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Carbohydrate Research 339 (2004) 1381–1387
Carbohydrate RESEARCH

Note

Preparation of polyhydroxyalkyl- and *C*-glycosylfuran derivatives from free sugars catalyzed by cerium(III) chloride in aqueous solution: an improvement of the Garcia González reaction ☆

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Received 24 October 2003; accepted 10 February 2004

Available online 2 April 2004

Abstract—Unprotected aldose sugars react smoothly with 1,3-diones or β-ketoesters in the presence of $CeCl_3 \cdot 7H_2O$ in aqueous solution to produce polyhydroxylalkyl- and *C*-glycosylfuran derivatives in excellent yield. Operationally simple, mild neutral reaction conditions in aqueous solution is the key feature of this methodology.

Keywords: Furan; *C*-glycoside derivatives; Cerium(III) chloride

Mimicking of structures and the biological functions of biologically interesting molecules has become front-line research in recent years.[1] Although proteins and peptides have been targeted extensively for designing the biomimetics,[2] a series of glycosamino acids, for example, furanoid sugar amino acids[3] and sugar dicarboxylic acids,[4] which are hybrids of carbohydrates and amino acids, have appeared as scaffolds for the preparation of glyco- and peptidomimetics. Carbohydrate-derived tetrahydrofurans[5] and pyrrolidines[6] have been used as peptidomimetics that adopt interesting secondary structures because of the rigidity generated due to the presence of furan and pyran moieties. Furan and pyran derivatives have been used as enzyme inhibitors[7] in glycobiology to modulate cellular functions where biosynthesis of cell-surface oligosaccharides uses glycosyl transferases and glycosidases for sequential incorporation of various sugar molecules to elongate the oligosaccharide chains. Besides their enzyme inhibitory activities, these classes of compounds are also potential drugs for new therapeutic strategies.[8] Among the various classes of heterocyclic compounds, furan ring systems form an important component of pharmacologically active compounds having a wide spectrum of biological activities ranging from antifungal,[9] to antitrypanosomal,[10] to gastrointestinal motility activity, to farnesyl transferase,[11] and phosphodiesterase inhibitory activity.[12] Having a number of useful properties, which include chirality, rigidity, lipophilicity, hydrophilicity, and flexibility in one system, polyhydroxyalkyl furans are quite interesting scaffolds for synthetic chemists to utilize in the synthesis of a variety of biologically interesting molecules. Very recently, researchers have used these classes of compounds as potential enzyme inhibitors and to construct mimics of peptidoglycans.[13]

Aiming to prepare a *C*-glycosyl-1,3-dione scaffold through the Knoevenagel condensation of a free sugar and a 1,3-dione, D-glucose was treated with acetylacetone in the presence of cerium(III) chloride heptahydrate in water at 90 °C. The reaction proceeded very well, leading to a single isolable product that was not glucosylpentane-2,4-dione, but was a β-linked dihydroxytetrahydrofuranylfuran derivative as confirmed by spectral analysis. From the literature it has been found that the preparation of this class of compound from the free sugar was reported only in late 1950s by

☆ CDRI communication no: 6447.

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doi:10.1016/j.carres.2004.02.011

