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5-(α-D-Glucosyloxymethyl)furfural: Preparation from Isomaltulose and Exploration of Its Ensuing Chemistry

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An effective, practical, large-scale adaptable procedure has been developed to selectively dehydrate the fructose portion of isomaltulose [glucosyl-α(1→6)-fructose] (6): heating in DMSO in the presence of a strongly acidic ion-exchange resin generates α-D-glucosyloxymethylfurfural (*α-GMF*, 3), isolable in yields up to 70%. A variety of ensuing reactions have been exploited concerning the generation of products with industrial application profiles such as aldol-type additions to the dicyanovinyl (16), nitrovinyl (20), and benzoylvinyl (21) derivatives, or to the polymerizable unsubstituted vinyl compound (25) and the GMF-acrylic acid (22). Oxidation to GMF-carboxylic acid (11) and reductive amination to GMF-amine (11) can be carried out without affecting the hydroxy groups in the glucosyl portion; esterification of GMF-amine with long-chain alcohols and N-acylation of GMF-acrylic acid with fatty acid chlorides provide novel surfactants in which hydrophilic and hydrophobic parts of the molecule are separated by a heteroaromatic spacer.

5-Hydroxymethylfurfural (HMF, 1), readily generated from fructose by acid-induced dehydration[2], has been designated as one of the few “petrochemicals” accessible from regrowing resources[3], and a key substance between carbohydrate chemistry and mineral oil-based industrial organic chemistry[4]. Despite the fact, however, that the technology for its pilot plant-size manufacture has been elaborated[2,4,5], it is not produced on an industrial scale for several obvious reasons: its chemistry is not fully developed with respect to products with industrial application profiles, and, more aggravatingly, raw materials from petrochemical sources are still more economical.

Glycosylated hydroxymethylfurfurals of type 2–5, if accessible economically on a large scale, would substantially broaden the scope of HMF applications: carbonyl olefination and polymerization yield hydrophilic polymers, attachment of long-chain alkyl residues via the respective furanic acid, for example, leads to novel APGs (alkylpolyglycosides), i.e. biodegradable surfactants in which the hydrophilic sugar moiety and hydrophobic alkyl portion of the molecule are separated by a heteroaromatic spacer.

HMF glycosides have occasionally been encountered. The β-D-xylopyranosyl derivative 2 was obtained from xylose and glucose via the β(1→6)-linked disaccharide in a ten-step, low-yield synthesis[6], not amenable to large-scale preparation. The hexosyl analogs 3–5 were assumed to be present in multicomponent mixtures resulting from heating HMF (1) with the respective hexose for 6 h at 150°C, in order to simulate caramelization processes[7]; however, neither their separation could be achieved, nor was their 1H-NMR characterization in the syrupy mixtures unequivocal at 100 MHz.
A more adequate preparation of HMF glycosides 2–5 would be anticipated from the application of modern glycosylation techniques to HMF and subsequent deblocking of the protecting groups used in the glycosyl donor. An undoubtedly more direct approach, however, would be their generation from the respective glycosyl-(1→6)-fructose, if acidic conditions can be found for dehydration of the fructose portion without cleaving the intersaccharide linkage. If so, isomaltulose (6) would yield α-D-glucosylxomethylfurfural (α-GMF, 3), gentiobiulose the respective β-anomer 4, and melibiulose the galacto analog 5. Of those glycosyl-(1→6)-fructoses, only isomaltulose (6) is well accessible, being produced on an industrial scale through Protaminobacter rubrum-induced glucosyl transfer from the O-2 of fructose to O-6. Consequently, 6 appeared to be an ideal starting material to probe the feasibility of a selective dehydration, which eventually could be accomplished in a preparatively satisfactory way. This paper describes the successful realization of the isomaltulose → α-GMF conversion and the exploitation of ensuing reactions with respect to the generation of products with potential industrial application profiles.

Given the sensitivity of isomaltulose (6) towards aqueous acidic conditions, which would be anticipated to mostly yield glucose and HMF, the many anhydrous systems that have been employed to convert fructose into HMF were evaluated, such as dimethylformamide, acetoniitre, quinoline, and dimethyl sulfoxide. The most propitious conditions found were heating a DMSO solution of 6 in the presence of a strongly acidic ion-exchange resin (H\(^+\)) form for 3 h at 120°C. From the resulting mixture of α-GMF (3, ca. 80%), dimeric isomaltulose anhydrides (10%), HMF, and glucose, the desired 3 can be isolated as well-shaped prisms in yields of up to 70%.

Aside from this batch conversion, the procedure can be moulded into a continuous process by using a flow reactor, thus making α-GMF (3) a product of bulk accessibility — two steps away from sucrose, the world's most abundantly produced organic compound. Consequently, we have chosen to evaluate α-GMF towards products with potential industrial application profiles, be it hydrophilic polymers, biodegradable surfactants, or pharmaceuticals. Thereby, two basic criteria of practicality were deemed important: simple reagents and avoidance of O-protection in the glucosyl portion.

