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ORIGINAL PAPER

Synthesis of pseudo-*C*-nucleosides from *β*-formyl-*α*,*β*-unsaturated ester bearing a *β*-furanosidic moiety

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Abstract Pseudo-*C*-nucleosides have potential biological activity, and an efficient synthesis of new pseudo-*C*-nucleosides has been developed via the reaction of a *β*-formyl-*α*,*β*-unsaturated ester bearing a *β*-sugar moiety with hydrazines in neutral and acidic conditions. The preparation of the *β*-formyl-*α*,*β*-unsaturated ester was accomplished by oxidation of the secondary hydroxyl group of 3-*O*-benzyl-1,2-*O*-isopropylidene-*α*-D-glucofuranose, followed by elongation of its carbon chain with (ethoxycarbonylmethylene)triphenylphosphorane and oxidation of the hydroxymethyl group.

Keywords Carbohydrates · Heterocycles · Pseudo-*C*-nucleosides · Pyridazinone · Wittig reaction

Introduction

Pseudo-*C*-nucleosides are *C*-nucleoside analogs that have a C–C linkage between C-4′ and C-5′ of a furanose or C-6′ of a pyranose sugar moiety and a heterocyclic base [1]. Their synthesis can be accomplished by two pathways: by heterocyclic ring construction in the sugar moiety bearing an appropriate functional group or by the reaction of both moieties [2]. Due to structural similarities with the *C*-nucleosides, these compounds may have interesting biological properties.

Compounds that have heterocyclic rings with two or more nitrogen atoms, such as triazole [3], pyrazole [4], and pyridazine [5] derivatives, present a wide range of biological activity, including anti-angiogenesis, antimetastatic, herbicidal, antibacterial, and fungicidal properties [6]. Pyrazoles are the most representative of five-membered heterocyclic systems [7]. Despite the fact that pyrazole rings are rarely a constituent of natural products, numerous synthetic pyrazole derivatives have found use in pharmaceutical, agrochemical, photographic, and various other applications [8]. The pyrazole motif makes up the core structure of numerous biologically active compounds, such as Celebrex and Viagra [9]. One of the most commonly used synthetic methods to synthesize pyrazoles involves the reaction of 1,3-dicarbonyl compounds with hydrazine derivatives, leading to a mixture of regioisomers via hydrazone formation and loss of water molecules. Occasionally, 3-hydroxy-3,4-dihydropyrazoles or hydroxypyrazolines can be observed as stable, isolable intermediates that can be fully characterized prior to the loss of the second molecule of water, which gives rise to pyrazole derivatives [10].

Many pyrazoline derivatives have found clinical application as non-steroidal anti-inflammatory drugs (NSAIDs). For example, antipyrine, 2,3-dimethyl-1-phenyl-3-pyrazolin-5-one, was the first pyrazolone derivative used in the management of pain and inflammation [11].

Pyridazines are interesting compounds due to their important pharmacological activities [12, 13], resulting in many of them being used as drugs [14]. Pyridazine derivatives can be synthesized by several methods [15], including reactions of 3-amino-2*H*-pyran-2-ones and chalcones with hydrazine hydrate [14].

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Microwave irradiation has been successfully applied as an alternative source of energy in organic chemistry. Spectacular accelerations, higher yields under milder reaction conditions, and higher product purities have been reported. Indeed, a number of authors have described success in reactions that do not occur by conventional heating, and even modifications of selectivity (chemo-, regio-, and stereoselectivity) have been found. The effects of microwave irradiation on organic synthesis reactions are caused by a combination of thermal effects, including the heating rate, superheating or "hot spots," and the selective absorption of radiation by polar substances. Such phenomena are not usually accessible by classical heating, and the existence of non-thermal effects such as highly polarizing radiation—the "specific microwave effect"—is still a controversial topic [16].

Continuing our work on the synthesis of pseudo-*C*-nucleosides bearing a pyrazole moiety, including the reaction of α,*β*-unsaturated esters with diazomethane followed by dehydrogenation of the intermediate pyrazoline with Cl_2/CCl_4, and the reaction of *β*-ketoesters with hydrazines [17], led us to study the reaction of a *β*-furanosidic *β*-formyl-α,*β*-unsaturated ester with hydrazine derivatives.