Garcia González[14] using zinc chloride in methanol under relatively harsh reaction conditions in about 32% yield. Despite the usefulness of this class of compounds as synthetic scaffolds, only a few attempts have been made to modify the reaction conditions and improve the yields, namely, the correction of the initial report by Kozikowski et al.[15] and the report on the unoptimized use of $Yb(OTf)_3$ by Rodrigues et al.[16] Thus a facile one-pot preparation of β-linked polyhydroxylated tetrahydrofuranylfuran derivatives having a keto or ester functionality to further their preparation from free sugars under neutral conditions would extend the scope of this transformation. Recently, considerable research interest is being shown toward the lanthanide salts because of their unique Lewis acid behavior.[17] Of various lanthanide salts, cerium(III) chloride, an inexpensive, water tolerant, relatively nontoxic, easy to handle neutral catalyst having Lewis acidic character has been used in a variety of chemical transformations.[18] As a part of our program to synthesize glycomimetics, we herein describe an efficient, high-yielding synthesis of β-linked hydroxylated tetrahydrofuranylfuran by cerium(III) chloride-catalyzed Knoevenagel condensation of a 1,3-dione or β-ketoester with unprotected carbohydrates in aqueous medium. Under these reaction conditions pentose sugars produced furan derivatives having polyhydroxylated alkyl side chains, whereas in the case of hexoses it further cyclizes to furnish β-linked hydroxylated tetrahydrofuranylfuran derivatives. Unprotected disaccharides also produced the corresponding glycosylated tetrahydrofuranylfuran derivatives in excellent yield, leaving the acid-labile interglycosidic bond intact. In order to optimize the amount of $CeCl_3 \cdot 7H_2O$ needed for a complete conversion, a series of experiments were performed by varying the amount of promoter from 0 to 25 mol % and the temperature from room temperature to 90 °C while keeping the molar ratio of 1:1.5 aldose to 1,3-dione the same in water (1.0 mL/mmol of aldose). Best results were obtained by using a molar ratio of 1.0:1.5:0.25 aldose–1,3-dione–$CeCl_3 \cdot 7H_2O$ in water (1.0 mL/mmol of aldose) at 90 °C for 6–10 h (as shown in Table 1). As a control experiment the reaction was performed in the absence of catalyst, and no reaction product could be isolated after an even longer period of time (~48 h) at 100 °C. Using 10 mol % of catalyst, the reaction did not go to completion after 32 h from which 40% expected product was isolated. However, the reaction was completed after 6.0 h using 25 mol % of $CeCl_3 \cdot 7H_2O$ to aldose. The use of water and no organic solvent as the reaction medium makes this protocol environmentally benign (Scheme 1).

Table 1. $CeCl_3 \cdot 7H_2O$-catalyzed transformation of free aldoses to polyhydroxylated furans in water

