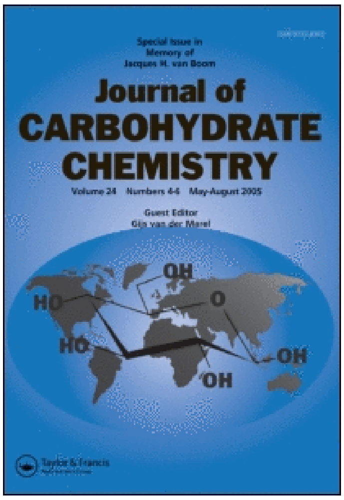

Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

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To cite this Article Goodwin, James C. and Tjarks, Larry(1988) 'Preparation and Structure of (*E*)-1-(3'-Hydroxy-2-Furanyl)-3-(3''-Hydroxy-4''-Methoxyphenyl)-2-Propen-1-One', Journal of Carbohydrate Chemistry, 7: 1, 133 — 140
To link to this Article: DOI: 10.1080/07328308808058908
URL: http://dx.doi.org/10.1080/07328308808058908

J. CARBOHYDRATE CHEMISTRY, 7(1), 133-140 (1988)

PREPARATION AND STRUCTURE OF (*E*)-1-(3'-HYDROXY-2'-FURANYL)-3-(3''-HYDROXY-4''-METHOXYPHENYL)-2-PROPEN-1-ONE†

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Received September 29, 1987 - Final Form November 13, 1987

ABSTRACT

A facile procedure is presented for the synthesis of (*E*)-1-(3'-hydroxy-2'-furanyl)-3-(3''-hydroxy-4''-methoxyphenyl)-2- propen-1-one (**6**). Galactosylisomaltol (**1**) was condensed with isovanillin (**2**) under strong alkaline conditions at 25 °C to form (*E*)-1-(3'-*O*-β-D-galactopyranosyloxy-2'-furanyl)-3-(3''- hydroxy-4''-methoxyphenyl)-2-propen-1-one (**4**). (*E*)-1-(3'-hydroxy-2'-furanyl)-3-(3''-hydroxy-4''-methoxyphenyl)-2-propen-1-one (**6**) was obtained by acid hydrolysis of **4** in a 53.9% yield. This heterocyclic 2-propen-1-one was characterized on the basis of spectral data (IR and ^{1}H NMR), physicochemical properties, and conversion to a mono-*O*-acetyl derivative.

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†The mention of firm names or trade products does not imply that they are endorsed or recommended by the U.S. Department of Agriculture over other firms or similar products not mentioned.

INTRODUCTION

During the bread-baking process, the water-soluble, nonvolatile, nonenzymic browning products galactosylisomaltol (1) and its α-D-gluco isomer[1] are formed by the action of free amino acids, amino functional groups of proteins and peptides on lactose and maltose (liberated by diastatic enzymes on wheat starch). Compound 1 (Scheme 1) was first prepared by dehydration of lactose with secondary amine salts,[2] and more recently 1 and glucosylisomaltol have been prepared chemically by dehydration of lactose and maltose with secondary amino acids.[1] In addition, it has been shown that compound 1 and glucosylisomaltol are transformed by triethylamine into 1,6-anhydro-β-D-hexopyranoses.[3]