Results and discussion

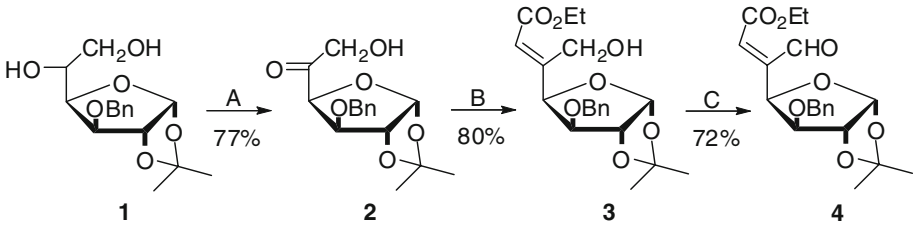
Chemistry

Our synthetic strategy started with the preparation of ethyl 3-*O*-benzyl-5,6-dideoxy-5-*C*-formyl-1,2-*O*-isopropylidene-α-D-*xylo*-hept-5-enofuranuronate (**4**, Scheme 1). The 5-hydroxyl group of 3-*O*-benzyl-1,2-isopropylidene-α-D-*xylo*-hexofuran-5-ulose (**1**) was oxidized with dibutyltin oxide (Bu_2SnO), followed by addition of NBS, and product **2** was obtained in 77% yield [18]. The carbon chain elongation of **2** was achieved using a Wittig type reaction with a stabilized phosphorane [(ethoxycarbonylmethylene)triphenylphosphorane], leading to **3** in 80% yield. Compound **4** was then obtained in 72% yield after oxidation of the 5-hydroxymethyl group of **3** with pyridinium chlorochromate (PCC)/molecular sieves 4 Å (powder).

The attempt to synthesize 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*allo*-hexafuran-5-ulose, an isomer of **2** bearing another configuration at C-3, was not successful. The oxidation of **5** with Bu_2SnO and NBS led to a new compound that was detected by TLC, but not isolated after workup, probably due to degradation. An alternative method involving the primary alcohol tritylation of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*allo*-furanose (**5**) was considered, and the protected derivative **6** was obtained in 90% yield (Scheme 2) [17]. The 5-hydroxyl group of **6** was oxidized with PCC to give **7** in 73% yield. Elongation of the carbon chain of **7,** using the same reaction conditions presented in Scheme 1, led to the formation of lactone **8** in 62% yield instead of the expected compound, ethyl 3-*O*-benzyl-5,6-dideoxy-5-*C*-hydroxymethyl-1,2-*O*-isopropylidene-α-D-*allo*-hept-5-(*E*)-enofuranuronate. The formation of this compound can be envisaged by considering a carbon chain elongation, then cleavage of the trityl group followed by lactone ring formation.

The reactivity of ethyl 3-*O*-benzyl-5,6-dideoxy-5-*C*-formyl-1,2-*O*-isopropylidene-α-D-*xylo*-hept-5-enofuranuronate (**4**) with methyl hydrazinocarboxylate (**9**), benzoylhydrazine (**10**), phenylhydrazine (**11**), and hydrazine hydrate (**12**) was studied by three methods (Scheme 3; Table 1). The treatment of **4** with hydrazine derivatives **9-11** in refluxing ethanol for 5 h (Method A) led to the formation of corresponding hydrazone derivatives **13-15**. However, when using hydrazine hydrate (**12**) a pyridazin-6-one **16** was obtained. These results indicate that the presence of electron-withdrawing groups on the hydrazone moiety of **13-15** prevents the formation of an heterocyclic ring, while in the absence of substitution on the hydrazone moiety the formation of a pyridazin-6-one ring **16** occurred. In this case the reaction was also faster; the product was obtained after 1 h, since longer reaction times led to the degradation of pyridazinone **16**. The formation of **16** can be envisaged by hydrazone formation followed by the attack of the nitrogen atom of the NH_2 group to the ester carbonyl

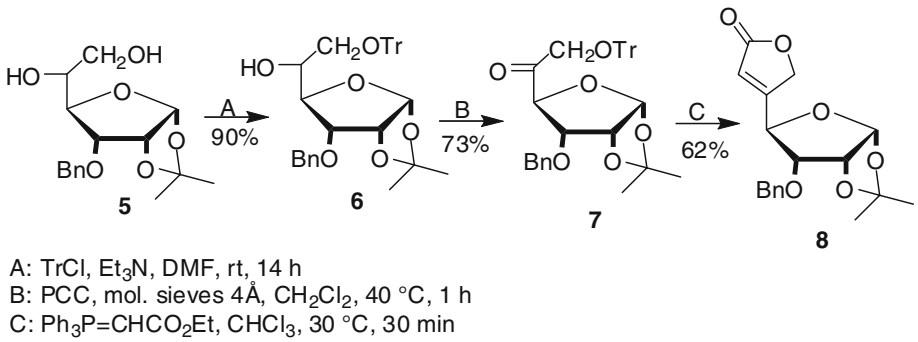
Scheme 1



A: 1) Bu_2SnO, $PhCH_3$, 120 °C, 6 h
2) NBS, $CHCl_3$, rt, 5 min

B: $Ph_3P{=}CHCO_2Et$, $CHCl_3$, 30 °C, 30 min
C: PCC, mol. sieves 4Å, CH_2Cl_2, rt, 10 min