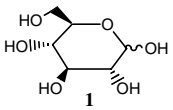
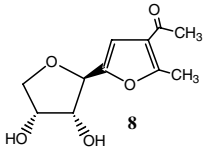
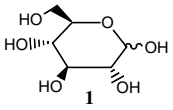
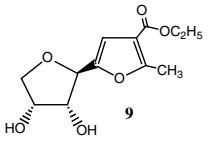
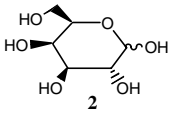
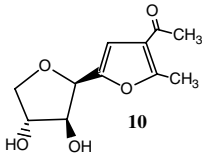
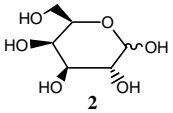
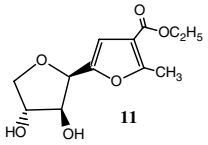
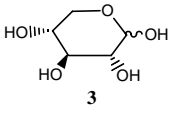
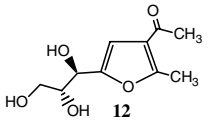
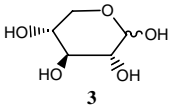
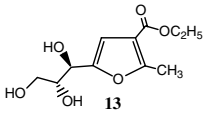
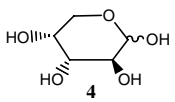
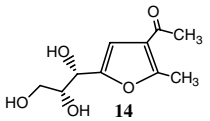
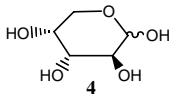
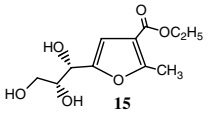
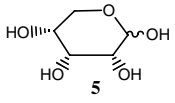
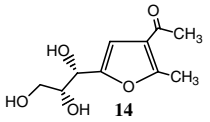
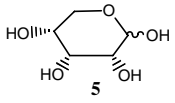
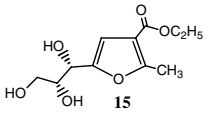
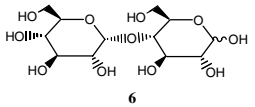
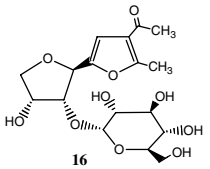
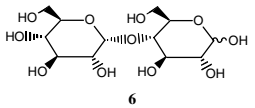
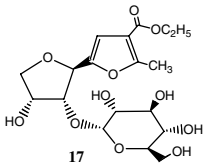
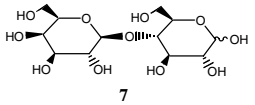
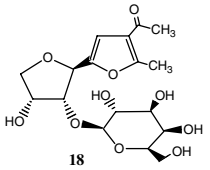
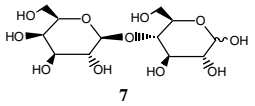
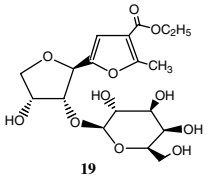
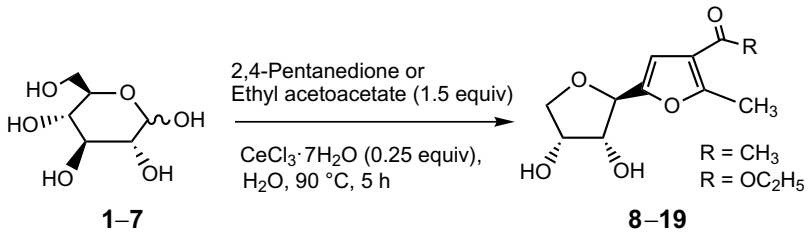
Entry	Aldoses	1,3-Dione	Furans	Reaction time (h)[a]	Yield (%)[b]
1	 **1**	Pentane-2,4-dione	 **8**	6.0	93
2	 **1**	Ethyl acetoacetate	 **9**	6.0	87
3	 **2**	Pentane-2,4-dione	 **10**	7.0	92
4	 **2**	Ethyl acetoacetate	 **11**	8.0	82
5	 **3**	Pentane-2,4-dione	 **12**	6.0	90
6	 **3**	Ethyl acetoacetate	 **13**	6.0	85

Table 1 (*continued*)

Entry	Aldoses	1,3-Dione	Furans	Reaction time (h)[a]	Yield (%)[b]
7	 **4**	Pentane-2,4-dione	 **14**	7.0	90
8	 **4**	Ethyl acetoacetate	 **15**	6.0	76
9	 **5**	Pentane-2,4-dione	 **14**	6.0	84
10	 **5**	Ethyl acetoacetate	 **15**	6.0	80
11	 **6**	Pentane-2,4-dione	 **16**	9.0	78
12	 **6**	Ethyl acetoacetate	 **17**	10	75
13	 **7**	Pentane-2,4-dione	 **18**	10	87
14	 **7**	Ethyl acetoacetate	 **19**	10	82

[a] Temperature = 90 °C.
[b] Isolated yield.



Scheme 1.

We presume that the formation of compounds **12**–**15** results from the initial condensation of the active methylene of the 1,3-dione or β-ketoester with the starting sugars **3**–**5**, β-elimination of water, and then cyclization, followed by aromatization to the furan derivatives. In the case of compounds **8**–**11** and **16**–**19**,

after the formation of polyhydroxylated alkyl furans, they further cyclize to form β-linked tetrahydrofuranylfuran derivatives. The structures of the cyclized products were established by their NMR spectral data and NOE experiments. For instance, in the case of compound **8**, the coupling constant (J value) between H-1 and H-2 was 6.30 Hz, while in the case of compound **10** the same was 4.0 Hz, indicating that the furan ring is linked to C-1 through a β-linkage. Apart from the J values, NOE experiments were carried out for further confirmation, and it has been found that for compound **8**, no NOE enhancement of H-2 was observed by irradiating the H-1 proton, which is possible only when the furan nucleus is linked to C-1 through a β-linkage (Fig. 1).