Reactions meeting these criteria are the reduction of 3 to the respective alcohol 7 (85%), the essentially quantitative reductive amination to the corresponding α-GMF-amine 8, characterizable as such, or its N-acetate 9 and peracetate 10. Oxidation with sodium chlorite in a slightly acidic buffered aqueous solution smoothly generated the furancarboxylic acid 11 (89%); since in the preparation of esters acidic conditions had to be avoided esterification was effected with diazomethane (→ 12) or by alcoholysis of the in situ generated DCC anhydride (→ 13), which in turn could be ammonolyzed to the corresponding amide 14. An-
other useful derivative of the furancarboxylic acid 11 is its nitrile, which can be prepared in form of the tetraacetate 17 by heating the oxime 15 in acetic anhydride (78%). However, application of the conditions previously used to convert furfural into furonitrile in a one-pot procedure[18], i.e. heating α-GMF with hydroxylammonium chloride in DMSO for 30 min at 110°C, allowed the direct generation of the unprotected nitrile 18, isolable as needles in 61% yield. It may be utilized as a dipolarophile in [3 + 2] cycloadditions, since heating with sodium azide in DMF affords the sodium tetrazolide 19 in high yield (90%).

α-GMF (3) readily undergoes aldol-type reactions without interference by the hydroxyl groups in the glucosyl portion. Thus, aluminium oxide-catalyzed[19] Knoevenagel reaction with malonodinitrile effectively provided the dicyanovinyl derivative 16, base-catalyzed addition of nitromethane and acetophenone, correspondingly, the 2-nitrovinyl 20 and 2-benzoylvinyl analogs 21, all being produced in nicely crystalline form.

To obtain α-GMF derivatives with polymerizable double bonds, attempts were made to prepare the 5-acrylic acid 22 and the 5-vinyl compound 25, inasmuch as 2-vinylfuran, generated by heating of furfural with malonic acid, is known to polymerize on standing[20]. Fortunately, the thermal stability of α-GMF is high enough as to survive heating with malonic acid in quinoline to 120–170°C, affording α-GMF-tetraacetate mixtures. Thus, the preparation of 23 in 52% yield. Further heating in the presence of copper sulfate to effect another decarboxylation to the vinyl compound 25, however, resulted in complex mixtures. Thus, the preparation of 25 was approached by carbonyl olefination of the α-GMF tetraacetate 23 (to ensure solubility in THF) with the Lombardo reagent (CH2Br2/Zn/TiCl4[21]). Indeed, smooth and complete olefination of 23 was achieved, as detected by TLC; isolation of 25 proved capricious though due to substantial polymerization during workup; eventually, by fast processing of the reaction mixture, 14% of syrupy 25, unequivocally characterized by ¹H-NMR analysis, could be obtained, which polymerized to a transparent solid within a few hours.

The hydroxyl groups in the glucosyl portion of α-GMF show different reactivities as evidenced by acetylation. Whilst treatment with pyridine/acetic anhydride (5:1 ratio, 24 h, 25°C) quantitatively gave the tetraacetate 23, the use of smaller amounts of acetic anhydride and shorter reaction times (1.5 h, 0→25°C) resulted in partial acetylation, allowing the isolation of 40% of the syrupy 24 and 15% of the crystalline 3,6-diacetate 25. The location of the acetyl groups could readily be secured from ¹H-NMR data, and, in the case of 24, by its PCC oxidation to the 3-ketohexosyl-α-GMF 26, a most useful building block for modifications at either of the carbonyl functions.

In further exploiting potential industrial application profiles of α-GMF, some long-chain alkyl esters of GMF-carboxylic acid 11 were prepared by alcoholysis of DCC-activated 11 with octanol (→27) and dodecanol (→28). Selective N-acetylation of GMF-amine 8 with fatty acid chlorides was readily achieved in methanol at −10°C to give the well-crystallized amides 29–31. Of these, the N-octanoyl derivative 29 melts at 51°C to a turbid glaze that turns clear at 64°C only — clearly indicative of a liquid crystalline state. Preliminary evaluation of their surface and interfacial tension properties shows the amides 29–30 to have critical micelle concentrations of around 1.5 mmol/l, whilst the two esters 27 and 28 exhibit Cm values of 0.08 and 0.06 mol/l, and, thus, are comparable to those of technical niotensides. Accordingly, α-GMF-esters and, to a lesser degree, the GMF-amides constitute novel, nonionic surfactants in such, as the hydrophilic and hydrophobic portions within these molecules are separated by a heteroaromatic spacer.

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**Experimental**

Melting points (uncorrected values): Bock monoskop instrument. – Spectral measurements: Perkin-Elmer 141 (rotations), Varian MAT 311 A (MS), and Bruker WM 300 instruments (¹H- and ¹³C-NMR analysis). – TLC on Kieselgel 60 F₄₅₄ plastic sheets (Merck) was used to monitor the reactions and to ascertain the
purity of the products; eluants employed: A = acetonitrile/water (4: 1); B = chloroform/methanol (3: 1); C = ethyl acetate; D = chloroform/methanol (2: 1); E = chloroform/methanol (7: 2); F = toluene/acetone (4: 1); G = toluene/acetone (3: 1); detection with UV light or by charring with sulfuric acid. – Column chromatography: Kieselgel 60 (70–230 mesh, Merck).

