidation with alkylamines – of novel non-ionic surfactants of type **28**, in which the hydrophilic and hydrophobic portions are separated by a hetero-aromatic spacer. The surface tension properties are in the range of other neutral surfactants; in the case of the α-GMF-dodecylester a c.m.c. (critical micelle concentration) of about 0.06 mmol/l is already sufficient for diminishing the surface tension of water by 60% to a value less than 30 mN/m. The same holds for compounds of type **29** resulting from α-GMF-amine **21**, accessible by reductive amination of α-GMF, in addition these amides show liquid crystalline behaviour on melting.




Aldol reactions of α-GMF may also be performed without *O*-protection: nitromethane (→**24**), acetophenone (→**25**), malonic ester, or malonodinitril, smoothly afford the corresponding products of carbonyl olefination [77]. In order to obtain polymerizable monomers, the acetylated α-GMF was treated with the Lombardo-modified Zn-$CH_2Br_2$-$TiCl_4$ reagent [79] giving the α-GMF-olefin **26** which polymerizes spontaneously

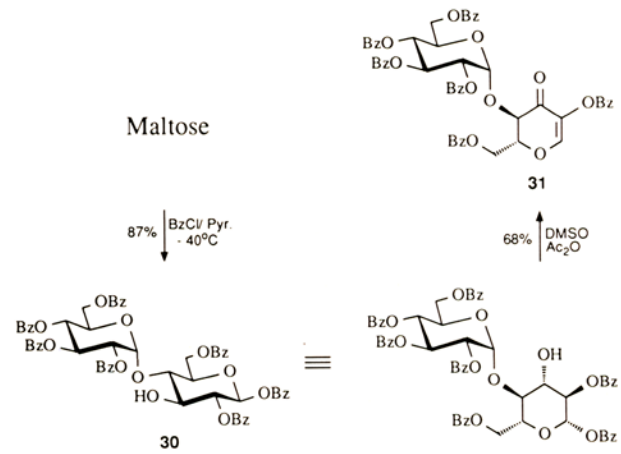



in absence of inhibitors – an interesting vein that is being further exploited. Reaction of α-GMF with zinc allyl bromide, in adaption of conditions of *Wilson* et al. [80], can be effected in an aqueous medium and, hence, without first introducing *O*-blocking; the resulting **27** may either be polymerized directly or after elimination of water to the respective butadienyl-furyl-glucoside, which now can even be utilized in *Diels-Alder* type reactions.

## 5 D-Maltose and D-Lactose

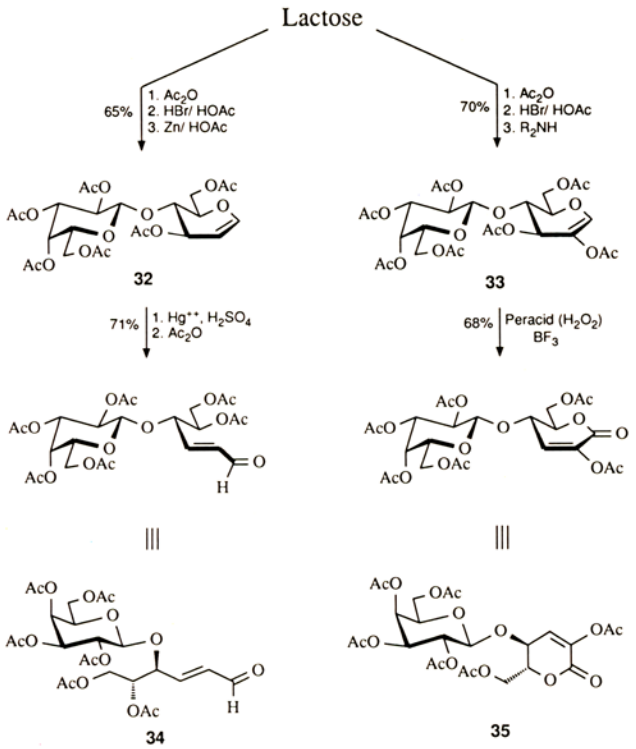
D-Maltose and D-lactose, readily available in large quantities from starch [81] and whey [82], respectively, have some applications in the form of their reduction products maltitol and lactitol as sweetening agents [83, 84] and of lactulose[82], a lactose isomerization product; however, despite of their basic chemistry being fairly well developed [85, 86], there, at present, does not seem to be any qualified chemical use on an industrial scale for these disaccharides.