Encouraged by the reports in the literature of a series of trifluoromethanesulfonate salts,[19] for example, $In(OTf)_3$, $Yb(OTf)_3$, $Sc(OTf)_3$, to promote acid-catalyzed reactions in water under mild conditions, a series of experiments were performed using D-glucose (1.0 mmol) and 2,4-pentanedione (1.5 mmol) in water catalyzed by above-mentioned promoters at 90 °C for 24 h. Each one of them produced almost same reaction products, which constitute the initially formed polyhydroxyalkyl furans (45%) and final cyclized tetrahydrofuranylfuran derivative (**8**, 20%), whereas the use of $CeCl_3 \cdot 7H_2O$ as a neutral promoter furnished the single product **8** in 92% yield.

In addition, this methodology has been extended toward the synthesis of substituted furfural or

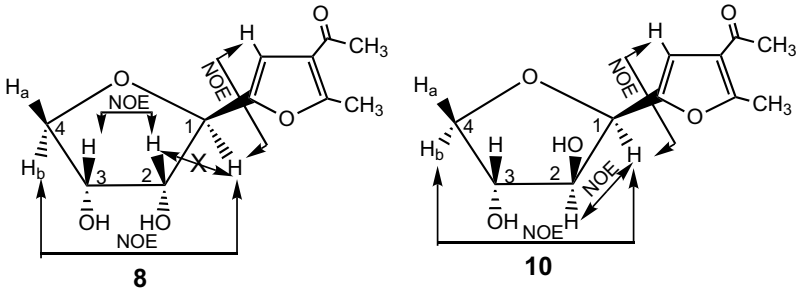
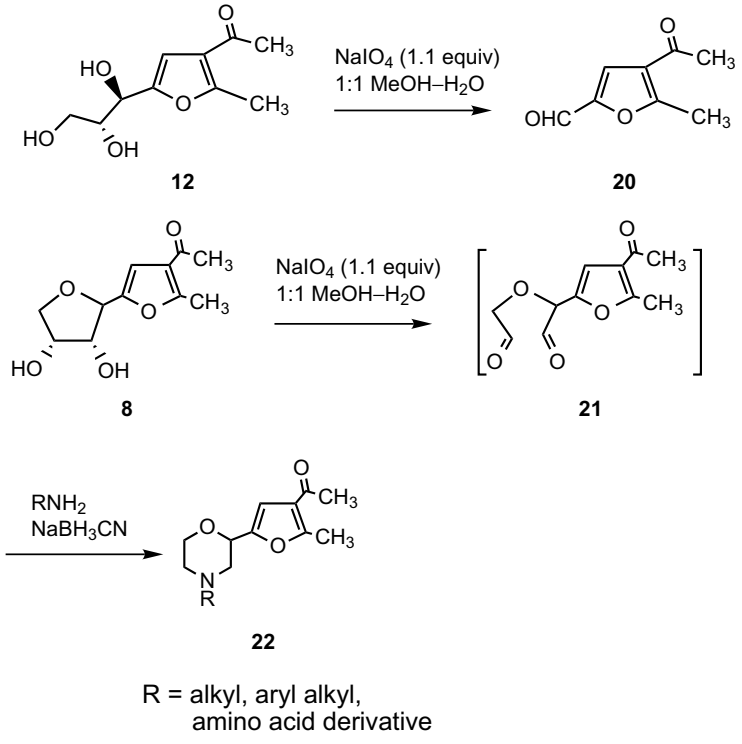


Figure 1. NOE enhancements for **8** and **10**.



Scheme 2.