5-[(a-D-Glucopyranosyloxymethyl)-2-furancarboxaldehyde (a-GMF, 3): In a 1.5-l round-bottomed flask, a solution of isomaltulose monohydrate (6 H2O, 90 g, 0.25 mol) in 900 ml of dimethyl sulfoxide was heated to 120°C, and 10 g of a strongly acidic, sulfonic acid-type ion exchange resin (Dowex 50-WX4, H+ form, dried in vacuo over P2O5 for 24 h) was added, followed by stirring at 120°C for 4 h. The resulting mixture consists of a-GMF (3, 65–70%), isomaltulose dimers (ca. 10%), HMFA + glucose (5–10%), and starting compound (ca. 10%) on the basis of HPLC and TLC [Rf = 0.48 (6) and 0.61 (HMFA) in eluent A]. Filtration of the mixture and removal of the solvent from the filtrate under reduced pressure at 80°C (bath temperature) yielded a brown syrup which was dissolved in water (500 ml), and the solution obtained was extracted with dichloromethane (2 × 200 ml). The aqueous layer was evaporated under reduced pressure to a volume of 200 ml and applied to a column of Lewatit TSW 40 (Ca++ form, 8 × 200 cm), preheated to 60°C, and eluted with water (10 l/h). After a preflow of about 3 l of water, the first fraction (2 l) contains the isomaltulose dimers and starting compound; glucose was then eluted, followed by a-GMF (approx. 6 l). Concentration of the GMF eluate in vacuo afforded 494 mg (85%) of 7 as a colorless syrup; [α]D +107°C (c = 1, methanol). – 1H NMR (300 MHz, CDCl3): δ = 3.13 (dd, 1H, 4'-H), 3.27 (dd, 1H, 2'-H), 3.41–3.70 (4H, 3'-H, 5'-H, 6'-H), 4.41 (s, 2H, 5-CH2), 4.41, 4.59 (2 d, 1H each, 2-CH2), 4.79 (d, 1H, 1'-H), 5.2 (5H, 5 OH), 6.28, 6.40 (2 d, 1H each, 3-H, 4-H); J1',2' = 3.3, J3,4' = 9.6, J4,5' = 9.0, J5,6' = 9.0 Hz. – 13C NMR (75.5 MHz, CDCl3): δ = 56.1, 60.6, 61.3 (2-CH2, 5-CH2, C6), 70.7, 72.2, 73.2, 73.6 (C2-C, C3-C, C4-C, C5-C), 99.1 (C1-C), 107.9 (C4), 110.5 (C3), 150.9 (C2), 156.0 (C5). – MS (FD): m/z = 290 (M+), – C12H18O6 (290.3); calcld. C 49.65, H 6.25; found C 49.58, H 6.30.

5-Aminomethyl-2-[(a-D-glycopyranosyloxymethyl)furan (8): In a 125-ml autoclave Raney nickel (1 g) was added to a solution of 5.76 g (0.02 mol) of a-GMF (3) in 50 ml of methanol saturated with ammonia at 10°C (ca. 5.5 M). Hydrogen was then passed into the autoclave until a pressure of 100 atm was reached, whereupon the temperature was raised to 60°C. After 1 h the mixture was allowed to cool to room temp. and depressurized. Filtration of the mixture and evaporation of the filtrate to dryness gave 5.8 g (97%) of 8 as a uniform solid foam, as revealed by TLC ([Rf = 0.04 in A). – 1H NMR (300 MHz, CDCl3 + D2O): δ = 3.10 (dd, 1H, 4'-H), 3.19 (s, 2H, 5-CH2), 3.24 (dd, 1H, 2'-H), 3.45 (2H, 2'-OH), 3.63 (3H, 2'-H), 3.84, 4.52 (2 d, 1H each, 2-CH2), 4.77 (d, 1H, 1'-H), 6.18, 6.35 (2 d, 1H each, 3-H, 4-H); J4,5' = 12.8, J3,4' = 3.3, J1',2' = 9.6. – 13C NMR (100 MHz, CDCl3): δ = 60.5 (C2-C), 60.6 (C5-C), 70.1 (C1-C), 71.8 (C2-C), 73.1 (C3-C, C5-C), 98.4 (C1-C), 112.0 (C4), 124.2 (C-3), 152.2 (C-2), 178.3 (CHO). – MS (FD): m/z = 288 (M+), 289 (M+ + 1). – C16H12O8 (288.3): calcld. C 50.00, H 5.59; found C 49.81, H 5.63.

Evaporation of the fraction containing isomaltulose and its dimers (cf. above) to dryness and subjection of the residue, after dissolution in dimethyl sulfoxide, to the reaction conditions mentioned above, gave after chromatographic purification another 11 g (15%) of syrup 3, thus raising the yield to 80% (based on the 6 monohydrate).

