Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: *Asymmetry* 17 (2006) 756–762
Tetrahedron: Asymmetry

Versatile building blocks from disaccharides: glycosylated 5-hydroxymethylfurfurals☆

Dierk Martin and Frieder W. Lichtenthaler*

Clemens-Schöpf-Institut für Organische Chemie und Biochemie, Technische Universität Darmstadt, Petersenstraße 22, D-64287 Darmstadt, Germany

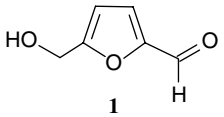
Received 10 December 2005; accepted 19 December 2005
Available online 15 March 2006

Dedicated to Professor Klaus Buchholz on the occasion of his 65th birthday

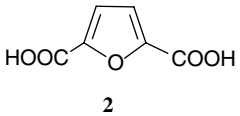
Abstract—A practical protocol for the elaboration of *O*-glycosyl-HMF's from glycosyl-(1→6)-glucoses is reported, the two steps involving aluminate-promoted isomerization to the respective 6-*O*-glycosyl-fructoses and subsequent selective dehydration of the fructose portion. Accordingly, melibiose, gentiobiose, and primeverose are converted into the corresponding 2-uloses and, then, into α-GalMF **11**, β-GMF **12**, and β-XylMF **13**. Pt/C-catalyzed oxidation with oxygen in NaOH at 25 °C efficiently generated the respective furoic acids from α-GalMF and α-GMF, whilst Pt/O_2 in water at 50 °C also oxidizes the primary OH to give the dicarboxylic acids **15** and **17**–key building blocks for the generation of novel types of polyesters and polyamides.

1. Introduction

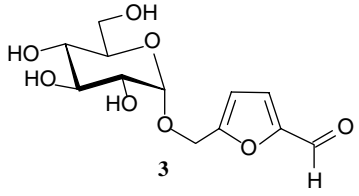
As carbohydrates represent 75% of the annually renewable biomass, their utilization for the generation of chemicals and materials that eventually replace those from fossil resources is a major challenge for green chemistry.[2,3] This entails the development of efficient methodologies for the simultaneous reduction of their oxygen content and introduction of C=C and C=O functionality toward industrially viable building blocks. Furan-type heterocycles are prototypes of such chemicals: *furfural*, already produced on an industrial scale from biomass-derived xylose,[4] 5-hydroxymethylfurfural **1** (HMF),[5] for which a pilot plant process for production from D-fructose or inulin is available,[6] and which—in the form of its oxidation product furan-2,5-dicarboxylic acid **2**—is considered to be one of the top 12 biomass-derived chemicals deserving further exploitation.[7]



1



2



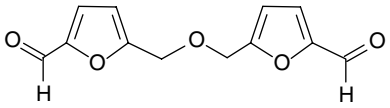
3

Since a hydrophilic version of HMF, 5-α-D-glucosyloxymethyl-furfural **3** (α-GMF)—accessible from sucrose-derived isomaltulose[8]—has gained interest as a building block for a novel type of liquid crystals,[9] as well as for a variety of hydrophilic pyrroles, pyridazines, and diazepinones,[10] we opted to investigate the preparation of O-glycosylated HMF's with other sugar portions and anomeric configurations—preferably not by glycosylation of HMF, as the yields obtainable are modest.[11] This has been attributed to the electron-withdrawing effect of the aldehyde moiety decreasing the nucleophilicity of the hydroxyl group,[11] yet is more likely due to the substantial formation of the known[12] bis-HMF-ether **4** under a variety of glycosylation conditions.[13]

☆ Part 38 of the series, Sugar-Derived Building Blocks. For Part 37, see Ref. 1.

* Corresponding author. Fax: +49 6151 166674; e-mail: lichtenthaler@chemie.tu-darmstadt.de

0957-4166/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2005.12.010



4

Hence, the approach followed for the generation of α-GMF—selective dehydration of the fructose portion of isomaltulose under conditions that retain the interglycosidic linkage[8]—was applied to other glycosyl-(1→6)-fructoses, namely melibiulose **8**, gentiobiulose **9**, and primeverulose **10**. Accordingly, we herein report their efficient preparation from the respective glycosyl-(1→6)-glucoses, their conversion into α-GalMF **11**, β-GMF **12**, and β-XylMF **13**, and some follow-up reactions.

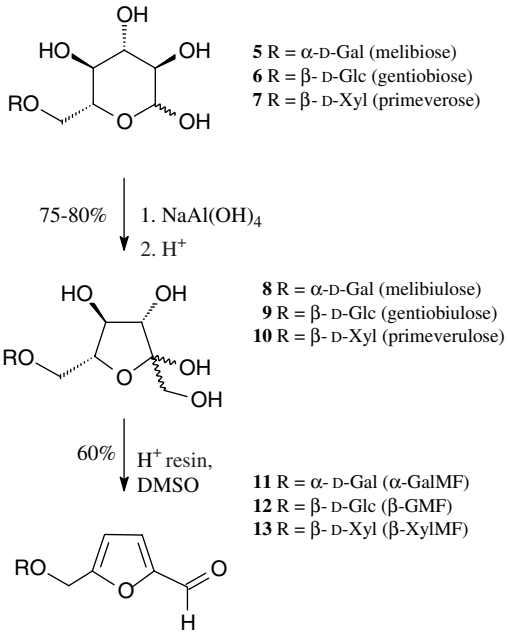
2. Results and discussion

2.1. Aluminate-mediated isomerizations of 6-*O*-glycosyl-glucoses

Unlike α-D-glucosyl-(1→6)-D-fructose (isomaltulose), which is produced on a ton scale from sucrose by bacterial O-2→O-6-transglucosylation,[14] other 6-*O*-glycosylated fructoses, such as melibiulose **8**, gentiobiulose **9**, and primeverulose **10**, although known,[15–18] are considerably less accessible.[19] The better accessibility of the respective 6-*O*-glycosyl-glucoses melibiose **5**,[20] gentiobiose **6**,[21] and primeverose **7**,[22] meant that a procedure had to be sought for effectively isomerizing their terminal glucose unit to fructose. Of the various methods evaluated,[23] the one most suitable was found to be one adapted from the aluminate-promoted conversion maltose into maltulose[24] (70% of crystalline product[25]), and lactose into lactulose (85%),[26] which in turn relied on an earlier patent for a glucose→fructose conversion (67%).[27] The protocol simply involves heating of an aqueous solution of the glycosyl-glucoses **5**–**7** with sodium aluminate (4 h, 45 °C) the respective reaction mixtures comprising about 85–90% of the desired glycosyl-fructoses **8**–**10** (HPLC) aside the educts, their component sugars and D-fructose (1–2% each), yet—notably—only trace amounts of the respective glycosyl-mannoses.