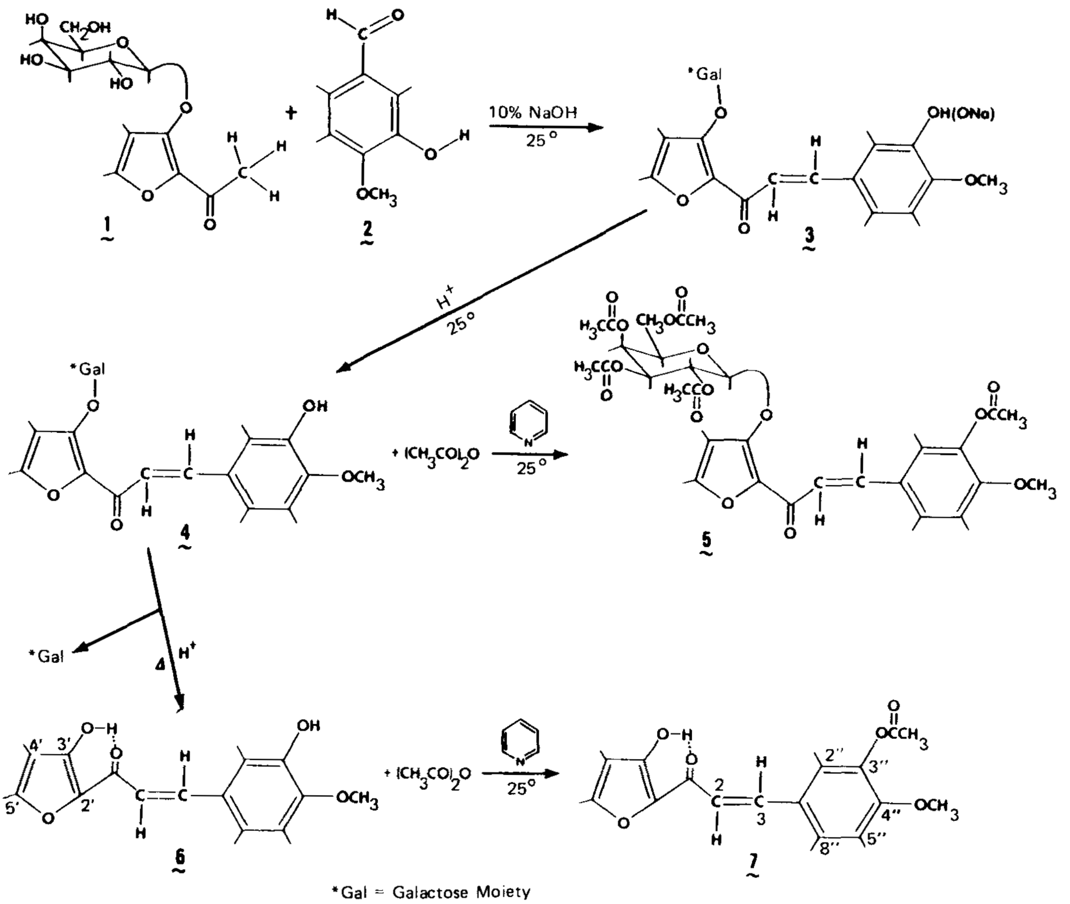
Various aldehydes[4-6] have been condensed at active methyl groups on several compounds. The preparation presented herein involves the alkaline condensation of an aldehyde, isovanillin, 2 (3-hydroxy-4-methoxybenzaldehyde) at the active methyl group on the isomaltol aglycon of galactosylisomaltol (1). This preparation will extend our knowledge of the physicochemical properties of the nonenzymic browning products, 1 and glucosylisomaltol, formed during the bread-baking process.

RESULTS AND DISCUSSION

When galactosylisomaltol (1) was dissolved in aqueous sodium hydroxide (10%, w/v), and isovanillin (2) is added into the solution, compound 2 was condensed at the active methyl group on the isomaltol moiety of 1 to form an orange-colored solid identified as the sodium salt (3) of (*E*)-1-(3′-*O*-β-D-galactopyranosyloxy-2′-furanyl)-3- (3″-hydroxy-4″-methoxyphenyl)-2-propen-1-one (4). The orange-colored sodium salt (3) was changed to a red-brick color upon drying in a vacuum oven overnight at 80 °C.

The red-brick colored sodium salt (3) gave a reddish brown colored, strongly lkaline solution when dissolved into water. A greenish yellow-colored crystalline olid (4) was precipitated from solution upon acidification with hydrochloric acid (≥

SCHEME 1



1N HCl). Compound 4 was washed with water and allowed to dry under reduced pressure; then, 4 was redissolved in absolute ethanol (30 mL) and obtained as crystals in a yield of 67.4% by adding water (150 mL) into the ethanolic solution (Scheme 1). Elemental analyses furnished the formula $C_{20}H_{22}O_{10}$ for 4. The structure for 4 was established by conversion to a pentaacetate derivative (5) as well as from its spectral data and physicochemical properties.