**Dinitrophenylhydrazone of 3:** Water (7.5 ml) was added dropwise to an agitated mixture of 2,4-dinitrophenylhydrazine and conc. H2SO4 (1.0 g in 5 ml), followed by the addition of ethanol (25 ml), and an ethanolic solution of a-GMF (3, 580 g in ml) to the still warm mixture. After standing for about 12 h, the red precipitate was filtered off, washed with water, and recrystallized from ethyl acetate to furnish 545 mg (58%) of orange crystals; m.p. 186°C; [α]D +81 (c = 1, dimethyl sulfoxide). – 1H NMR (300 MHz, CDCl3/DMSO): δ = 3.15 (dd, 1H, 4'-H), 3.25 (dd, 1H, 2'-H), 3.4–3.7 (4H, 3'-H, 5'-H, 6'-H), 4.7 (4H-m, 4 OH), 4.66, 4.78 (2 d, 1H each, 5-CH2), 4.86 (d, 1H, 1'-H), 6.78, 7.11 (2 d, 1H each, 3-H, 4-H), 7.61 (s, 1H, CH=N), 7.96 (d, 1H, Ph-6-H), 8.37 (dd, 1H, Ph-5-H), 8.83 (d, 1H, Ph-3-H), 12.72 (s, 1H, NH); J3,4' = 9.0, J5,6' = 9.2, Jgem(3-CH2) = 13.6, J1',2' = 3.6, J2',3' = 9.7, J3,4' = 9.0, J5,6' = 9.2, Jgem(5-CH2) = 2.5, J5,6' = 9.6 Hz. – 13C NMR (75.5 MHz, CDCl3/DMSO): δ = 60.5 (C6-C), 60.9 (5-CH2), 68.9 (C4-C), 71.6 (C-2'), 72.9, 73.0 (C5-C, C3-C), 98.7 (C1-C'), 111.5 (C4-C), 116.0 (Ph-C-6), 118.7 (C-3-C), 122.7 (Ph-C-3), 129.6, 137.5, 144.4 (Ph-C-1-C, C-2-C, and C-4), 130.0 (Ph-C-5), 131.5 (2-CH), 147.0 (C-2), 152.5 (C-5). – C16H12N4O11 (468.4); calcld. C 46.16, H 4.30, N 11.96; found C 46.23, H 4.29, N 11.84.

2-[(a-D-Glucopyranosyloxymethyl)-5-hydroxyfuran (7): To a stirred solution of a-GMF (3, 520 mg, 1.8 mmol) in methanol (30 ml) was added NaBH4 (138 mg, 3.6 mmol), and stirring was continued for 2 h at room temp., thereafter TLC (in eluent B) indicated absence of the starting compound. Removal of the solvent in vacuo left a syrup which was purified by elution from a silica gel column (3 × 30 cm) with chloroform/methanol (3: 1). Concentration of the appropriate eluates gave 443 mg (85%) of 7 as a colorless syrup; [α]D +970 F. W. Lichtenthaler, D. Martin, T. Weber, H. Schiweck (1993), Liebigs Ann. Chem. 1993, 967–974.
was added dropwise with stirring over a period of 15 min. The mixture was subsequently allowed to warm to ambient temp, and after standing for 24 h, it was poured into ice-water (10 ml). Concentration in vacuo gave a brownish syrup which was dissolved in chloroform (50 ml), and the solution was washed successively with 2 N H₂SO₄, a satd. aqueous NaHCO₃ solution, and water, followed by drying (MgSO₄) and removal of the solvent in vacuo. Purification of the residue by elution of the crude product from a silica gel column (3 × 30 mm) with ethyl acetate and evaporation of the solvent from the eluates with Rf = 0.19 (C) yielded 0.54 g (65%) of syrup 10; [α]D₂⁰ = +119 (c = 0.9, chloroform). — H-NMR (300 MHz, CDCl₃): δ = 1.98, 2.01, 2.02, 2.03, 2.11 (five 31H-s, 5 Ac CH₃), 4.30–4.34, 4.39 (2H, 3'-H, 5'-H₂), 4.55 (2H, 2'-H, 6'-H₂), 5.00 (d, 1H, 1'-H), 5.34 (d, 1H, 3'-H), 6.11, 6.27 (2H, 2'-H); J₁,₂ = 7.7, J₂,₃ = 7.2, J₃,₄ = 11.6, J₄,₅ = 11.2, J₅,₆ = 10.2, J₆,₇ = 12.1 Hz. — MS (FD): m/z = 399 (M+), 123 (100), 119, 117, 105, 99, 97, 79, 77, 75, 67, 65, 63. — ['H NMR (300 MHz, D₂O): δ = 7.45-7.49 (m, 1H, 2'-H), 7.51-7.55 (m, 1H, 3'-H), 7.57 (d, 1H, 1'-H), 7.63, 7.67 (2 d, 2H each, 3-H, 4-H); J₁,₂ = 7.7, J₂,₃ = 7.2, J₃,₄ = 11.6, J₄,₅ = 11.2, J₅,₆ = 10.2, J₆,₇ = 12.1 Hz. — MS (FD): m/z = 332 (M+).]