Compared with the large variety of reactions induced on exposure of aldoses to alkali—C-2-epimerization,[23] rearrangement to the ketose,[23] retro-aldolization with subsequent recombination of the fragments,[28] and formation of saccharinic acids[29]—the aluminate-mediated treatment of the 6-*O*-glycosyl-glucoses **5**–**7** takes a distinctly more uniform course: rearrangement to the respective glycosyl-fructoses **8**–**10** is highly preferred (85–90%), such that the glucose→fructose conversion is the predominant if not exclusive reaction path followed.

A *mechanism* capable of explaining this preference obviously has to rely on aluminate complexes of the two sugars and/or the respective reaction intermediates as differences in their stabilities are likely to shift the equilibria involved to the fructose side. Evidence toward this end may be drawn from the fact that 1:1 complexes of



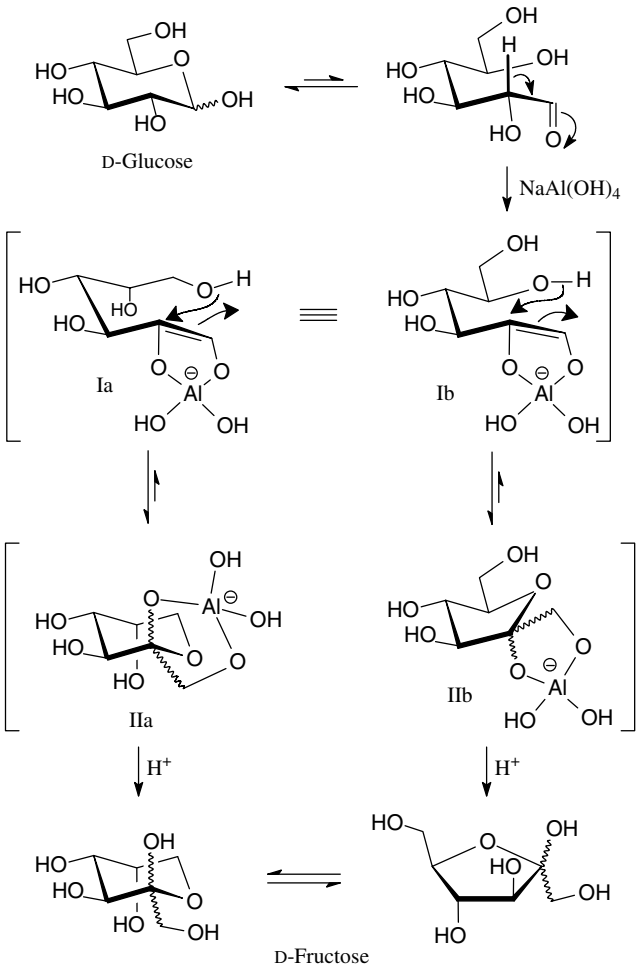
Scheme 1. Sodium aluminate-mediated isomerization of 6-*O*-glycosylated glucoses to their fructose analogs (**5**–**7**→**8**–**10**) and their dehydration to the respective 5-*O*-glycosylated HMFs **11**–**13**.

aluminate with D-glucose and D-fructose have been prepared[30,31] and that the association constant of the D-fructose–aluminate complex is 5–10 times higher than the one formed from D-glucose.[31] The higher affinity of D-fructose to aluminate was also inferred from its pronouncedly larger retentivity on columns with resins in the aluminate form, such that glucose/fructose mixtures can be readily separated due to fast elution of the less strongly complexed glucose part.[30,31]

As of now, structural characterizations of these reducing sugar/aluminate complexes are not available. As it is generally accepted, however, that the first step in alkali-promoted transformation of aldoses is the formation of a 1,2-enediolate[23,28] through abstraction of H-2 from the aldehydro form of the sugar, an enediol–aluminate complex of type I (Scheme 2) appears to be the most plausible intermediate in the D-glucose→D-fructose conversion. The subsequent step then can be conjectured as a cyclization analogous to the common hemiacetalization, which can occur by attack of either *O*-6 or of *O*-5 at the C-2 of the enediolate, thereby elaborating the spiro-1,2-aluminate complexes of fructose in the pyranose (IIa) and furanose forms (IIb), respectively. As these transformations, in principle, are reversible, a shift of the equilibria Ia ↔ IIa and Ib ↔ IIb to the fructose side must be operative to account for the high fructose yields obtained on acidification—a reasonable assumption as aluminate stabilizes fructose distinctly stronger than the isomeric glucose.[30,32]

Of the two pathways delineated in Scheme 2, there are no arguments for a preference, as of now. That aqueous solutions of D-fructose mainly contain the β-pyranoid tautomer (73% at 25 °C[33]) may accentuate the fructopyranose complex IIa, yet its furanoid counterpart IIb

appears equally important as conversion of the 6-*O*-blocked glucoses **5**–**7** to their respective fructoses **8**–**10** can only proceed through furanose intermediates.