The ^{1}H NMR spectral data (Table 1) for compounds 4 and 5 showed the expected chemical shift signals for the furan, phenol, and galactose ring protons. The data also showed the expected small coupling constants of $J_{4',5'}$=2.0 Hz for the two furan ring

Table 1. ^1H-NMR Chemical Shifts and Coupling Constants at 90 MHz (Hz)

Proton	Chemical shifts[a]			
	Compound 4 $C_{20}H_{22}O_{10}$	5 $C_{30}H_{32}O_{15}$	6 $C_{14}H_{12}O_5$	7 $C_{16}H_{13}O_6$
4'-HC=	6.92d J=2.0	6.46d J=2.0	6.34d J=2.0	6.33d J=2.0
5'-HC=	7.54d	7.51d	7.36d	7.35d
2-HC=	7.94d J=15.6	7.28d J=15.6	7.15d J-15.6	7.13d J=15.6
3-HC=	7.99d	7.82d	7.79d	7.80d
2"-HC=	7.47d J=2.0	7.45d J=2.0	7.27d J=2.0	7.38d J=2.1
5"-HC=	6.68d J=8.3	7.00d J=8.4	6.85d	6.98d
6"-HC=	7.22dd	7.55dd	7.15dd J=8.4	7.48dd J=8.4
Beta-D-Gal[b]				
H-1	5.45d J=7.9	5.18d J=7.8		
H-2	4.72dd J=7.9,9.2	5.64dd J=7.8,10.3		
H-3	4.43dd J=9.2,3.1	5.15dd J=10.3,3.2		
H-4		5.48d J=3.2		
H-5,6,6'	4.1-4.3	$\sim$ 4.2		
OH	5.95bs[c]		6.11bs[c]	7.5bs[d]
CH_3O	3.68s	3.88s	3.94s	3.88s
CH_3OCO		2.33,2.21,2.06 2.04,2.02		2.33s
Solvent	C_5D_5N	$CDCl_3$	$CDCl_3$	$CDCl_3$

[a] In p.p.m. downfield from internal Me_4 Si. Peak multiplicities: s, singlet; d, doublet; dd, doublet of doublet; bs, broad singlet. [b] Beta-D-Gal, galactosyl moiety. [c] Phenolic hydroxyl. [d] H-bonded furyl hydroxyl.

protons,[7] and a large coupling constant of $J_{1,2}=7.9$ Hz for the anomeric proton, which is confirmation of the β-D-*galacto*-configuration for the β-D-galactose moiety. A large coupling constant of $J_{2,3}=15.6$ Hz was observed for the two 2-propen-1-one protons, whereby a trans-configuration structure is indicated for the 2-propen-1-one protons. By hydrolysis of 4 with hydrochloric acid, (*E*)-1-(3'-hydroxy-2'-furanyl)-3-(3"-hydroxy-4"-methoxyphenyl)-2-propen-1-one (6) was isolated in a yield of 53.9%.

Elemental analyses for the heterocyclic compound **6** indicated the formula $C_{14}H_{12}O_5$. The IR spectrum (KBr disk) for **6** showed a strong absorption band at 3480 cm^{-1} that indicated a hydrogen bonded (C=C-OH······O=C-CH) structure. Additional absorption bands were C=O (1645 cm^{-1}, strong H-bonding), four C=C bands (1585, 1510, 1485, and 1455 cm^{-1}),[1,2] HC=CH vibrations on furan-type structures (3030-3080 cm^{-1}),[8,9] and an absorption band at 3280 cm^{-1} for vibrations on 2-propen-1-one-type ($\overset{O}{\overset{\|}{C}}$-HC=CH) structure.[8] The mono-*O*-acetyl derivative (**7**) of compound **6** showed strong absorption at 3460 cm^{-1} for an H-bonded (C=C-OH···O=C-CH) structure, CH_3OCO (1755 cm^{-1}, ester), and C=O (1644 cm^{-1}, strong H-bonding). Compound 7 did not form the expected di-O-acetyl derivative (under the reported conditions). The IR spectral data for the 2-propen-1-one carbonyl absorption frequencies of **6** (1645 cm^{-1}) and 7 (1644 cm^{-1}) indicated the effects of intramolecular H-bonding; therefore, it is reasonable to assume that the hydroxyl proton at C-3′ on the furan ring is strongly H-bonded to the 2-propen-1-one carbonyl oxygen atom. This H-bonding probably involves the two 2-propen-1-one protons at C-2 and C-3, whereupon a resonance system involving the C-3′-OH-proton, 2-propen-1-one carbonyl oxygen atom, protons at C-2 and C-3 of 2-propen-1-one may exist to induce a steric effect at the C-3′-OH (Scheme 1).