Scheme 2



Scheme 3

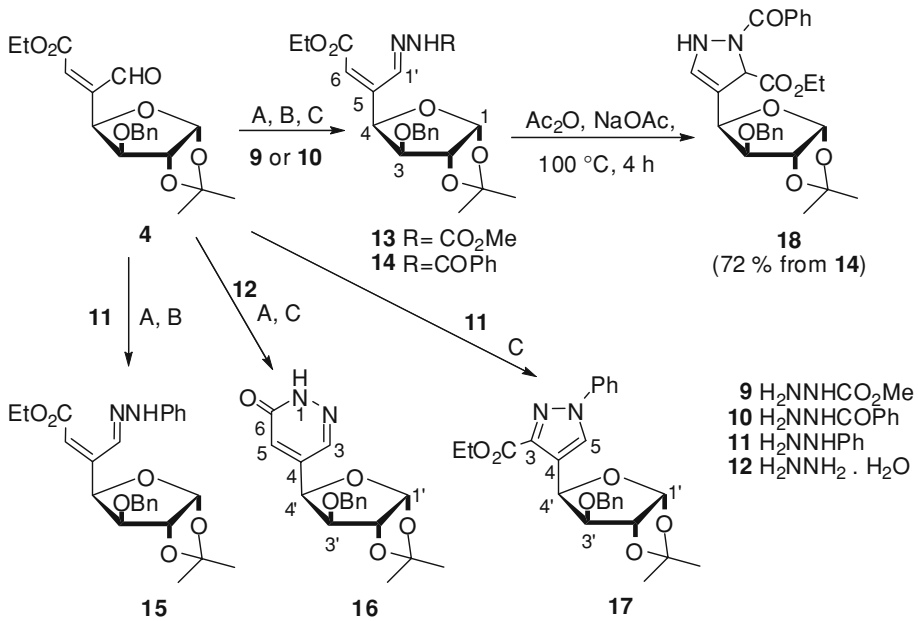


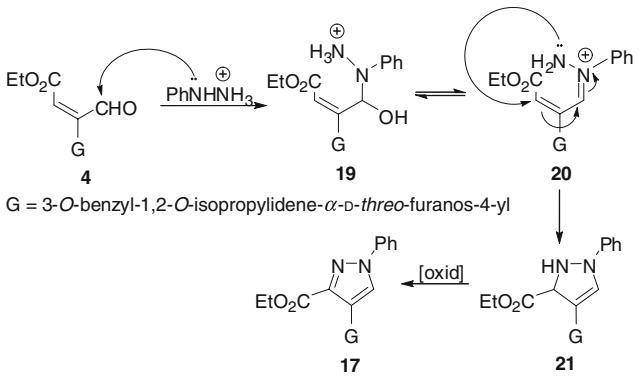
Table 1 Formation yields and reaction conditions in the treatment of **4** with hydrazine derivatives **9–12**

Method	Hydrazine derivatives	Time (min)	Product	Yield (%)
A EtOH, reflux	Methyl hydrazinocarboxylate (**9**)	300	**13**	81
	Benzoylhydrazine (**10**)	300	**14**	64
	Phenylhydrazine (**11**)	300	**15**	64
	Hydrazine hydrate (**12**)	60	**16**	45
B EtOH, MW (450 W)	**9**	6	**13**	86
	10	6	**14**	73
	11	6	**15**	71
C EtOH, AcOH, 80°C	**9**	180	**13**	66
	10	180	**14**	61
	11	180	**17**	69
	12	60	**16**	45

group, which then undergoes ethoxyl group elimination and intramolecular ring closure.

The reaction of **4** with the hydrazine derivatives **9–11** under microwave irradiation led to the formation of the same hydrazone derivatives **13–15** in better yields, a shorter reaction time, and using roughly half the amount of solvent (Method B).

The reaction of ethyl 3-*O*-benzyl-5,6-dideoxy-5-*C*-formyl-1,2-*O*-isopropylidene-α-D-*xylo*-hept-5-enofuranuronate (**4**) with hydrazine derivatives **9, 10**, and **12** in



Scheme 4

refluxing ethanol and using glacial acetic acid as catalyst (Method C) also led to the formation of **13, 14**, and **16** as referred to in Method A. However, the reaction of **4** with phenylhydrazine (**11**) led to the formation of a new pyrazole-type compound **17**. The formation of this product **17** can be envisaged by the mechanism depicted in Scheme 4. In the acidic medium protonation of the more nucleophilic nitrogen of the phenylhydrazine occurs, the secondary nitrogen atom then attacks the formyl group of **4** leading to the hydrazonium compound **20**, which gives **17** after cyclization and oxidation processes.

Intramolecular cyclization of **13** and **14** was tried, since it is known that compounds bearing hydrazone and α,β-unsaturated ester moieties in their structure can be cyclized with Ac_2O/NaOAc [17]. The TLC analysis of the reaction of **13** with Ac_2O/NaOAc, at 100°C for 8 h, revealed that no reaction occurred, and **13** was recovered. This reaction was repeated with **14**, and a new compound was detected. The product was identified as **18** (72%). It is possible to conclude that the intramolecular cyclization of **13** did not occur because the hydrazone moiety of this molecule is less reactive than the corresponding moiety of **14**.