Scheme 2. Conceivable mechanism for the aluminate-mediaterd rearrangement of glucose to fructose proceeding through pyranoid or furanoid fructose–aluminate complexes. In the case of the 6-*O*-substituted analogs **5**–**7** only the 'furanoid' pathway to the 6-*O*-glycosyl-fructofuranoses **8**–**10** is followed.

The simplicity and consistency of this mechanistic rationalization—another via sterically unusual intermediates has been advanced[34]—is tempting, and this the more, as the favourable effect of borate in the alkaline isomerization of a variety of aldoses to ketoses,[35] most notably of the industrially important lactose → lactulose conversion,[36] may readily be understood on the basis of borate complexation intermediates of type I and IIa/b, the aluminium atom simply being replaced by boron. Any definite mechanistic proof, however, will have to await the unequivocal structural characterization of aluminate or boronate complexes. Studies towards this end are presently being pursued.

2.2. Selective dehydration 6-*O*-glucosyl-fructoses

For the selective dehydratization of the fructose portion of these glycosyl-fructoses, conditions used previously for the conversion of isomaltulose into α-GMF **3**—heating in an anhydrous DMSO solution in the presence of a dry, strongly acidic ion exchange resin for 3 h at 120 °C[8]—were applied. Mixtures of the corresponding glycosyl-HMF's (ca. 70–75%), dimeric glycosyl-fructoses (5–10%), HMF, and the respective aldose (~5%) were obtained, which were readily separated to give α-GalMF **11**, β-GMF **12**, and β-XylMF **13** in crystalline form and in yields of around 60% (Scheme 1). From a practical point of view though, these glycosyl-HMF's are more readily prepared from the respective glycosyl-(1→6)-glucoses **5**–**7**, as the two steps involved—base-promoted glucose→fructose isomerization and acid-induced dehydration of the crude glycosyl-fructoses **8**–**10**—can be readily combined into a continuous operation with overall yields also in the 60% range.

2.3. Catalytic oxidation of glycosyl-HMFs

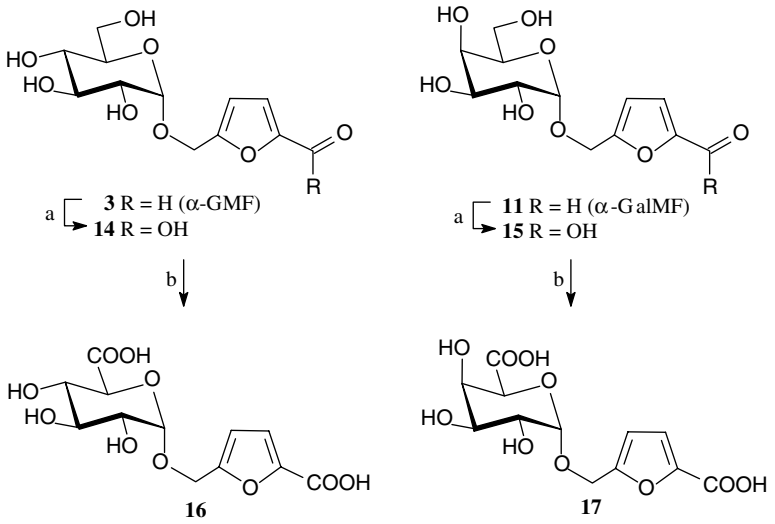
α-GMF **3** and α-GalMF **11** being the most readily accessible 'hydrophilic' HMF's—the former from bulk-scale available isomaltulose,[8] the latter from raffinose-derived[20] melibiose—their oxidative conversion into dicarboxylic acids was evaluated, as these were deemed to have industrial potential as building blocks for polyesters and polyamides.

As in the case of α-GMF,[8] the aldehyde function of α-GalMF **11** was readily oxidized on exposure to slightly acid-buffered aqueous sodium chlorite to provide the galactosyloxymethyl-furoic acid **15** (83%). The same conversion could also be effected in a more benign way by adapting conditions used previously[37] for the oxidation of HMF **1** into its 2-furoic acid: Pt/C-catalyzed oxidation with oxygen (1–2 h, 25 °C in 1 M NaOH), affording **15** in 85% yield (Scheme 3). Similarly, α-GMF **3** cleanly gave the respective glucosylated furoic acid **14** when subjected to these conditions.

In non-reducing mono- and disaccharides, the Pt-catalyzed oxidation with oxygen takes place at the primary hydroxyl group with high selectivity;[38] hence, when employing somewhat more vigorous conditions—Adams catalyst, freshly prepared by hydrogenation of PtO_2, higher temperature (70 °C), and slightly longer reaction times (3–5 h)—not only was the aldehyde group in α-GMF and α-GalMF oxidized, but the 6′-OH as well, to smoothly provide the respective dicarboxylic acids **16** and **17** in yields of 79% and 84%. Studies on their utilization toward the generation of di- and polyamides by aminolysis of their dimethyl esters with fatty amines and diamines of the hexamethylenediamine type are currently being implemented.

3. Conclusion

With 5-hydroxymethylfurfural **1** (HMF) being a key intermediate in the quest to utilize carbohydrates as organic raw materials,[2] this account provides an indication of the potential ease of access to a number of *O*-glycosylated, hence, hydrophilic HMF analogues, that is, α-GalMF, β-GMF, and β-XylMF. Their generation, each



Scheme 3. Reagents and conditions: (a) 5% Pt/C, O_2, N NaOH, 2 h, 25 °C, 85% (**14**), 76% (**15**); (b) Pt/O_2, H_2O, 3–5 h, 50 °C, 84% (**16**), 79% (**17**).

in crystalline form, from the respective glycosyl-(1→6)-glucoses melibiose, gentiobiose, and primeverose comprise a simple two-step process, which can be combined into one continuous operation: base-promoted isomerization of their glucose portion to fructose and subsequent acid-induced dehydration of the fructose unit. The utility of these glycosylated HMF's as versatile building blocks toward products with industrial application profiles was demonstrated by the high-yielding conversion of α-GalMF and α-GMF into dicarboxylic acids, deemed of relevance for the generation of novel types of polyesters and polyamides.