The ^1H NMR spectral data for **6** and 7 showed the expected chemical shift signals for the unsaturated protons (Table 1). The spectral data also showed OH chemical shift signals at $\delta 6.11$ and $\delta 7.50$ for compounds **6** and 7, respectively. A single chemical shift signal was observed at $\delta 2.33$ for acetyl methyl protons of 7, which supported the formation of a mono-*O*-acetyl derivative. Compounds 6 and 7 showed the expected small and large coupling constants for the furan ring, 2-propen-1-one, and aryl ring protons (Table 1). The IR spectral data for 6 and 7 complemented the ^1H NMR spectral data.

EXPERIMENTAL

General Methods.- Galactosylisomaltol (1) (3-*O*-*β*-D-galactopyranosyloxy-2-furanyl methyl ketone) was obtained by the method of Hodge and Nelson.[2] Commercial sodium hydroxide (MCB Manufacturing Chemists, Inc., Cincinnati, OH) and isovanillin (**2**) (3-hydroxy-4-methoxybenzaldehyde), (Aldrich Chemical Co., Milwaukee, WI) were used. Melting points were recorded on a Thomas-Hoover Unimelt Apparatus and were not corrected. IR spectra were determined using potassium bromide pellets (1.22mm thick containing ≥0.1M concentrations) with a Beckman IR-33 spectrophotometer. Purity of the compounds was established by TLC, melting point (mp), and elemental analyses. TLC was conducted on 0.25mm of EM Reagent Silica Gel G (Brinkman Instruments, Inc.) with air-dried plates. The spots were detected by spraying with 5% ethanolic sulfuric acid and charring. TLC was performed with 80% methanol-ethyl acetate (v/v) for compounds **4** and **6** and with 75% ethyl acetate-hexane for **5** and 7. ^{1}H NMR spectra were recorded with a Bruker WH-90 spectrometer; chemical shifts are referenced to internal tetramethylsilane. Products were vacuum-dried in presence of phosphorus pentoxide for 24-48 h at room temperature before analysis. Microchemical analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN 37921.

Sodium salt of (*E*)-1-(3′-*O*-*β*-D-galactopyranosyloxy-2′-furanyl)-3-(3″-hydroxy-4″-methoxyphenyl)-2-propen-1-one (3).- To a solution of galactosylisomaltol (1) (1.15 g., 4.0 mmol) in aqueous sodium hydroxide (25 mL, 10% w/v) was added isovanillin (2) (0.6g, 4.0 mmol), and the mixture was stirred at 25 °C. After compound **3** precipitated as an orange-colored solid, the reaction was continued for 1.0 h. The orange-colored solid (3) was collected by filtration and washed with absolute ethanol and dried overnight at 80 °C. The orange-colored amorphous solid (3) (0.98g; 56.2%) changed to a brick-red color: mp > 250 °C. Anal. Calcd. for $C_{20}H_{21}NaO_{10}$: C, 54.06; H, 4.76; Na, 5.17. Found: C, 53.90; H, 4.88; Na, 5.34.