N-substituted morpholinofuran derivatives for their use as heterocyclic scaffolds for synthetic organic chemistry. Oxidative cleavage of compound **12** using $NaIO_4$ in 1:1 MeOH–H_2O furnished 4-acetyl-5-methylfuran-2-carbaldehyde (**20**) in a quantitative yield, whereas treatment of compound **8** with $NaIO_4$, followed by reductive alkylation with a primary amine in presence of $NaBH_3CN$, afforded compound **22** (Scheme 2).

In conclusion, a facile one-pot procedure has been developed for the preparation of hydroxyalkylfurans or β-linked polyhydroxytetrahydrofuranylfurans in excellent yield. Preparation of 4-acetyl-5-methylfuran-2-carbaldehyde using this protocol is certainly a valuable addition to the process industry. This operationally simple, high-yielding methodology will certainly find wide application in organic synthesis by using less toxic, economically convenient, neutral catalysts, and environmentally friendly reaction conditions.

1. Experimental

1.1. General methods

NMR spectra were measured with an Avance DPX 200 FT Bruker Robotics Spectrometer for solutions in $CDCl_3$ using Me_4Si as internal reference. FAB mass spectra were recorded on a Jeol SX 102/DA 6000 mass spectrometer using argon/xenon (6 kV, 10 mA) as the FAB gas. Aluminum sheets coated with Silica Gel 60 F_{254} (E. Merck) were used for TLC. Viewing under a short wavelength UV lamp, followed by heating the plates sprayed with 5% H_2SO_4 in EtOH effected detection of the reaction products. Column chromatography was performed with Silica Gel 100–200 mesh (SRL, India). Cerium(III) chloride heptahydrate was purchased from Aldrich Chemical Company.

1.2. Typical experimental protocol

To a solution of D-glucose (1.80 g, 10.0 mmol) and acetylacetone (2,4-pentanedione, 1.50 g, 1.50 mmol) in distilled water (10 mL) was added $CeCl_3 \cdot 7H_2O$ (930 mg, 2.50 mmol) in one portion at room temperature. The reaction mixture was placed in a preheated oil bath and stirred at 90 °C for 6 h. After completion of the reaction as indicated by TLC (1:1 toluene–acetone), the reaction mixture was evaporated to dryness under reduced pressure. The crude mass was purified over SiO_2 using 6:1 toluene–acetone to furnish pure compound **8** (2.10 g, 93%). A portion of the crude mass was acetylated conventionally using Ac_2O and pyridine at room temperature, which after column chromatography over SiO_2 afforded the acetylated furan derivative in quantitative yield.

1.3. Spectroscopic and elemental analysis data for compounds 8–19 after O-acetylation

1.3.1. 3-Acetyl-5-*C*-(2,3-di-*O*-acetyl-1,4-anhydro-β-D-*erythro*-tetrofuranosyl)-2-methylfuran (O-acetylated 8). ^{1}H NMR: δ 6.65 (s, 1H), 5.49 (m, 2H), 4.87 (d, *J* 6.3 Hz, 1H), 4.38 (dd, *J* 7.0 and 4.8 Hz, 1H), 3.95 (dd, *J* 7.0, 3.6 Hz, 1H), 2.59 (s, 3H), 2.40 (s, 3H), 2.13 and 2.07 (2s, 6H). ^{13}C NMR: δ 193.9, 170.2, 169.7, 159.2, 148.7, 122.3, 110.3, 75.2, 74.5, 72.0, 69.7, 29.3, 20.8, 20.7, 14.7. FABMS: calcd *m*/*z* 311 (M+1); found *m*/*z* 311. Anal. Calcd for $C_{15}H_{18}O_7$: C, 58.06; H, 5.85. Found: C, 57.95; H, 5.97.