4. Experimental

4.1. General

Melting points were determined with a Bock hot-stage microscope and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter at 20 °C using a cell of 1 dm path length; concentration (*c*) in g/100 mL and solvent are given in parantheses. ^1H and ^{13}C NMR spectra were recorded on a Bruker ARX-300 spectrometer in the solvents given. Mass spectra were acquired on Varian MAT 311 and MAT 212 spectrometers. Microanalyses were determined on a Perkin–Elmer 240 elemental analyzer. Analytical thin layer chromatography (TLC) was performed on precoated Merck plastic sheets (0.2 mm silica gel 60 F_{254}) with detection by UV (254 nm) and/or spraying with H_2SO_4 (50%) and heating. Column and flash chromatography was carried out on Fluka silica gel 60 (70–230 mesh) using the specified eluents.

4.2. 6-*O*-(β-D-Galactopyranosyl)-D-fructofuranose (melibiulose, *syn* planteobiose), 8

Melibiose monohydrate (**5**·H_2O, 10.5 g, 29 mmol) was added to a sodium aluminate solution, freshly prepared by gradual dissolution of aluminium granulate (3.5 g) in 30 mL of 20% aqueous NaOH (H_2 evolution), filtration after cessation of gas evolution, and addition of water to 35 mL. The mixture was then kept at 45 °C for 4.5 h, whereby it had attained a red color and TLC indicated an approximate 90% conversion[39] ($R_f = 0.20$ in *n*-PrOH/water/EtOAc for educt, 0.31 for product). Subsequent dilution with water (200 mL) was followed by dropwise addition of 10 M H_2SO_4 (→pH 4) and addition of $CaCO_3$ until CO_2 evolution ceased (→pH 6.7). Filtration of the $Al(OH)_3$ precipitate, thorough washings with water, and evaporation of the combined filtrates to dryness in vacuo left a syrup, which was fully deionized by passing through a mixed-bed column (10 mL each of Amberlite IRA-410, OH^- form and IR 120, H^+ form) and elution with water. In vacuo removal of the solvent from the eluate and drying over P_2O_5 left 8.6 g (82%) of **8** as a colorless syrup with $[\alpha]_D^{20} = +127$ (*c* 1.0, water, after equilibration for 2 h) {lit.[16] $[\alpha]_D = +125$ (*c* 1.8, water)}.

Another specific rotation value given for **8** ($[\alpha]_D^{25} = +55.2$ in H_2O[15]) is obviously due to the impure product.

4.3. 1′,2′,3′,4′-Tetra-*O*-acetyl-6′-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-β-D-fructofuranose (octa-*O*-acetyl-β-melibiulose)

A solution of 1.0 g (2.9 mmol) of melibiulose **8** in pyridine (50 mL) was cooled to 0 °C, followed by dropwise addition of Ac_2O (20 mL) and stirring overnight at ambient temperature. Ice was then added to the reaction mixture, which after stirring for 2 h was evaporated to dryness in vacuo. The residual syrup was dissolved in $CHCl_3$ (100 mL) and the solution successively washed with H_2SO_4 (50 mL), aqueous satd $NaHCO_3$, and water, dried over $MgSO_4$ and taken to dryness. Elution of the residue from a silica gel column (2 × 25 cm) with toluene-acetone (3:1), concentration of the eluates of R_f 0.44 (toluene/acetone, 3:1), and trituration of the syrup left with ether/*n*-hexane gave 1.60 g (81%) of octaacetate; mp 119 °C; $[\alpha]_D^{20} = +105$ (*c* 0.8, $CHCl_3$); ^1H

NMR (300 MHz, $CDCl_3$; Me_4Si): δ 1.9–2.1 (8s, 3H each, 8CH_3CO), 3.62 (dd, 1H, $J_{5,6a}$ 3.5, $J_{6,6}$ 12.0, 6-H_a), 3.87 (dd, 1H, $J_{5,6b}$ 5.1, $J_{6,6}$ 10.8, 6-H_b), 4.07 (m, 2H, 6′-H_2), 4.25 (t, 1H, 5′-H), 4.32 and 4.57 (2d, 1H each, $J_{1,1}$ 12.0, 1-H_2), 4.40 (m, 1H, 5-H), 5.06–5.14 (3H-m, 1-H, 3-H, 4-H), 5.30 (dd, 1H, $J_{1',2'}$ 3.5, $J_{2',3'}$ 10.3, 2′-H), 5.43 (m, 1H, 4′-H), 5.81 (d, 1H, $J_{3',4'}$ 3.8, 3-H). Anal. Calcd for $C_{28}H_{38}O_{19}$ (678.6): C, 49.56; H, 5.64. Found: C, 49.48; H, 5.62.

4.4. 6-*O*-(β-D-Glucopyranosyl)-D-fructofuranose (gentiobiulose), 9

A 1.70 g (5 mmol) portion of gentiobiose **6** was subjected to sodium aluminate-mediated isomerization as described for **5**→**8**. Analogous workup afforded a colorless syrup, which was further purified by elution from a sephadex column (2 × 15 cm) with water. In vacuo removal of the solvent from the product-containing eluates (R_f 0.31 in *n*-PrOH/water/EtOAc, 7:2:1 vs R_f 0.21 for educt) gave 1.28 g (75%) of **9** as a colorless syrup; $[\alpha]_D^{20} = +9.1$ (*c* 1.0, H_2O after equilibration for 3 h). ^{13}C NMR data (75.5 MHz, D_2O) correlated well with those described previously.[17]

4.5. 6-*O*-(β-D-Xylopyranosyl)-D-fructofuranose (primeverulose), 10

Following the procedure given for **5**→**8**, 3.0 g (9.6 mmol) of primeverose **7**[22] (R_f 0.32 in *n*-PrOH/water/EtOAc, 7:2:1) was nearly quantitatively converted into **10** (R_f 0.40). The resulting colorless syrup was purified by elution from a silica gel column (2 × 25 cm) with 7:2:1 *n*-PrOH/water/EtOAc: 2.30 g (77%) of **10** as a colorless foam; $[\alpha]_D^{20} = -28.9$ (*c* 1.0, H_2O, after 3 h) {lit.[18] $[\alpha]_D^{20} = -27.5$ (*c* 2.6, H_2O)}.