Characterization of the obtained products

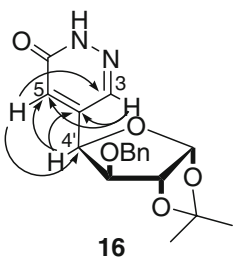
The main features of the ^{1}H NMR spectrum of compound **3** are the singlet at $\delta_H = 6.06$ ppm, due to the resonance of H-6, and a multiplet at $\delta_H = 4.59$–4.56 ppm, which is assigned to the methylene signals of the hydroxymethyl group. The ^{13}C NMR spectrum of **3** presented two quaternary carbon signals at $\delta_C = 165.5$ and 156.8 ppm, which were assigned to C-7 and C-5, while the signals at $\delta_C = 115.5$ and 63.5 ppm were attributed to C-6 and to the methylene carbon of the hydroxymethyl group. The ^{1}H and ^{13}C NMR spectra of **4** present new signals at $\delta_H = 9.86$ ppm, as a singlet, and $\delta_C = 192.0$ ppm, due to the proton and carbon resonances of the formyl group that has been formed.

The ^{1}H NMR spectrum of **7** showed a multiplet at $\delta_H = 7.45$–7.18 ppm, due to the aromatic protons of the benzyl and trityl groups, while the methylene protons of the benzyl group appear as an AB spin system ($J = 11.7$ Hz) at $\delta_H = 4.52$ and 4.37 ppm, and the H-6 resonance appears in a multiplet at $\delta_H = 3.34$–3.20 ppm. The resonance of the ketone carbonyl group of **7** appears at $\delta_C = 201.5$ ppm in the ^{13}C NMR spectrum. Besides the resonances of the aromatic and furanosidic carbons, it is possible to assign the signals at $\delta_C = 71.4$ and 63.6 ppm to the resonances of the benzyl group and C-6 methylene carbons. In the ^{1}H NMR spectrum of **8** the signals from the trityl group disappeared, and no signals from the ethyl group were detected. The vinyl and methylene protons of the lactone moiety of **8** appear, respectively, as a singlet at $\delta_H = 6.05$ ppm and as a multiplet at $\delta_H = 4.81$–4.51 ppm. The carbonyl carbon of the lactone moiety of **8** appears in the ^{13}C NMR spectrum at $\delta_C = 173.2$ ppm, whereas the signals of the other lactone carbons C-3, C-4, and C-5 appear at $\delta_C = 115.8$, 166.3, and 70.8 ppm.

The ^{1}H NMR spectra of hydrazones **13**, **14**, and **15** showed three singlets at $\delta_H = 10.41$–8.68, 8.19–7.78, and 6.85–6.34 ppm due to the resonances of NH, H-1′, and H-6, respectively. The ^{13}C NMR spectra of these compounds present the carbonyl carbon resonances of the unsaturated ester groups at $\delta_C = 166.6$–165.3 ppm and those of the hydrazone moiety at $\delta_C = 164.2$–154.0 ppm. Other important carbon resonances to be noticed are those of C-1′ and C-5 appearing at $\delta_C = 145.2$–133.8 and 146.6–145.8 ppm, respectively. The ^{1}H and ^{13}C NMR spectra of **13**, **14**, and **15** indicate the presence of only one isomer, which was assumed to be the (*E*) isomer of the hydrazone double bond, based on the literature data of other hydrazones [19, 20].

The ^{1}H NMR spectrum of **16** presented the proton resonances of the NH (broad singlet), H-3 (doublet), and H-5 (singlet) at, respectively, $\delta_H = 12.12$, 7.75, and 6.89 ppm. In the ^{13}C NMR spectrum the signals of the pyridazinone ring appear at $\delta_C = 162.0$, 142.7, 137.0, and 126.6 ppm and were assigned to the resonances of C-6, C-4, C-3, and C-5, respectively. In its HMBC spectrum, it was possible to observe connectivities of H-3 with C-4 and C-5, H-5 with C-3 and C-4′, and of H-4′ with C-4 and C-5 (Fig. 1).

Fig. 1 Most important correlations in HMBC spectrum of **16**



16

In the NMR spectra of **17**, the pyrazole signals appear at $\delta_H = 8.12$ ppm (H-5, as a singlet) and at $\delta_C = 140.7$, 129.1, and 122.1 ppm, assigned to C-4, C-5, and C-3, respectively.

Compound **18** was characterized by a ^{1}H NMR spectrum that showed two singlets at $\delta_H = 7.03$ and 5.94 ppm, which were assigned to the resonances of H-3 and H-5. The NH signal was not detected, but the IR spectrum showed a band at 3,241 cm^{-1} attributed to the NH vibration. The ^{13}C NMR spectrum presented signals at $\delta_C = 149.2$, 119.8, and 89.3 ppm, which were assigned to C-4, C-5, and C-3 of the pyrazoline ring.