1.3.2. Ethyl 5-*C*-(2,3-di-*O*-acetyl-1,4-anhydro-β-D-*erythro*-tetrofuranosyl)-2-methyl-3-furanoate (O-acetylated 9). ^{1}H NMR: δ 6.64 (s, 1H), 5.48 (m, 2H), 4.87 (d, *J* 6.0 Hz, 1H), 4.36 (m, 1H), 4.29 (q, 2H), 3.92 (dd, *J* 4.0 and 10.0 Hz, 1H), 2.57 (s, 3H), 2.11 and 2.06 (2s, 6H), 1.39 (t, 3H). ^{13}C NMR: δ 170.2, 169.9, 163.9, 160.3, 148.7, 114.7, 110.7, 75.5, 75.2, 71.6, 71.1, 60.5, 20.9, 20.8, 14.6, 14.2. FABMS: calcd *m*/*z* 341 (M+1); found 341. Anal. Calcd for $C_{16}H_{20}O_8$: C, 56.47; H, 5.92. Found: C, 56.39; H, 6.02.

1.3.3. 3-Acetyl-5-*C*-(2,3-di-*O*-acetyl-1,4-anhydro-β-D-*threo*-tetrofuranosyl)-2-methylfuran (O-acetylated 10). ^{1}H NMR: δ 6.65 (s, 1H), 5.45 (m, 1H), 5.23 (m, 1H), 4.47 (d, *J* 4.0 Hz, 1H), 4.10 (ddd, 2H), 2.59 (s, 3H), 2.38 (s, 3H), 2.13, 2.11 (2s, 6H); ^{13}C NMR: δ 194.1, 170.5, 170.2, 159.3, 148.7, 122.4, 109.8, 79.9, 78.6, 78.2, 72.3, 29.4, 21.1, 20.9, 14.7; FABMS: Cacd *m*/*z* 311 (M+1); found 311. Anal. Calcd for $C_{15}H_{18}O_7$: C, 58.06; H, 5.85. Found: C, 57.93; H, 6.01.

1.3.4. Ethyl 5-*C*-(2,3-di-*O*-acetyl-1,4-anhydro-β-D-*threo*-tetrofuranosyl)-2-methyl-3-furanoate (O-acetylated 11). ^{1}H NMR: δ 6.66 (s, 1H), 5.44 (m, 1H), 5.21 (m, 1H), 4.77 (d, *J* 4.5 Hz, 1H), 4.25 (dd, 2H), 4.05 (ddd, 2H), 2.58 (s, 3H), 2.12, 2.10 (2s, 6H), 1.33 (t, 3H). ^{13}C NMR: δ 170.1, 169.8, 163.6, 159.2, 148.1, 114.2, 110.4, 79.5, 78.1, 76.2, 71.8, 60.0, 20.5, 19.8, 14.2, 13.7. FABMS: calcd *m*/*z* 341(M+1); found *m*/*z* 341. Anal. Calcd for $C_{16}H_{20}O_8$: C, 56.47; H, 5.92. Found: C, 56.53; H, 6.05.

1.3.5. 3-Acetyl-2-methyl-5-[(1*R*,2*R*)-1,2,3-triacetoxypropyl]furan (O-acetylated 12). ^{1}H NMR: 6.65 (s, 1H), 6.01 (d, *J* 8 Hz, 1H), 5.55 (m, 1H), 4.32 (dd, *J* 12.0 and 3.6 Hz, 1H), 3.94 (dd, *J* 12.0 and 6.0 Hz, 1H), 2.58 (s, 3H), 2.38 (s, 3H), 2.09 and 2.05 (2s, 6H), 1.98 (s, 3H). ^{13}C NMR: δ 193.9, 170.8, 170.2, 169.7, 159.3, 147.1, 122.4, 111.1, 70.6, 66.6, 62.2, 29.4, 21.0, 20.9 (2C), 14.7. FABMS: calcd *m*/*z* 341 (M+1); found *m*/*z* 341. Anal. Calcd for $C_{16}H_{20}O_8$: C, 56.47; H, 5.92. Found: C, 56.40; H, 6.07.