4.6. 5-[(α-D-Galactopyranosyloxy)methyl]-2-furancarboxaldehyde ('α-GalMF'), 11

A solution of 3.4 g (10 mmol) melibiulose **8** in anhydrous DMSO (35 mL) was heated to 120 °C, 0.4 g of Dowex 50 WX4 (H^+ form) and freshly desiccated molecular sieve (4 Å, 2.0 g)[40] were added, and stirring was continued for 3 h at 120 °C, whereafter TLC indicated absence of educt in favor of α-GalMF (R_f 0.48 in acetonitrile/water, 4:1) and some HMF. Filtration, removal of the solvent in vacuo, dissolution of the remaining dark-brown syrup in water (30 mL), extraction with CH_2Cl_2 (2 × 30 mL) for removal of traces of DMSO and HMF, and evaporation of the aqueous phase in vacuo provided a syrup, which was purified by elution from a silica gel column with acetone. Concentration of the product-containing eluates resulted in crystallization: 1.85 g (65%) of **11** as colorless needles; mp 143 °C; $[\alpha]_D^{20} = +158$ (*c* 1, MeOH); ^1H NMR (300 MHz, [D_6]DMSO): δ 3.5–3.7 (6H-m, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H_2), 4.54 and 4.66 (d, 1H each, J_{gem} 13.1, 5-CH_2), 4.78 (d, 1H, $J_{1',2'}$ 3.6, 1′-H), 6.76 and 7.52 (2d, 1H each, $J_{3,4}$ 3.5, 3-H, 4-H), 9.57 (s, 1, C*H*O); δ_C (75.5 MHz; [D_6]DMSO) 60.6 (C-6′), 60.7 (5-*C*H_2), 68.3 (C-2′), 68.9 (C-4′), 69.6 (C-3′), 71.8 (C-5′), 98.8 (C-1′), 112.0 (C-4), 124.2 (C-3), 152.3 (C-5), 158.2 (C-2), 178.4 (*C*HO). Anal. Calcd for $C_{12}H_{16}O_8$ (288.25): C, 50.00; H, 5.60. Found: C, 49.89; H, 5.56.

4.7. 5-[(β-D-Glucopyranosyloxy)methyl]-2-furancarboxaldehyde ('β-GMF'), 12

Gentiobiose (**6**, 5.0 g, 14.6 mmol) was subjected to aluminate-mediated isomerization to gentiobiulose **9**, as described for **5**→**8**, and worked up analogously. The resulting syrupy **9** (3.95 g) contained small amounts of educt (<3%, R_f 0.21 vs 0.31 for **9** in 7:2:1 *n*-PrOH/water/EtOAc), and was used without further purification for dehydratization by dissolving in 40 mL of DMSO and heating in the presence of Dowex 50 (H^+ form) for 2.5 h at 120 °C. Processing of the mixture as described for α-GalMF gave 2.14 g (51% based on gentiobiose) of **12**; mp 144 °C; $[\alpha]_D^{20} = -159$ (*c* 1, MeOH); ^1H NMR (300 MHz, [D_6]DMSO): δ 2.9–3.7 (several m, 6H, glucosyl 2′-H, 3′-H, 4′-H, 5′-H, 6′-H_2), 4.28 (d, 1H, $J_{1',2'}$ 7.7, 1′-H), 4.66 and 4.85 (2d, 1H each, J_{gem} 13.3, 5-CH_2), 6.78 and 7.51 (2d, 1H each, $J_{3,4}$ 3.5, 3-H and 4-H), 9.58 (s, 1H, C*H*O); δ_C (75.5 MHz; [D_6]DMSO) 60.8 (C-6′), 61.6 (5-*C*H_2), 69.2 (C-4′), 73.1 (C-2′), 76.4 (C-3′), 76.7 (C-5′), 101.9 (C-1′), 111.4 (C-4), 123.6 (C-3), 151.9 (C-5), 157.5 (C-2), 177.9 (C*H*O); MS (FD) *m*/*z* 288 (M^+). Anal. Calcd for $C_{12}H_{16}O_8$ (288.25): C, 50.00; H, 5.60. Found: C, 49.90; H, 5.55.

Performing the acid-promoted dehydration on gentiobiulose **9** as described above for the melibiulose →α-GalMF conversion gave β-GMF **12** in 57% yield.

4.8. 5-[(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-methyl]-2-furancarboxaldehyde (β-GMF tetraacetate)

To a cooled (0 °C) solution of β-GMF **12** (290 mg, 1 mmol) in pyridine (15 mL) was added, with stirring, acetic anhydride (5 mL) and the mixture was then kept at ambient temperature overnight, followed by pouring into ice water (10 mL). Concentration in vacuo gave a syrup, which was dissolved in CH_2Cl_2 (40 mL) and the solution washed successively with 2 M H_2SO_4, a satd aqueous $NaHCO_3$ solution, and water, followed by drying over $MgSO_4$ and removal of the solvent in vacuo. Purification of the residue by elution from a silica gel column (2 × 20 cm) with 3:1 toluene/acetone, evaporation of the solvent from the eluates, and trituration of the residue with ether gave 370 mg (81%) of β-GMF tetraacetate; mp 130 °C; $[\alpha]_D^{20} = -36$ (*c* 1, $CHCl_3$) {lit.[11] mp 130 °C; $[\alpha]_D^{20} = -39$ (*c* 1, CH_2Cl_2) for a product obtained by low-yield glycosylation of HMF with acetobromoglucose}. ^1H and ^{13}C NMR data ($CDCl_3$) correlated well with those reported.[11]