Conclusions

We have prepared new pseudo-*C*-nucleosides bearing pyrazole and pyridazinone rings by the reaction of the appropriate *β*-sugar-*β*-formyl-α,*β*-unsaturated ester with hydrazine derivatives. Under neutral conditions (with classical heating or with microwave irradiation), hydrazones and a pseudo-*C*-nucleoside **16** were formed, while under acidic conditions the reaction with phenylhydrazine and hydrazine hydrate led to pseudo-*C*-nucleosides bearing a pyrazole and a pyridazinone ring, respectively. The cyclization of a *γ*-phenylhydrazono-α,*β*-unsaturated ester derivative with Ac_2O/NaOAc also leads to a pseudo-*C*-nucleoside.

Experimental

Melting points were determined on a Leitz-Biomed with platinum plate apparatus. Infrared (IR) spectral data were obtained using a FT-IR Mattson Genesis II spectrophotometer. NMR spectra were recorded on Bruker AC-P 250 (250.13 MHz for ^{1}H and 62.9 MHz for ^{13}C) and Bruker Avance 300 spectrometers (300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C), with $CDCl_3$ as solvent if not stated otherwise. Chemical shifts (δ) are reported in ppm values and coupling constants (J) in Hz. The internal standard was TMS. ^{13}C NMR assignments of compound **16** and **17** were made using 2D *g*HSQC and *g*HMBC (delays for one bond and long-range J C/H couplings were optimized for 145 and 7 Hz, respectively) experiments. Mass spectra were performed on an APEX III FT-ICR MS (Bruker Daltonics, Billerica, MA), equipped with a 7-T actively shielded magnet. Ions were generated using an Apollo API electrospray ionization (ESI) source. Ionization was achieved by an electrospray ionization source (Bruker Daltonics, Billerica, MA), with a voltage of between 1,800 and 2,200 V (to optimize ionization efficiency) applied to the needle, and counter voltage of 450 V applied to capillary. Samples were prepared by adding a spray solution of 50:49.5:0.5 (v/v/v) water/methanol/formic acid to the sample at a v/v ratio of 1–5% to give the best signal-to-noise ratio. Data acquisition and data processing were performed using the XMASS software version 6.1.2 (Bruker Daltonics). HRMSs were in good agreement (±0.5 ppm) with the calculated values. Elemental analyses were obtained with a Vario EL CHN analyzer (University of Beira Interior) and were in good agreement (±0.4%) with the calculated values. A domestic microwave oven (Electrolux, 850 W, 20-l capacity) was used in the reactions carried out under microwave irradiation. The progress of all reactions was monitored by thin-layer chromatography using aluminium sheets pre-coated with silica gel $60F_{254}$ to a thickness of 0.2 mm (Merck), and spots were developed in a UV chamber (256 nm) or with 3% of vanillin in ethanol/H_2SO_4 (100 cm^3/1.5 cm^3) followed by heating. Column chromatography (CC) was conducted under low pressure by elution of the columns filled with silica gel (0.040–0.063 mm, Merck). All other chemicals and solvents used were obtained from commercial sources and used as received or dried using standard procedures.

3-O-Benzyl-1,2-O-isopropylidene-α-D-xylo-hexafuran-5-ulose (**2**)

Yield: 0.24 g (77%); syrup; $R_f = 0.64$ (1:1 ethyl acetate:toluene); IR and ^{1}H NMR spectra were found to be identical with the ones described in Ref. [18].

Ethyl 3-O-benzyl-5,6-dideoxy-5-C-hydroxymethyl-1,2-O-isopropylidene-α-D-xylo-hept-5-(E)-enofuranuronate (**3**, $C_{20}H_{26}O_7$)

A solution of 0.72 g ethoxycarbonylmethylene triphenylphosphorane (2.03 mmol) in 5 cm^3 dry $CHCl_3$ was added dropwise to a solution of 1.11 g **2** (3.6 mmol) in 5.0 cm^3 dry $CHCl_3$. The mixture was stirred for 30 min at 30°C, concentrated, and the obtained residue was purified by CC eluting with a 1:5 mixture of ethyl acetate:toluene. Yield 0.28 g (80%); syrup; $R_f = 0.57$ (1:2 ethyl acetate:toluene); ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = 7.32$–7.22 (m, C_6H_5), 6.06 (s, H-6), 5.95 (d, $J = 3.4$ Hz, H-1), 4.59–4.56 (m, $CH_2C_6H_5$, CH_2OH, H-2, H-3, H-4), 4.05 (q, $J = 7.2$ Hz, CH_2CH_3), 2.92 (br s, CH_2OH), 1.48 and 1.31 [2 s, $C(CH_3)_2$], 1.22 (t, $J = 7.2$ Hz, CH_2CH_3) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 165.5$ (C-7), 156.8 (C-5), 137.0 (C-1, C_6H_5), 128.2, 128.0, 127.7 (CH, C_6H_5), 115.5 (C-6), 111.7 [$C(CH_3)_2$], 104.7 (C-1), 83.1 (C-3), 82.4 (C-2), 79.7 (C-4), 72.1 ($CH_2C_6H_5$), 63.5 (CH_2OH), 59.9 (CH_2CH_3), 26.7 and 26.2 [$C(CH_3)_2$], 14.0 (CH_2CH_3) ppm; IR (neat): $\bar{\nu} = 3{,}500$ (OH), 1,700 (C=O), 1,685 (C=C) cm^{-1}; ESI(+)-HRMS: found 379.1754 (379.1757 calcd for $C_{20}H_{27}O_7$).