1.3.6. Ethyl 2-methyl-5-[(1*R*,2*R*)-1,2,3-triacetoxypropyl]-3-furanoate (O-acetylated 13). ^{1}H NMR: δ 6.67 (s, 1H), 6.01 (d, *J* 7.6 Hz, 1H), 5.60 (m, 1H), 4.25 (m, 3H), 3.95 (dd, 1H), 2.56 (s, 3H), 2.09, 2.08, 2.06 (3s, 9H), 1.33 (t, 3H). ^{13}C NMR: δ 170.6, 170.2, 169.6, 163.7, 159.9, 146.8, 114.8, 111.7, 70.5, 66.6, 62.3, 60.6, 21.0. 20.9 (2C), 14.6, 14.1. FABMS: calcd *m*/*z* 371 (M+1); found *m*/*z* 371. Anal. Calcd for $C_{17}H_{22}O_9$: C, 55.13; H, 5.99. Found: C, 55.02; H, 6.08.

1.3.7. 3-Acetyl-2-methyl-5-[(1*S*,2*R*)-1,2,3-triacetoxypropyl]furan (O-acetylated 14). ^{1}H NMR: 6.65 (s, 1H), 6.00 (d, *J* 7.7 Hz, 1H), 5.52 (m, 1H), 4.28 (m, 1H), 3.91 (dd, 1H), 2.63 (s, 3H), 2.38 (s, 3H), 2.09, 2.08, 2.06 (3s, 9H). ^{13}C NMR: 193.9, 170.8, 170.0, 169.7, 159.5, 147.1, 122.5, 111.4, 70.6, 66.8, 62.2, 29.6, 21.1, 20.9 (2C), 14.7. FABMS: calcd *m*/*z* 341 (M+1); found *m*/*z* 341. Anal. Calcd for $C_{16}H_{20}O_8$: C, 56.47; H, 5.92. Found: C, 56.38; H, 6.07.

1.3.8. Ethyl 2-methyl-5-[(1*S*,2*R*)-1,2,3-triacetoxypropyl]-3-furanoate (O-acetylated 15). ^{1}H NMR: δ 6.67 (s, 1H), 5.98 (d, *J* 7.5 Hz, 1H), 5.51 (m, 1H), 4.25 (m, 4H), 2.56 (s, 3H), 2.09, 2.06, 2.03 (3s, 9H), 1.30 (t, 3H). ^{13}C NMR: δ 170.9, 170.1, 169.9, 163.8, 160.2, 147.0, 114.8, 111.8, 70.6, 66.7, 62.4, 60.6, 21.1 (3C), 14.7, 14.1. FABMS: calcd *m*/*z* 371 (M+1); found *m*/*z* 371. Anal. Calcd for $C_{17}H_{22}O_9$: C, 55.13; H, 5.99. Found: C, 55.04; H, 6.10.

1.3.9. 3-Acetyl-5-[3-*O*-acetyl-1,4-anhydro-2-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-β-D-*erythro*-tetrofuranosyl]-2-methylfuran (O-acetylated 16). δ 6.61 (s, 1H), 5.43 (m, 2H), 5.06 (m, 2H), 4.74 (m, 2H), 4.29 (dd, 1H), 4.19 (dd, 1H), 4.15 (m, 4H), 2.58 (s, 3H), 2.39 (s, 3H), 2.22–1.90 (5s, 15H). ^{13}C NMR: δ 193.9, 171.3, 170.8, 170.6, 170.0, 169.6, 159.7, 149.1, 122.5, 110.5, 96.4, 79.2, 75.3, 72.6, 71.4, 71.0, 70.5, 68.5, 62.1, 60.6, 29.3, 21.3, 21.1, 20.9, 20.8, 20.6, 14.5. FABMS: calcd *m*/*z* 599 (M+1); found *m*/*z* 599. Anal. Calcd for $C_{27}H_{34}O_{15}$: C, 54.18; H, 5.73. Found: C, 54.10; H, 5.81.