4.9. 5-[(β-D-Xylopyranosyloxy)methyl]-2-furancarboxaldehyde ('β-XylMF'), 13

A solution of primeverulose **10** (1.55 g, 5 mmol) in anhydrous DMSO (15 mL) containing 80 mg of dry Dowex 50 (H^+ form) and freshly desiccated molecular sieve (4 Å, 1.5 g)[40] was kept for 3 h at 120 °C, whereafter TLC indicated the absence of educt in favor of β-XylMF (R_f 0.65 in 4:1 acetonitrile/water) and traces of HMF

and xylose. Workup of the mixture as described for α-GalMF **11** afforded a syrup, which crystallized from acetone/EtOAc: 1.18 g (58%) of **13**; mp 124 °C; $[\alpha]_D^{20} = -35$ (*c* 1, MeOH) {lit.[41] mp 124–126 °C; $[\alpha]_D^{20} = -23$ (*c* 1, $CHCl_3$) for a product obtained in 11 steps from glucose and xylose as educts}; ^{1}H NMR (300 MHz, [D_6]DMSO): δ 3.05 (m, 3H, 2′-H, 3′-H, 4-H), 3.26 (m, 1H, 5′-Ha), 3.73 (dd, 1H, $J_{4',5'}$ 3.1, $J_{5',5'}$ 11.2, 5′-Hb), 4.25 (d, 1H, $J_{1',2'}$ 3.5, 1′-H), 4.62 and 4.76 (2d, 1H each, 5-CH_2), 5.0–5.2 (m, 3H, 3 OH), 6.76 and 7.50 (2d, 1H each, 3-H, 4-H), 9.58 (s, 1H, C*H*O); MS (FD) *m*/*z* 258 [M^+]. Anal. Calcd for $C_{11}H_{14}O_7$ (258.2): C, 51.16; H, 5.47. Found: C, 51.05; H, 5.43.

4.10. 5-[(α-D-Glucopyranosyloxy)methyl]-2-furoic acid, 14

At room temperature, oxygen was passed through a vigourously stirred solution of α-GMF **3** (2.90 g, 10 mmol) in 25 mL of 1 M NaOH containing 1.0 g of 5% Pt on carbon. Monitoring the progress of the oxidation (TLC in 4:1 acetonitrile/water) indicated the consumption of the educt after ~1.5 h, whereafter the mixture was filtered, followed by deionization with Dowex 50 (H^+ form) and evaporation in vacuo to dryness. Purification of the residue by fast elution from a silicagel column with 2:1 MeOH/$CHCl_3$ and in vacuo removal of the solvents from the product-containing eluates gave 2.70 g (85%) of **14** as a uniform, amorphous solid; $[\alpha]_D^{20} = +104$ (*c* 0.7, MeOH); ^{1}H and ^{13}C NMR data in [D_6]DMSO matched those obtained previously.[8]

4.11. 5-[(α-D-Galactopyranosyloxy)methyl]-2-furoic acid, 15

To a solution of α-GalMF **9** in NaOH (575 mg, 2 mmol, in 5 mL) was added 250 mg of 5% Pt/C, and oxygen was passed through with vigorous agitation for about 1.5 h as described for the conversion **3**→**14** (cf. above). Analogous workup afforded 460 mg (76%) of **15** as a uniform, amorphous solid; $[\alpha]_D^{20} = +147$ (*c* 0.8, MeOH); ^{1}H NMR (300 MHz, [D_6]DMSO): δ 3.5–3.7 (6H-m, 2′-H through 6′-H_2), 4.53 and 4.67 (2d, 1H each, J_{gem} 13.0, 5-CH_2), 4.74 (d, 1H, $J_{1',2'}$ 3.5, 1′-H), 6.38 and 6.65 (2d, 1H each, $J_{3,4}$ 3.5, 3-H and 4-H); MS (FD) *m*/*z* 305 (M^++1), 327 (M^++Na). Anal. Calcd for $C_{12}H_{16}O_9$ (304.3): C, 47.37; H, 5.30. Found: C, 47.29; H, 5.25.

4.12. 5-[(α-D-Glucopyranuronosyloxy)methyl]-2-furoic acid, 16

Freshly prepared Adams catalyst (1.0 g) was added to an aqueous solution of α-GMF **3** (2.9 g, 10 mmol, in 50 mL) and O_2 passed through the suspension with vigorous stirring for 3 h at 50 °C, maintaining pH 8 by gradual addition of solid $NaHCO_3$. After filtration, the solution was taken to dryness in vacuo, the residue was suspended in methanolic HCl (40 mL of saturated solution), and stirred for 1 h at ambient temperature. Filtration of insolubles, removal of the solvent from the filtrate, purification of the resulting syrup by elution from a silica gel column (2 × 20 cm) with 5:1 CH_2Cl_2/MeOH, and evaporation of the eluates containing **16** gave 2.70 g (84%) of a colorless syrup, uniform by TLC ($CHCl_3$/MeOH, 4:1). $[\alpha]_D^{20} = +97$ (*c* 0.9, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ 3.50 (dd, 1H, $J_{3',4'}$ 9.6, $J_{4',5'}$ 10.3, 4′-H), 3.60 (dd, 1H, $J_{1',2'}$ 3.9, $J_{2',3'}$ 9.9, 2′-H), 3.78 (dd, 1H, $J_{2',3'}$ 9.9, $J_{3',4'}$ 9.6, 3′-H), 4.31 (d, 1H, $J_{4',5'}$ 10.3, 5′-H), 4.43 and 4.71 (2d, 1H each, 5-CH_2), 5.43 (d, 1H, $J_{1,2}$ 3.9, 1′-H), 6.40 and 6.64 (2d, 1H each, 3-H and 4-H). Anal. Calcd for $C_{12}H_{14}O_{10}$ (318.23): C, 45.29; H, 4.43. Found: C, 45.14; H, 4.37.