Ethyl 3-O-benzyl-5,6-dideoxy-5-C-formyl-1,2-O-isopropylidene-α-D-xylo-hept-5-enofuranuronate (**4**, $C_{20}H_{24}O_7$)

A solution of 0.38 g **3** (1.00 mmol) in 0.8 cm^3 dry CH_2Cl_2 was added to a suspension of 0.63 g PCC (2.92 mmol) and 1.20 g molecular sieves 4 Å (powder) in 3.0 cm^3 dry

CH_2Cl_2, and the resulting mixture stirred for 10 min at room temperature. The reaction mixture was added to 40 cm^3 diethyl ether and strongly stirred for 20 min. The inorganic salts were separated by filtration, and the obtained solution was purified by florisil. Yield 0.27 g (72%); syrup; $R_f = 0.73$ (1:2 ethyl acetate:methanol); ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = 9.86$ (s, C*H*O), 7.37–7.23 (m, C_6H_5), 6.60 (s, H-6), 6.06 (d, $J = 3.7$ Hz, H-1), 5.86 (d, $J = 2.9$ Hz, H-4), 4.69 (d, $J = 3.7$ Hz, H-2), 4.60 and 4.43 (AB system, $J = 12.0$ Hz, $CH_2C_6H_5$), 4.32 (d, $J = 2.9$ Hz, H-3), 4.16 (q, $J = 7.0$ Hz, CH_2CH_3) 1.53 and 1.35 [2 s, $C(CH_3)_2$], 1.28 (t, $J = 7.0$ Hz, CH_2CH_3) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 192.0$ (*C*HO), 165.3 (*C*O_2*Et*), 143.4 (C-5), 136.9 (C-1, C_6H_5), 128.5, 127.9, 127.6 (CH, C_6H_5), 126.4 (C-6), 113.1 [*C*$(CH_3)_2$], 105.7 (C-1), 83.7 (C-4), 83.0 (C-2), 78.1 (C-3), 72.4 ($CH_2C_6H_5$), 61.3 (CH_2CH_3), 27.1 and 26.5 [C(CH_3)$_2$], 14.2 (CH_2CH_3) ppm; IR (neat): $\bar{\nu} = 1{,}720$ (C=O), 1,691 (C=C) cm^{-1}; ESI(+)-HRMS: found 377.1600 (377.1599 calcd for $C_{20}H_{25}O_7$).

3-O-Benzyl-1,2-O-isopropylidene-6-O-triphenylmethyl-α-D-ribo-hexafuranose (**6**)

Yield: 2.35 g (90%); syrup; $R_f = 0.69$ (2:1 ethyl acetate:toluene); IR and ^{1}H NMR spectra were found to be identical with the ones described in Ref. [17].

3-O-Benzyl-1,2-O-isopropylidene-6-O-triphenylmethyl-α-D-ribo-hexafuran-5-ulose (**7**, $C_{35}H_{34}O_6$)

A solution of 0.54 g **6** (1.00 mmol) dissolved in 1.5 cm^3 dry CH_2Cl_2 was added to a suspension of 1.0 g activated powdered molecular sieves 4 Å, and 0.66 g PCC (3.05 mmol) in 3.0 cm^3 dry CH_2Cl_2. The reaction mixture was stirred at 40°C for 1 h, and then added to 60 cm^3 diethyl ether under vigorous stirring. Inorganic salts were filtered, and the mixture was passed by florisil in vacuum until the filtrate was colorless. The solvent was evaporated at low temperature to give 0.38 g (73%) pure **7** (this compound is unstable and must be conserved at low temperature and freshly prepared to be used in the synthesis of **8**). Syrup; $R_f = 0.71$ (2:1 ethyl acetate:toluene); ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = 7.45$–7.18 (m, 20H, C_6H_5), 5.67 (d, $J = 3.6$ Hz, H-1), 4.52 and 4.37 (AB system, $J = 11.7$ Hz, $CH_2C_6H_5$), 4.42 (t, $J = 4.0$ Hz, H-2), 4.03 (d, $J = 8.7$ Hz, H-4), 3.85 (dd, H-3, $J = 4.0$, 8.7 Hz), 3.34–3.20 (m, CH_2-6), 1.54 and 1.31 [2 s, C(CH_3)$_2$] ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 201.5$ (C-5), 143.9, 143.7, 142.4 (C-1, C_6H_5), 137.1 (C-1, $CH_2C_6H_5$), 128.3, 128.0, 127.6, 127.5, 127.4, 127.1, 126.3, 124.6 (CH, C_6H_5), 112.1 [*C*$(CH_3)_2$], 103.4 (C-1), 86.1 [*C*$(C_6H_5)_3$], 77.8 (C-4), 77.0 (C-2), 76.1 (C-3), 71.4 ($CH_2C_6H_5$), 63.6 (CH_2-6), 26.2 and 25.9 [*C*$(CH_3)_2$] ppm; IR (neat): $\bar{\nu} = 1{,}710$ (C=O) cm^{-1}.