A recently developed, maltose-specific entry into a versatile pyranoid building block stems from the observation, that low temperature benzoylation affords a heptabenzoate **30** in high yield [87], in which the 3-OH of the reducing glucosyl residue remains free. The easily accessible **30** suggested oxidation to the respective 3-ulose, which is smoothly obtained on exposure to pyridinium chlorochromate as the oxidant; however, when subjecting **30** to oxidation with dimethyl sulfoxide/acetic anhydride, both is effected, oxidation of the 3-OH and β-elimination to provide the *O*-glucosylated dihydropyranone **31** [88]:




Accordingly, a versatile, enantiopure six-carbon building block with suitable blocking groups – base-sensitive benzoyl functions and an acid-labile glucosyl residue – and appropriate functionality for a variety of ensuing reactions is accessible in two steps and 58% yield from maltose.

An analogous entry to building blocks of type **31** is also possible starting from cellobiose and from lactose, however, the initial step, i.e. their low temperature acylation to a disaccharide derivative with a free 3-OH proceeds with much less regioselectivity, yields of isolable heptabenzoyl analogs of **30** being in the 15–20% range only [89].

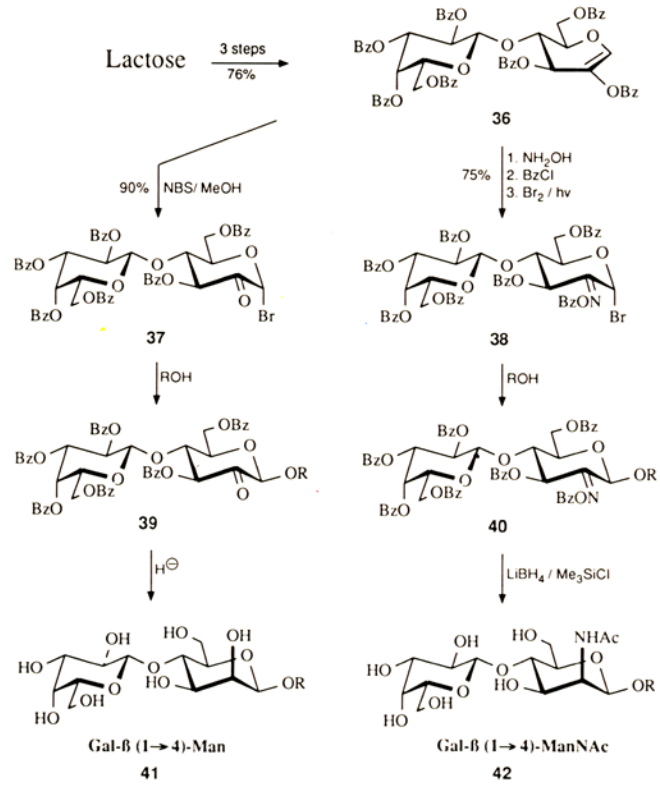



Other preparatively very useful reaction channels starting from any of these disaccharides, i.e. maltose, cellobiose or lactose, are opened up by their respective glycal or hydroxyglycal esters, which are accessible in three simple steps, involving acylation, anomeric bromination, and elimination either under reductive conditions (Zn/HOAc) or by base. With lactose, for example, the respective hexa-*O*-acetyl-D-lactal (**32**) [90] and its 2-acetoxy analog **33** [91] are readily obtainable; simple exposure of **32** to $HgSO_4/H_2SO_4$ in dioxane leads to the opening of the pyranoid ring to yield the 4-*O*-galactosylated trihydroxy-2-hexenal **34** [92] in a mechanistically quite interesting sequence of steps [93]. Such enals, of course, are suitably functionalized acyclic six-carbon synthons with high potential for a vibrant ensuing chemistry.

The same applies to products derived from the 2-hydroxylactal esters **33** and **36**. An effective and convenient one-pot procedure, simply involving treatment with boron trifluoride and a peracid in dichloromethane for 15 min, smoothly converts **33** into the enollactone **35** [94]. This quite versatile building block is a counterpart to the maltose-derived dihydropyranone **31**, the difference being that the enolone structural element in the pyranoid ring is realized in the reverse arrangement.

Disaccharide-derived glycal and hydroxyglycal esters have also high synthetic potential in the regio- and stereocontrolled elaboration of biologically important oligosaccharides such as, for example, the human blood group determinants. Thereby, the lactal and 2-hydroxylactal esters appear to be the most important, since the galactosyl-β(1→4)-glucosyl residue, and – biologically even more important – the N-acetyllactosaminyl moiety is often realized in nature. A promising development along this vein is their transformation into 2-oxo- and 2-oximino glycobiosyl bromides, i.e. disaccharide building blocks suitably functionalized for direct glycobiosylation [95, 96]. The methodology elaborated starts with the conversion of lactose, for example, by benzoylation, HBr treatment, and dehydrobromination into its 2-hydroxyglycal ester as illustrated below (→**36**); this is followed by an N-bromosuccinimide-promoted methanolysis, which effectively delivers the hexa-*O*-benzoyl-lactosulosyl bromide **37**. Alternatively, application of the high-yielding, three-step sequence hydroxylaminolysis → benzoylation → photobromination provides the 2-oximino-lactulosyl bromide **38** [95].