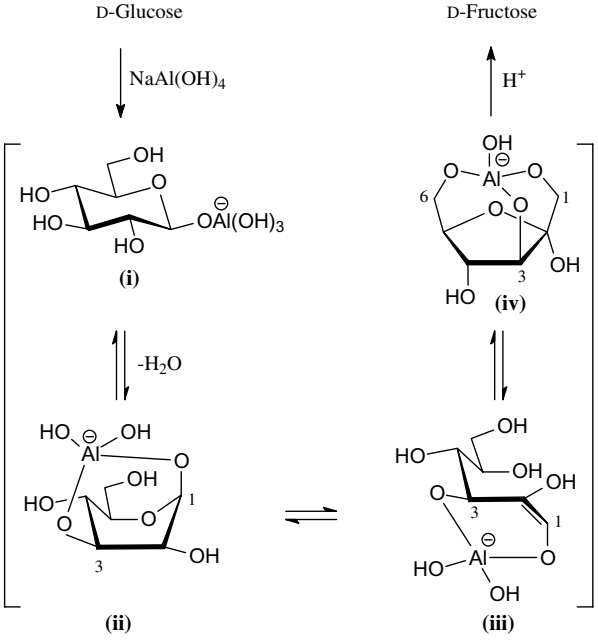
4.13. 5-[(α-D-Galactopyranuronosyloxy)methyl]-2-furoic acid, 17

An aqueous solution of α-GalMF **11** (865 mg, 3 mmol, in 20 mL) containing 500 mg of Adams catalyst was stirred vigorously at 50 °C while bubbling oxygen into the flask and keeping the pH 8 by the addition of small portions of $NaHCO_3$ as the oxidation proceeded. After 5 h, the mixture was worked up as described for **16** (cf. above) to afford 755 mg (79%) of **17** as a colorless, chromatographically uniform syrup; $[\alpha]_D^{20} = +108$ (*c* 0.7, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ 3.80 (dd, 1H, $J_{1',2'}$ 3.7, $J_{2',3'}$ 10.0, 2′-H), 3.92 (dd, 1H, $J_{2',3'}$ 10.0, $J_{3',4'}$ 3.5, 3′-H), 4.32 (dd, 1H, $J_{3',4'}$ 3.5, $J_{4',5'}$ 1.5, 4′-H), 4.41 and 4.72 (2d, 1H each, J_{gem} 13.1, 5-CH_2), 5.31 (d, 1H, $J_{1',2'}$ 3.7, 1′-H), 6.38 and 6.65 (2d, 1H each, $J_{3,4}$ 3.5, 3-H and 4-H). Anal. Calcd for $C_{12}H_{14}O_{10}$ (318.2): C, 45.29; H,4.43. Found: C, 45.19; H 4.33.

References

1. Lichtenthaler, F. W.; Cuny, E.; Sakanaka, O. *Angew. Chem.* **2005**, *117*, 5024–5028; *Angew. Chem., Int. Ed.* **2005**, *44*, 4944–4948.
2. Lichtenthaler, F. W. In *Biorefineries—Industrial Processes and Products*; Kamm, B., Gruber, P. R., Kamm, M., Eds.; Wiley-VCH: Weinheim, 2006; pp 3–59.
3. (a) Lichtenthaler, F. W.; Peters, S. *C.R. Chim.* **2004**, *7*, 65–90; (b) Lichtenthaler, F. W. *Acc. Chem. Res.* **2002**, *35*, 728–737; (c) Lichtenthaler, F. W. *Carbohydr. Res.* **1998**, *313*, 69–89.
4. (a) McKillip, W. J.; Collin, G.; Höke, H.; Zeitsch, K. J. Furan and Derivatives, *Ullmann's Encyclopedia Industrial Chem.*, 2000; http://www.mrw.interscience.wiley.com/ueic/articles/a12_119/frame.html; (b) Zeitsch, K. J. *The Chemistry and Technology of Furfural and its Many Byproducts*; Elsevier: Amsterdam, 2000; p 374.
5. (a) Lewkowski, J. *ARKIVOC* **2001**, 17–54; (b) Kuster, B. F. M. *Starch/Stärke* **1990**, *42*, 314–321.
6. Schiweck, H.; Munir, M.; Rapp, K.; Vogel, M. In *Carbohydrates as Organic Raw Materials*; Lichtenthaler, F. W., Ed.; Wiley-VCH: Weinheim, 1991; pp 78–82; *Zuckerind. (Berlin)* **1990**, *115*, 561.
7. *Top Value Added Chemicals from Biomass. Screening for Potential Candidates from Sugars*; US Department of Energy, 2004; pp 13–16; http://www.nrel.gov/docs/fy04_osti/35523.pdf.
8. Lichtenthaler, F. W.; Martin, D.; Weber, T.; Schiweck, H. *Liebigs Ann. Chem.* **1993**, 967–974.
9. Hanemann, T.; Haase, W.; Lichtenthaler, F. W. *Liquid Cryst.* **1997**, *22*, 47–50.
10. Lichtenthaler, F. W.; Brust, A.; Cuny, E. *Green Chem.* **2001**, *3*, 201–209.