**5-(a-D-Glucopyranosyloxymethyl)-2-furancarboxamide (14):** Methyl ester 12 was dissolved in a solution of methanolic ammonia (5 ml), and the mixture was stirred for 2 h at room temp. After completion of the aminolysis (monitoring by TLC in eluant A), solvent and excess ammonia were removed in vacuo; the resulting solid crystallized on trituration with methanol/water: 270 mg (86%) of 14 as a crystalline powder, opalescent under the microscope; m.p. 218°C, [α]D₂⁰ = +97 (c = 0.8, methanol). — H-NMR (300 MHz, CDCl₃): δ = 3.07 (m, 1H, 4'-H), 3.23 (m, 1H, 2'-H), 3.35–3.61 (m, 4H, 3'-H, 5'-H, 6'-H₂), 4.47, 4.60 (2 d, 1H each, 5'-CH₃), 4.53 (t, 1H, 6'-OH), 4.76 (m, 3H, 1'-H, 2 OH), 4.89 (d, 1H, OH), 6.57, 7.07 (2 d, 1H each, 3'-H, 4'-H), 7.37, 7.74 (two 1H-s, NH₂); J₃,₄ = 3.3, J₅₋₆₋₇₋₈ = 13.2, J₆₋₇₋₈ = 5.7 Hz. — MS (FD): m/z = 303 (M+), 304 (M+ + 1). — C₁₂H₁₈N₂O₅ (303.3) calcld. C 57.18, H 7.30, N 11.21; found C 57.07, H 7.41, N 11.26.

**5-(a-D-Glucopyranosyloxymethyl)-2-furancarboxaldehyde Oxime (15):** To a solution of 3.1 g (10.7 mmol) of a-GMF (3) in 50 ml of ethanol was added a solution of 2.2 g (31.6 mmol) of hydroxylmonium hydrochloride and 2.1 g (25 mmol) of sodium acetate in 10 ml of water. After stirring of the mixture for 10 min at room temp, TLC in eluant A indicated absence of the starting compound. Removal of the solvent in vacuo leaves a syrup which was dissolved in 2-propanol and freed from the precipitated salts by filtration. The syrup obtained after concentration of the filtrate was further purified by elution from silica gel with chloroform/methanol (7:2); removal of the solvents from the eluates in vacuo yielded 15 as colorless crystals: 2.3 g (71%); m.p. 138–139°C, [α]D₂⁰ = +118 (c = 1.5, methanol). — H-NMR (300 MHz, CDCl₃): δ = 3.4–3.8 (m, 5H, 2'-H, 3'-H, 4'-H, 6'-H₂), 3.57 (dd, 1H, 5'-H), 4.64–4.97 (m, 2H, 2'-CH₂), 5.04 (d, 1H, 1'-H), 6.66, 7.27 (2 d, 1H each, 3'-H, 4'-H), 8.06 (s, 1H, CH-NO₂); J₃,₄ = 3.4, J₁₋₂ = 3.6, J₅₋₆ = 9.8, J₆₋₇ = 1.3 and 3.5 Hz. — MS (FD): m/z = 303 (M+), 304 (M+ + 1). — C₁₂H₁₇NO₅ (303.3) calcld. C 57.18, H 7.30, N 11.21; found C 57.07, H 7.41, N 11.26.
1H NMR (300 MHz, D2O): δ = 3.44 (dd, 1H, 4'-H), 3.58 (dd, 1H, 2'-H), 3.68 – 3.76 (m, 4H, 3'-H, 5'-H, 6'-H), 4.77, 4.84 (2 d, 1H each, 5-CH2), 5.09 (d, 1H, 1'-H), 6.83, 7.39 (2 d, 1H each, 3-4-H), 7.91 (s, 1H, 2-CH), J1x:J2 = 3.7, J2y:J3 = 9.8, J3:J4 = 3.7, Jgem(5-CH2) = 13.5 Hz. – MS (FD): m/z = 336 (M+). – C13H16N2O7 (336.3): calcd. C 53.57, H 4.80, N 8.33; found C 53.52, H 4.85, N 8.32.

2-Cyano-5-(2,3,4,6-tetra-O-acetyl-a-D-glucopyranosylacetylmethyl) furan (17): A suspension of 3.0 g of GFM oxime (15) and 1.0 g of freshly melted sodium acetate in 10 ml of aceitic anhydride was stirred for 30 min at room temp. The now clear methylene homogenous syrup; dichloromethane (200 ml), and the resulting syrup was purified by elution from a silica gel column (3 x 30 cm) with chloroform/methanol (4:1) and immediately concentrated in vacuo. Elution of the residue from a silica gel column (3 x 30 cm) with chloroform/methanol (4:1) and immediately concentrated in vacuo. Evaporation of the residue afforded 220 mg (90%) of the chromatographically purified residue.