(*E*)-1-(3′-*O*-*β*-D-Galactopyranosyloxy-2′-furanyl)-3-(3″)-hydroxy-4″-methoxyphenyl)-2-propen-1-one (4).- Compound 3 in water (25 mL), [reddish-brown, strongly alkaline] was acidified with ≥1N HCl (1.0 mL), whereupon a greenish-yellow colored, free-phenol (4) was precipitated from solution. The product was collected, washed with water, and dried under reduced pressure at 118 °C for 2.0 h. The crude product was dissolved in hot absolute ethanol (30 mL), treated with activated charcoal (Darco G 60); crystallized by adding water (150 mL) to the ethanol filtrate; to yield 0.97 g (67.4%) of pure **4**: mp 179.5-181 °C. Anal. Calcd. for $C_{20}H_{22}O_{10}$: C, 56.87; H, 5.25. Found: C, 56.86; H, 5.36.

(*E*)-1-(3′-*O*-2,3,4,6-Tetra-O-Acetyl-*β*-D-galactopyranosyloxy-2′-furanyl)-3-(3″-O-acetyl-4″-methoxyphenyl)-2-propen-1-one (5).- A solution of **4** (1.0 g, 2.4 mmol) in dry pyridine (10 mL) containing acetic anhydride (1.0 mL), was heated on steam bath for 10 min, and allowed to stand overnight at 25 °C. The solvents were evaporated under diminished pressure with toluene to afford **5** [0.98 g, (64.5%) crystals from absolute ethanol] mp 100.5-101 °C. Anal. Cacld. for: $C_{30}H_{32}O_{15}$: C, 56.96; H, 5.10. Found: C, 56.88; H, 5.28.

(*E*)-1-(3′-hydroxy-2′-furanyl)-3-(3″-hydroxy- 4″-methoxyphenyl)-2-propen-1-one (6).- Compound **4** (2.0 g, 4.7 mmol) in aqueous ethanol (50 mL, 1:1 v/v), was acidified with ≥ 1N HCl (1.0 mL) and was allowed to heat on a steam bath overnight . The reaction mixture was poured into ice water and extracted with chloroform (100 mL) three times. Compound 6 (0.7 g, 53.9%) was obtained as crystals from absolute ethanol; mp 171.5-173 °C; IR $^{\nu}$max (KBr disk) 3480 cm^{-1} (C=C-OH···O=C-CH), 3280 cm^{-1} 2-propen-1-one $(\overset{O}{C}\text{-}CH{=}CH)$,[8] 3080 cm^{-1} (furan, HC=CH),[8,9] 2870-2960 cm^{-1} (OCH_3), 1645 cm^{-1} (C=O), 1585, 1510, 1485, 1455 cm^{-1} (C=C vibrations) and 1385 cm^{-1} (CH_3). Anal. Calcd. for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65. Found: C, 64.70; H, 4.70.

(*E*)-1-(3′-Hydroxy-2′-furanyl)-3-(3″-O-acetyl-4″-methoxyphenyl)-2-propen-1-one (7).- Compound **6** (1.0 g, 3.8 mmol) was acetylated in dry pyridine (15 mL) containing acetic anhydride (1.0 mL), overnight at 25 ^{o}C. The solvents were removed by evaporation with toluene under diminished pressure. Compound 7 [0.79 g; (65.3%)] was obtained as crystals from absolute ethanol: mp 136-137.5 ^{o}C; IR ^{v}Max (KBr disk) 3460 cm^{-1} (C=C-OH···O=C-CH), 3160 cm^{-1} 2-propen-1-one ($\overset{O}{C}$-CH=CH),^{8} 3000-3040 cm^{-1} (furan, HC=CH),^{8,9} 2870-2950 cm^{-} (OCH_3), 1755 cm^{-1} (CH_3OCO), 1644 cm^{-1} (C=O), 1590, 1565, 1510, 1480 cm^{-1} (C=C), and 1375 cm^{-1} (CH_3).

Anal. Calcd. for $C_{16}H_{14}O_6$: C, 63.57; H, 4.67. Found: C, 63.36; H, 4.81.

ACKNOWLEDGMENTS

Thanks is extended to H. B. Sinclair and R. F. Vesonder, for critical evaluation of this manuscript, and to Kurt Loening, Chemical Abstracts Service, for help with nomenclature.

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