The broad utility of these novel disaccharide building blocks with a non-participating group next to the anomeric center resides in the ease and uniformity with which stereocontrol over glycosidations can be effected: silver carbonate-induced alcoholysis with simple primary and secondary hydroxyl components exclusively provides the β-D-lactosidulose **39** or its oximino analog **40**.




Reduction of the 2-oxo ($NaBH_4$) and 2-benzoximino functions (diborane or $LiBH_4/Me_3SiCl$) proceed with stereoanomeric control such that hydride addition takes place from the side opposite to the anomeric substituent; as a result disaccharides with β-D-mannose (**41**), and β-D-mannosamine units (**42**) are generated in a most satisfactory way [97, 98].

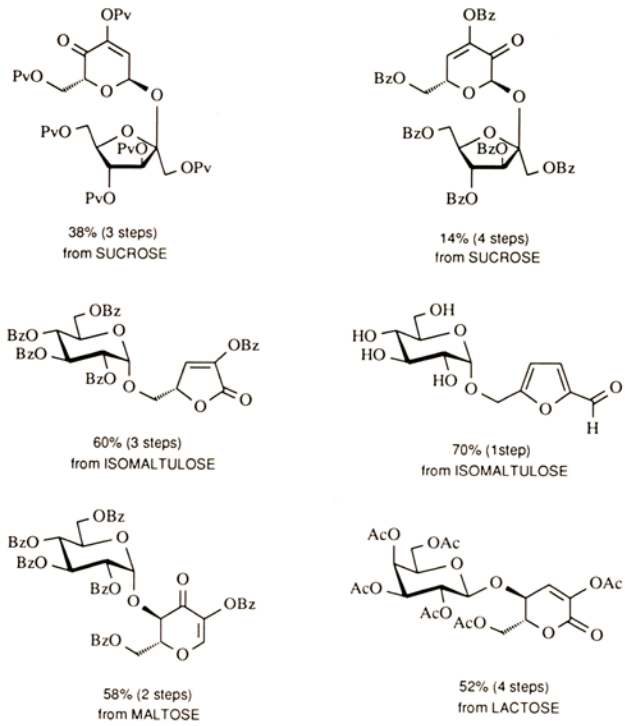
Accordingly, these disaccharide building blocks are expected to lend themselves to the efficient attachment of α-linked lactosamine units to any given sugar hydroxyl group. The method's prime strength, though, would appear to lie in the anellation of glycosyl-(1→4)-β-D-mannose and glycosyl-(1→4)-β-D-mannosamine blocks onto a sugar chain inasmuch as difficulties still prevail with the direct incorporation of β-D-mannose or 2-acetamido-2-deoxy-β-D-mannose residues.

## 6 Conclusion

By way of summary, this account describes some novel, practical, large-scale adaptable (if required) reaction channels from bulk disaccharides to versatile building blocks which, in one of

the two sugar portions have an array of functional groups, to which the huge arsenal of preparative organic methodology may directly be applied. The essentials are given in the following compilation:

Disaccharide Building Blocks




These examples provide a conceptual framework by which the chemistry of low-molecular weight carbohydrates in general, and of disaccharides in particular, are moulded towards the practical elaboration of products with industrial application profiles. The synthetic potential, however, inherent in cheap, bulk-scale available disaccharides is far from being exhausted. Thus, in view of the comparatively few reaction sequences meeting process chemistry demands, there is an urgent necessity to further develop practical, large-scale adaptable *reaction channels* from sugars to versatile building blocks.

The desired replacement of fossile raw materials by those annually regrowing is not to be judged on the basis of the present state of development or on comparative economic evaluations. Instead, basic research in the entire spectrum of promising applications is required to decisively improve the competitiveness of carbohydrates over petrochemical raw materials – with systematic utilization of the present arsenal of organic reactions and with reliance on the most advanced computer modelling possibilities, which make research (not results!) largely planable.

The prospects to open up new fields of application for carbohydrates in general, and for those of low-molecular weight in particular, are bright, if a generous "horizon of time" is being granted until which returns are brought in the forms of marketable products, and if chemical industry is willing to commit itself more pronouncedly than heretofore with these issues, making an all-out effort to either do the basic research required itself, or enable it in academic institutions by generous support. Only in this way, economically sound alternatives for the production and application of renewable carbohydrates will eventually be elaborated.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