The mixture was filtered, the filtrate evaporated to dryness in vacuo, and the residue was diluted with 30 ml of water and extracted with dichloromethane (2 x 30 ml). Concentration of the solution resulted in crystallization affording 820 mg (71%) of syrupy 22; m.p. 141°C, [a]D 58.4° (c = 1.0, methanol). – 1H NMR (300 MHz, [D6]DMSO): δ = 3.07 (t, 1H, 4'-H), 3.23 (m, 1H, 2'-H), 3.36 – 3.61 (m, 4H, 3'-H, 5'-H, 6'-H), 4.46 (m, 1H, OH), 4.52, 4.64 (2 d, 1H each, 2-CH2), 4.76 (d, 1H, 1'-H), 4.76 (m, 2H, 2 OH), 4.86 (m, 1H, OH), 6.72, 7.24 (2 d, 1H each, 3-4-H), 7.69 (d, 1H, CH=), 7.99 (d, 1H, CHNOZ); Jgem = 13.3, Jgem(2-CH2) = 13.5, J3:J4 = 3.4, J2x:J3 = 3.6, J2y:J3 = 8.7 Hz – MS (FD): m/z = 331 (M+). – C13H11NO3 (331.3): calcd. C 47.13, H 5.17, N 4.23; found C 47.10, H 5.06, N 4.05.

2-(Chloroacetyl)-2-(a-D-glucopyranosylacetylmethyl) furan (21): To a cooled (0°C) and stirred solution of 4.5 g (15 mmol) of a-GMF (3) and 1.8 g (15 mmol) of acetylene in 50 ml of ethanol was added dropwise 15 ml of 10% NaOH solution. After 30 min the mixture was diluted with 50 ml of water, extracted with dichloromethane (3 x 30 ml), the combined extracts were washed neutral with a saturated KHSO4 solution and water. Drying (MgSO4) and concentration of the solution resulted in crystallization affording 4.1 g (70%) of 21 as yellowish crystals; m.p. 127°C, [a]D 58.4° (c = 1.0, methanol). – 1H NMR (300 MHz, CDCl3): δ = 3.48 – 3.78 (m, 7H, 2'-H, 3'-H, 4'-H, 5'-H, 6'-H, OH), 4.10 (d, 1H, OH), 4.50, 4.57 (2 d, 1H each, 2-CH2), 4.75 (s, 1H, OH), 4.92 (d, 1H, 1'-H), 4.98 (s, 1H, OH), 6.39, 6.56 (2 d, 1H each, 3-4-H), 7.3 – 7.5 (m, 5H, CH), 7.93 (m, 2H, CH=CH); J1x:J2 = 3.2, J3:J4 = 3.3, Jgem(2-CH2) = 13.5 Hz. – 13C NMR (75.5 MHz, CDCl3): δ = 20.5, 20.6, 20.7 (4 AC CH2), 61.5, 61.8 (5-CH2, C-5), 67.9, 68.5, 69.8, 70.7 (C-2', C-3', C-4', C-5'), 95.3 (C-1', 111.1 (C-5), 111.2 (C-5), 122.7 (C-3), 125.6 (C-5), 155.7 (CN), 165.9, 169.9, 170.1, 170.5 (4 AC CO). – MS (FD): m/z = 453 (M+), 454 (M+ + 1). – C20H22O9 (390.4): calcd. C 61.53, H 5.68; found C 61.49, H 5.65.

3-(5-(2-Nitrovinyl)-2-(a-D-glucopyranosylacetylmethyl) furan (23): A solution of a-GMF (3, 500 mg, 1.7 mmol) and malonic acid (300 mg, 3 mmol) in quinoline (5 ml) was heated to 120°C. The bath temp. was raised to 170°C over a period of 1 h; meanwhile, the formation of CO2 is detectable. The cooled, brownish solution was extracted with water (2 x 30 ml), and the combined aqueous layers are subsequently washed with chloroform (30 ml). Concentration of the aqueous solution in vacuo and elution of the residue from a silica gel column (3 x 30 cm) with chloroform/methanol (2:1) afforded 0.3 g (52%) of syrupy 22; [a]D 58.4° (c = 1.3, water). – 1H NMR (300 MHz, [D6]DMSO): δ = 3.09 (t, 1H, 4'-H), 3.22 (dd, 1H, 2'-H), 3.4 – 3.6 (m, 4H, 3'-H, 5'-H, 6'-H), 4.42, 4.56 (2 d, 1H each, 5-CH2), 4.75 (d, 1H, 1'-H), 4.4 – 4.8 (m, 4H, 4 OH), 6.18 (d, 1H, 5-CH2), 6.48, 6.57 (2 d, 1H each, 3-4-H), 7.07 (d, 1H, CH=CHCOO–); Jvinyl = 15.8, Jgem(5-CH2) = 13.0, J3:J4 = 3.2, J2x:J3 = 3.6, J2y:J3 = 9.7, J3:J4 = 9.2 Hz. – MS (FD): m/z = 331 (M+ + 1), 353 (M+ + Na). – C14H18O9 (331.3): calcd. C 53.91, H 5.49; found C 53.72, H 5.41.
Partial Acetylation of α-GMF (3). To a cooled (0°C) solution of 1.0 g (3.5 mmol) of α-GMF (3) in pyridine (50 ml) was added droppwise with stirring anhydride (2.7 ml, 28 mmol). After 30 min the ice bath was removed and the solution is stirred for an additional hour at ambient temp. The resulting mixture, containing 23 (Rf = 0.54 in eluant C), 24 (0.48), diacetates (0.25), monoacetates (0.13), and some starting compound, was hydrolyzed with iced water (20 ml), concentrated in vacuo, the residue was extracted with chloroform, the extract washed successively with 2 N H2SO4, NaHC03 solution and water. Elution from a silica gel column (30 cm) with ethyl acetate followed by removal of the solvent gave 1.5 g (95%) of syrupy oil. The 'H NMR data for 23 and 0.45 for 25). Subsequent distillation with dichloromethane (150 ml), gradual addition of a satd. aqueous NaHCO3 solution (100 ml) and solid NaHCO3 (20 g), stirring for 1 h, removal of the organic layer, extraction of the aqueous phase with dichloromethane (2 x 50 ml), concentration of the organic solutions, and drying (Na2SO4) gave a residue which was purified by elution from a silica gel column (3 x 30 cm) with toluene/aceton (4:1). Concentration of the appropriate eluates afforded 25 (180 mg, 14%) as a uniform syrup; [α]D = +110 (c = 0.6, chloroform). Substantial polymerization of the product is responsible for the low yield.