4-(3-O-Benzyl-1,2-O-isopropylidene-α-D-ribo-furanos-4-yl)-2(5H)-furanone (**8**, $C_{18}H_{20}O_6$)

Compound **8** was obtained by the method used in the preparation of **3**, followed by CC purification, eluting with a 1:5 mixture of ethyl acetate:toluene. Yield 0.21 g (62%); m.p.: 153–154°C; $R_f = 0.62$ (1:1 ethyl acetate:toluene); ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = 7.41$–7.22 (m, 5H, C_6H_5), 6.05 (s, H-3), 5.82 (d, $J = 3.6$ Hz, H-1′), 4.87 and 4.21 (AB system, $J = 8.6$ Hz, $CH_2C_6H_5$), 4.81–4.51 (m, H-2′, H-4′, CH_2-5), 3.64 (dd, $J = 4.1$, 9.3 Hz, H-3′), 1.61 and 1.38 [2 s, C(CH_3)$_2$] ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 173.2$ (C-2), 166.3 (C-4), 136.4 (C-1, C_6H_5), 128.7, 128.6, 128.3 (CH, C_6H_5), 115.8 (C-3), 113.6 [*C*$(CH_3)_2$], 104.4 (C-1′), 81.4 (C-2′), 76.8 (C-3′), 74.4 (C-4′), 72.4 ($CH_2C_6H_5$), 70.8 (C-5), 26.7 and 26.4 [C(CH_3)$_2$] ppm; IR (KBr): $\bar{\nu} = 1{,}710$ (C=O), 1,675 (C=C) cm^{-1}; ESI(+)-HRMS: found 333.1333 (333.1338 calcd for $C_{18}H_{21}O_6$).

General procedure for preparation of hydrazone derivatives

Method A

A solution of the appropriate hydrazine derivative (1.10 mmol) in 1 cm^3 ethanol was added dropwise to a solution of 0.38 g compound **4** (1.00 mmol) in 1.0 cm^3 ethanol. The mixture was stirred for the appropriate time (see Table 1) at 80°C, and then cooled to room temperature, concentrated, and the obtained residue was purified by CC. Reaction of methyl hydrazinocarboxylate (**9**) led to **13** in 81% yield (0.36 g); benzoylhydrazine (**10**) led to **14** in 64% yield (0.32 g); phenylhydrazine (**11**) led to **15** in 64% yield (0.30 g), and hydrazine hydrate (**12**) yielded **16** in 45% yield (0.16 g).

Method B

A mixture of hydrazine derivative (1.10 mmol) in 0.5 cm^3 ethanol was added dropwise to a solution of 0.38 g compound **4** (1.00 mmol) in 0.5 cm^3 ethanol. The mixture was heated in a microwave oven at 450 W for 6 min, the disappearance of the starting material being monitored every 2 min by TLC. The obtained residue, after concentration, was purified by CC. Reaction of **9** led to **13** in 86% yield (0.39 g); **10** led to **14** in 73% yield (0.36 g); **11** yielded **15** in 71% yield (0.33 g).

Method C

A solution of hydrazine derivative (1.10 mmol) in 1 cm^3 ethanol was added dropwise to a solution of 0.38 g **4** (1.00 mmol) in 1.0 cm^3 ethanol. Then glacial acetic acid (0.10 mmol) was added to the reaction mixture, which was heated at 80°C for the appropriate time (see Table 1). The disappearance of the starting material was monitored every

hour by TLC. The mixture was concentrated after cooling and purified by CC. **13** was obtained in 66% yield (0.30 g) by reaction with **9**; **10** reacted with **4** to form **14** in 61% yield (0.27 g); **11** led to **17** in 69% yield (0.31 g); **12** led to **16** in 45% yield (0.16 g).

Ethyl 3-O-benzyl-5,6-dideoxy-5-C-(methoxycarbonylhydrazonomethyl)-1,2-O-isopropylidene-α-D-xylo-hept-5-enofuranuronate (**13**, $C_{22}H_{28}N_2O_8$)