1.3.10. Ethyl 5-[3-*O*-acetyl-1,4-anhydro-2-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-β-D-*erythro*-tetrofuranosyl]-2-methyl-3-furanoate (O-acetylated 17). ^{1}H NMR: δ 6.56 (s, 1H), 5.35 (m, 2H), 4.94 (m, 2H), 4.67 (m, 2H), 4.06–4.02 (m, 7H), 2.49 (s, 3H), 2.15—1.84 (5s, 15H), 1.30 (t, 3H). ^{13}C NMR: δ 171.0 (2C), 170.4, 170.1, 169.9, 163.8, 160.4, 148.9, 114.8, 111.1, 96.7, 79.5, 75.1, 71.5, 70.9, 70.6, 68.5, 67.5, 62.2, 60.6, 30.0, 21.1, 21.0, 20.7 (3C), 14.7, 14.2. FABMS: calcd *m*/*z* 629 (M+1); found *m*/*z* 629. Anal. Calcd for $C_{28}H_{36}O_{16}$: C, 53.50; H, 5.77. Found: C, 53.56; H, 5.85.

1.3.11. 3-Acetyl-[3-*O*-acetyl-1,4-anhydro-2-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-*erythro*-tetrofuranosyl]-2-methylfuran (O-acetylated 18). ^{1}H NMR: δ 6.61 (s, 1H), 5.43 (m, 2H), 5.08 (d, *J* 2.0 Hz, 1H), 5.0 (t, 1H), 4.7 (m, 2H), 4.48 (t, 1H), 4.25 (m, 1H), 4.17 (m, 4H), 2.63 (s, 3H), 2.39 (s, 3H), 2.22 (s, 3H), 2.08 (s, 3H), 2.03 (s, 3H), 2.0 (s, 3H), 1.9 (s, 3H). ^{13}C NMR: δ 193.9, 170.8, 170.7, 170.6, 170.2, 170.0, 159.7, 149.1, 122.5, 110.5, 94.6, 79.2, 75.3, 73.4, 71.4, 71.0, 70.5, 68.5, 62.1, 60.6, 29.6, 21.2, 21.1, 20.9, 20.8, 20.6, 14.7. FABMS: calcd *m*/*z* 599 (M+1); found *m*/*z* 599. Anal. Calcd for $C_{27}H_{34}O_{15}$: C, 54.18; H, 5.73. Found: C, 54.08; H, 5.85.

1.3.12. Ethyl 5-[3-*O*-acetyl-1,4-anhydro-2-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-*erythro*-tetrofuranosyl]-2-methyl-3-furanoate (O-acetylated 19). ^{1}H NMR: δ 6.64 (s, 1H), 5.29 (m, 2H), 5.20 (m, 1H), 4.94 (m, 2H), 4.52 (d, *J* 7.0 Hz, 1H), 4.25–3.75 (m, 6H), 2.58 (s, 3H), 2.15–1.96 (5s, 15H), 1.32 (t, 3H). ^{13}C NMR: δ 170.6, 170.5, 170.3, 169.7, 169.2, 164.0, 159.8, 149.8, 128.5, 125.6, 110.0, 101.7, 80.8, 73.0, 71.8, 71.1, 70.9, 68.9, 67.1, 60.5, 29.5, 21.7, 21.1, 21.0, 20.9, 20.8, 14.6, 14.2. FABMS: calcd *m*/*z* 629 (M+1); found *m*/*z* 629. Anal. Calcd for $C_{28}H_{36}O_{16}$: C, 53.50; H, 5.77. Found: C, 53.42; H, 5.88.

Acknowledgements

The authors thank Director, Central Drug Research Institute (CDRI) for his constant encouragement and support. Instrumentation facilities from RSIC, CDRI is gratefully acknowledged. This work is partly funded by DST, New Delhi (project no. SR/FTP/CSA-10/2002).

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