-1 H NMR (300 MHz, CDCl3): δ = 1.99, 2.00, 2.02, 2.10 (4 s, 3H each, 4 Ac CH3), 4.0-4.1 (m, 3H each, 3 Ac CH3), 4.31 (m, 2H, 5'-CH2), 4.49 (m, 2H, 6'-CH2), 4.54, 4.62 (2 d, 1H each, 2-CH2), 4.85 (dd, 1H, 2'-H), 5.08 (t, 1H, 4'-H); 5.18 (dd, 1H, H2a), 5.21 (d, 1H, 1'-H), 5.50 (t, 1H, 3'-H), 5.67 (dd, 1H, =CH2), 6.21, 6.32 (2 d, 1H each, 3-3', 4-H), 6.46 (dd, 1H, CH=); Jgem(Z-CH2) = 13.2, Jgem(2-CH2) = 11.2, Jgem(4-CH2) = 17.6, Jgem-To = 13.7 Hz. The 'H NMR data for 24 in Table 24 and 0.36 (28) in eluant G). Addition of ethyl acetate (25 ml) to the reaction mixture, filtration with suction, washing of the residue with ethyl acetate (10 ml), and evaporation of the solvent from the combined filtrate and washing gave a residue which was purified by elution from a silica gel column (1.5 x 20 cm) with toluene/aceton (3:1). Evaporation of the eluate to dryness and crystallization of the residue gave 30 mg (50%) of 26 as colorless needles; m.p. 171°C, [α]D = +122 (c = 0.5, chloroform). -1 H NMR (300 MHz, CDCl3): δ = 2.12, 2.17, 2.18 (3 s, 3H each, 3 Ac CH3), 4.24-4.33 (m, 3H, 5'-H, 6'-H2), 4.69, 4.75 (2 d, 1H each, 5-CH2), 4.90 (d, 1H, 1'-H), 5.35 (d, 1H, 4'-H), 5.41-5.45 (m, 2H, 2'-H, 2'-H), 6.57, 7.21 (2 d, 1H each, 3-3', 4-H), 9.63 (s, 1H, CHO); J3,4 = 3.6, Jgem(5-CH2) = 13.7 Hz. - MS (FD): m/z = 412 (M+). - C16H24O11 (412.4): calc'd. C 52.43, H 4.89; found C 52.36, H 4.84.

Octyl 5-(a-D-Glucopyranosylxymethyl)-2-furancarbonate (27): To a solution of GMF-carboxylic acid (3 ml) was added to a stirred suspension of pyridinium dichromate (0.4 g, 1.1 mmol) and freshly desiccated molecular sieves (4 A, 0.5 g) in a mixture of acetic anhydride (1 ml) and dichlormethane (9 ml). Refluxing for 2 h led to complete conversion ([Rf = 0.25 (24) and 0.36 (28) in eluant G). Addition of ethyl acetate (25 ml) to the reaction mixture, filtration with suction, washing of the residue with ethyl acetate (10 ml), and evaporation of the solvent from the combined filtrate and washing gave a residue which was purified by elution from a silica gel column (1.5 x 20 cm) with toluene/aceton (3:1). Evaporation of the eluate to dryness and crystallization of the residue gave 30 mg (50%) of 26 as colorless needles; m.p. 171°C, [α]D = +122 (c = 0.5, chloroform). -1 H NMR (300 MHz, CDCl3): δ = 2.12, 2.17, 2.18 (3 s, 3H each, 3 Ac CH3), 4.24-4.33 (m, 3H, 5'-H, 6'-H2), 4.69, 4.75 (2 d, 1H each, 5-CH2), 4.90 (d, 1H, 1'-H), 5.35 (d, 1H, 4'-H), 5.41-5.45 (m, 2H, 2'-H, 2'-H), 6.57, 7.21 (2 d, 1H each, 3-3', 4-H), 9.63 (s, 1H, CHO); J3,4 = 3.6, Jgem(5-CH2) = 13.7 Hz. - MS (FD): m/z = 412 (M+). - C16H24O11 (412.4): calc'd. C 52.43, H 4.89; found C 52.36, H 4.84.