11. Cottier, L.; Descotes, G.; Soro, Y. *J. Carbohydr. Chem.* **2005**, *24*, 55–71.
12. Chundury, D.; Szmant, H. H. *Ind. Eng. Chem. Prod. Res. Dev.* **1981**, *20*, 158–163; Musau, R.; Munavu, R. M. *Biomass* **1987**, *13*, 67–74; Larousse, C.; Rigal, L.; Gaset, A. *J. Chem. Tech. Biotechnol.* **1992**, *53*, 111–116.
13. D. Martin, Ph.D. Thesis, TU Darmstadt, 1993.
14. Kunz, M. *Ullmann's Encyclopedia Industrial Chemistry*, 5th ed. 1994; Vol. A25, pp 426–429.
15. French, D.; Wild, G. M.; Young, B.; James, W. J. *J. Am. Chem. Soc.* **1953**, *75*, 709–712.
16. Hough, L.; Jones, J. K. N.; Richards, E. L. *J. Chem. Soc.* **1954**, 295–297.
17. Leitner, C.; Mayr, P.; Riva, S.; Volc, J.; Kulbe, K. D.; Nidetzky, B.; Haltrich, D. *J. Mol. Catal. B: Enzym.* **2001**, *11*, 407–414.
18. Rutherford, D.; Richtmyer, N. K. *Carbohydr. Res.* **1969**, *11*, 341–345.
19. Melibiulose **8** has been obtained in an undisclosed yield by acid hydrolysis of the glucose portion of the naturally occurring trisaccharide planteose,[15] and from melibiose **5** either by isomerization with aqueous ammonia[16] (2.7% yield), or enzymatically in a two-step oxido-reduction process (no yield given).[17] Similarly unavailing in preparative terms are the low-yield obtention (<3%) of primeverulose **10** by base-induced isomerization of primeverose **7**,[18] or the biotransformation of gentiobiose into gentiobiulose **6**→**9**.[17]
20. (a) Fletcher, H. G., Jr.; Diehl, H. W. *J. Am. Chem. Soc.* **1952**, *74*, 5774–5776; (b) Whistler, R. L.; BeMiller, J. N. *Methods Carbohydr. Chem.* **1962**, *1*, 366–369.
21. Wolfrom, M. L.; Thompson, A. *Methods Carbohydr. Chem.* **1962**, *1*, 316–318.
22. Primeverose was obtained by hydrogenolysis of its benzyl primeveroside, which in turn was isolated by extraction of green fruits of *Prunus laurocerasus* following the procedure of Weinges, K.; Schick, H.; Lautenschläger, M.; Schilling, G. *Liebigs Ann. Chem.* **1991**, 703–705.
23. For a recent review on aldose→ketose rearrangements see: Angyal, S. J. *Topics Current Chem.* **2001**, *215*, 1–14.
24. Machida, I.; Kanaeda, J.; Miki, H.; Kubomura, S.; Toda, H.; Shiroishi, T. *Jpn. Kokai* 48049938 (1973); *Chem. Abstr.* **1973**, *9*, 126 744v, see also Ref. 25.
25. Lichtenthaler, F. W.; Rönninger, S. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1496.
26. Tumerman, L; Guth J. L. *U.S. Pat* 3,822,249 (1974); *Chem Abstr.* **1974**, *81*, 463, 927.
27. Haack, E.; Braun, F.; Kohler, K. *Ger. Pat.* 1,163,307 (1964); *Chem. Abstr.* **1964**, *60*, 83149.
28. Speck, J. C., Jr. *Adv. Carbohydr. Chem.* **1958**, *13*, 63–103.
29. Sowden, J. C. *Adv. Carbohydr. Chem.* **1957**, *12*, 35–79.
30. Rendleman, J. A., Jr.; Hodge, J. E. *Carbohydr. Res.* **1975**, *44*, 155–167.
31. Shaw, A. J., III; Tsao, G. T. *Carbohydr. Res.* **1978**, *60*, 327–335.
32. Rendleman, J. A., Jr.; Hodge, J. E. *Carbohydr. Res.* **1979**, *75*, 83–99.
33. Schneider, B.; Lichtenthaler, F. W.; Steinle, G.; Schiweck, H. *Liebigs Ann. Chem.* **1985**, 2443–2453.
34. A previous mechanistic conception for the aluminate-mediated glucose→fructose isomerization[31] is based on a β-D-glucose aluminate complex (**i**), which via a β-D-glucopyranose-1,3-aluminate (**ii**) and the acyclic 1,3-bridged enediolate intermediate **iii** proceeds to a 1,3,6-tridentate complex of type **iv**, that yields fructose on acidification:



Of the intermediates formulated, **ii** appears precarious in that the pyranoid ring is forced into a sterically unfavourable boat conformation, and postulation of the sterically demanding tridendate complex **iv** is not essential since the 6-*O*-glycosyl-glucose→fructose conversions **5**–**7**→**8**–**10**, in which intermediates of type **iv** are precluded, proceed with comparative ease and efficiency.

35. Mendicino, J. F. *J. Am. Chem. Soc.* **1960**, *82*, 4975–4979.
36. (a) Carubelli, R. *U.S. Pat.* 3,505,309 (1970); *Chem. Abstr.* **1970**, *73*, 15169; (b) Fazekas, J.; Farkas, I.; Balint, J.; Miskolczi, I.; Jakob, A.; Bognár, R.; Kovács, A.; Boor, K. *Hung. Teljes* 35,267 (1985); *Chem. Abstr.* **1986**, *105*, 115372; (c) Dorscheid, M.; Krumbholz, R. *Eur. Pat.* 375,046 (1990); *Chem. Abstr.* **1990**, *113*, 231930.
37. (a) Lew, B. W. *U.S. Pat.* 3,326,944 (1967); *Chem. Abstr.* **1967**, *68*, 49434; (b) Verdeguer, P.; Merat, N.; Gaset, A. *J. Mol. Catal.* **1993**, *85*, 327–344.
38. Arts, S. J. H. F.; Mombarg, E. J. M.; van Bekkum, H.; Sheldon, R. A. *Synthesis* **1997**, 597–613; Heyns, K.; Paulsen, H. *Adv. Carbohydr. Chem. Biochem.* **1962**, *17*, 169–221.
39. HPLC indicated aside melibiulose **8** (~90%) the presence (~1–2% each) of melibiose **5** of the component sugars galactose, glucose and fructose with traces of higher saccharides.
40. The presence of molecular sieve appears essential to bind the water formed during dehydration; otherwise substantial hydrolysis of the glycosyl-HMF's occurs.
41. Aspinall, G. O.; Khan, R.; King, R. R.; Pawlak, Z. *Can. J. Chem.* **1973**, *51*, 1359–1362.