Octyl 5-(a-D-Glucopyranosylxymethyl)-2-furancarbonate (27): To a solution of GMF-carboxylic acid 11 (300 mg, 1 mmol), 1- octanol (1.7 g, 13 mmol), p-toluenesulfonic acid (20 mg), and pyridine (3 ml) was added 200 mg (1 mmol) of dicyclohexylcarbodiimide. The mixture was stirred at room temp. for 24 h. Filtration, concentration of the filtrate, and repeated reevaporations of the residue from toluene left a syrup which was purified by elution from a silica gel column (3 x 20 cm) with chloroform/methanol (7:3). Evaporation of the solvents from the fractions with Rf = 0.31 (eluant E) gave 190 mg (60% of 27) as an amorphous powder; [α]D = +86 (c = 0.7, methanol). -1 H NMR (300 MHz, CDCl3): δ = 0.86 (t, 3H, CH3), 1.03-1.77 (m, 12H, 6 CH2), 3.09 (m, 1H, 2'-H), 3.23 (m, 1H, 4'-H), 3.3-3.6 (m, 4H, 3'-H, 5'-H, 6'-H2), 4.23 (t, 2H, OCH2), 4.48 (m, 1H, OCH), 4.52, 4.64 (two H, 5'-CH2, 6'-CH2), 4.75-4.82 (m, 2H, 3'-H, 1'-H, 2'-H), 4.90 (d, 1H, OCH), 6.56 (d, 1H, 4'-H), 6.87 (d, 1H, 3'-H); J3,4 = 3.4, Jgem(5-CH2) = 13.4, J2,3 = 3.6 Hz. - MS (FD): m/z = 416 (M+), 417 (M+ + 1). - C20H30O14 (416.5): calc'd. C 57.68, H 7.74; found C 57.73, H 7.81.
mmol) in methanol (25 ml) was added octanoyl chloride (0.3 ml, 1.7 mmol), and the mixture was stirred for 30 min, then allowed to warm to room temp., whereafter TLC indicated complete conversion (30; \( R_f = 0.41 \) in eluant A). Evaporation to dryness in vacuo (bath temp. below 35°C), quick elution of the residue from a silica gel column (2 × 20 cm) with acetone, and removal of the solvent from the eluate resulted in crystallization affording 450 mg (64%) of 29 as colorless needles, m.p. 51°C, the turbid glaze produced becoming clear at 64°C; \( [\alpha]_D^{20} = +88 \) (c = 0.9, methanol). \textsuperscript{-1}H NMR (300 MHz, \([\text{D}_2]\text{DMSO})\): \( \delta = 0.86 \) (t, 3H, \( \text{CH}_3 \)), 1.23 (s, 12H, \( \text{CH}_2 \)), \( 1.48 \) (m, \( 2\text{H} \), \( \text{CH}_2 \)), \( 2.09 \) (t, \( 2\text{H} \), \( \text{COCH}_2 \)), \( 3.07 \) (dd, \( 1\text{H} \), \( \text{H}_3 \)), \( 3.21 \) (dd, \( 1\text{H} \), \( \text{H}_2 \)), 3.35–3.64 (m, 4H, \( 3'\text{-H}, 5'\text{-H}, 6'\text{-H}_2 \)), \( 4.22 \) (d, \( 2\text{H} \), \( 5'\text{-CH}_2 \)), \( 4.35, 4.51 \) (2d, \( 1\text{H} \), \( \text{CH}_2 \)), \( 4.73 \) (d, \( 1\text{H} \), \( \text{H}_1 \)), \( 5.6, J_{\text{gem}(2.3') \text{H}_2} \), \( 7.4, J_{\text{1',2'}} \), \( 8.28 \) (t, \( 1\text{H} \), \( \text{NH} \)); \( J_{\text{CH}_2\text{NH}} = 5.6, J_{\text{gem}(2,\text{CH})} = 12.8 \), \( J_{\text{C}O\text{C}H_2\text{CH}_2} = 7.4 \), \( J_{1',\text{x}} = 3.6, J_{2',\text{x}} = 9.6 \) Hz. \( -\text{MS (FD); } m/\text{z} = 415 \) (M\textsuperscript{+}), 416 (M\textsuperscript{+} + 1).

5-(Decanoylamidomethyl)-2-(\( \alpha \)-D-glucopyranosyloxymethyl)-furan (30) and Its 5-Dodecanoylamidomethyl Analog (31): N-Acylation of 8 with the chlorides of capric and lauric acid, respectively, in a manner analogous to the one described for the conversion of 8 to 29 (cf. above) gave 30 (m.p. 92–94°C, \( [\alpha]_D^{20} = +87 \) (c = 1, methanol)) and 31 (m.p. 100–102°C; \( [\alpha]_D^{20} = +78 \) (c = 0.6, methanol)) in yields of 65–70%. The \( -\text{H-NMR data closely corresponded to those obtained for 28.} \)

\[\text{References}\]


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