The obtained residue was purified by CC eluted with a 1:10 mixture of ethyl acetate:toluene. Syrup; $R_f = 0.63$ (4:1 ethyl acetate:toluene); ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = 8.95$ (s, N*H*), 7.78 (s, H-1′), 7.50–7.30 (m, C_6H_5), 6.74 (br s, H-6), 5.97 (d, $J = 3.7$ Hz, H-1), 5.91 (d, $J = 2.9$ Hz, H-4), 4.60 (d, $J = 3.7$ Hz, H-2), 4.53 and 4.40 (AB system, $J = 11.8$ Hz, C*H*$_2$C$_6$H$_5$), 4.33 (d, 1H, H-3), 4.10 (q, $J = 7.0$ Hz, C*H*$_2$CH$_3$), 3.79 (s, OC*H*$_3$), 1.50 and 1.30 [2 s, C(C*H*$_3$)$_2$], 1.24 (t, CH$_2$C*H*$_3$) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 165.3$ (*C*O$_2$*Et*), 154.0 (*C*O$_2$*Me*), 146.3 (C-5), 142.2 (C-1′), 136.8 (C-1, *C*$_6$H$_5$), 128.1, 128.0, 127.6 (CH, *C*$_6$H$_5$), 117.8 (C-6), 112.0 [*C*(CH$_3$)$_2$], 104.8 (C-1), 83.3 (C-3), 82.8 (C-2), 76.6 (C-4), 72.2 (*C*H$_2$C$_6$H$_5$), 60.2 (*C*H$_2$CH$_3$), 52.6 (OC*H*$_3$), 26.7, 26.2 [C(*C*H$_3$)$_2$], 13.9 (CH$_2$*C*H$_3$) ppm; IR (neat): $\bar{\nu} = 3{,}239$ (NH), 1,782 (C=O), 1,721 (C=O) cm^{-1}.

Ethyl 5-C-(benzoylhydrazonomethyl)-3-O-benzyl-5,6-dideoxy-1,2-O-isopropylidene-α-D-xylo-hept-5-enofuranuronate (**14**, $C_{27}H_{30}N_2O_7$)

The obtained residue was purified by CC eluted with a 1:5 mixture of ethyl acetate:toluene. Syrup; $R_f = 0.39$ (1:2 ethyl acetate:toluene); ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = 10.41$ (s, N*H*), 8.19 (s, H-1′), 7.86 (d, $J = 7.5$ Hz, C$_6$*H*$_5$), 7.46–7.16 (m, 8H, C$_6$*H*$_5$), 6.85 (s, H-6), 5.91 (d, $J = 3.9$ Hz, H-1), 5.82 (d, $J = 2.9$ Hz, H-4), 4.54–4.49 (m, H-2, C*H*$_2$C$_6$H$_5$), 4.39 (AB system, $J = 11.8$ Hz, C*H*$_2$C$_6$H$_5$), 4.30 (d, H-3), 4.07 (q, $J = 6.9$ Hz, C*H*$_2$CH$_3$), 1.44 and 1.25 [2 s, C(C*H*$_3$)$_2$], 1.23 (t, CH$_2$C*H*$_3$) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 165.5$ (*C*O$_2$*Et*), 164.2 (*C*OPh), 145.8 (C-5), 145.2 (C-1′), 136.7 (C-1, CH$_2$*C*$_6$H$_5$), 132.6 (C-1, *C*$_6$H$_5$), 131.8, 128.5, 128.2, 127.8, 127.7, 127.6, 127.5 (CH, *C*$_6$H$_5$), 118.9 (C-6), 111.9 [*C*(CH$_3$)$_2$], 104.9 (C-1), 83.4 (C-3), 82.9 (C-2), 78.0 (C-4), 72.4 (*C*H$_2$C$_6$H$_5$), 60.3 (*C*H$_2$CH$_3$), 26.7 and 26.2 [C(*C*H$_3$)$_2$], 13.9 (CH$_2$*C*H$_3$) ppm; IR (neat): $\bar{\nu} = 3{,}243$ (NH), 1,780 (C=O), 1,720 (C=O) cm^{-1}; ESI(+)-HRMS: found 495.2119 (495.2126 calcd for $C_{27}H_{31}N_2O_7$).

Ethyl 3-O-benzyl-5,6-dideoxy-5-C-(phenylhydrazonomethyl)-1,2-O-isopropylidene-α-D-xylo-hept-5-enofuranuronate (**15**, $C_{26}H_{30}N_2O_6$)

The obtained residue was purified by CC eluted with a 1:10 mixture of ethyl acetate:toluene. Syrup, $R_f = 0.47$ (1:2 ethyl acetate:toluene); ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = 8.68$ (s, N*H*), 8.04 (s, H-1′), 7.26–6.87 (m, 10H, C$_6$*H*$_5$), 6.34 (s, H-6), 6.03 (d, $J = 3.7$ Hz, H-1), 5.44 (d, $J = 3.2$ Hz, H-4), 4.64 (d, $J = 3.7$ Hz H-2,), 4.50 and 4.35 (AB system, $J = 11.7$ Hz, C*H*$_2$C$_6$H$_5$), 4.43 (d, $J = 3.2$ Hz, H-3), 4.17 (q, $J = 6.9$ Hz, *C*H$_2$CH$_3$), 1.56 and 1.37 [2 s, C(C*H*$_3$)$_2$], 1.27 (t, $J = 6.9$ Hz, CH$_2$C*H*$_3$) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 166.6$ (*C*O$_2$*Et*), 146.6 (C-5), 143.4 (C-1, CH$_2$*C*$_6$H$_5$), 137.1 (C-1, *C*$_6$H$_5$), 133.8 (C-1′), 129.2, 128.1, 128.0, 127.9, 127.6, 120.7, 112.7 (CH, *C*$_6$H$_5$), 116.6 (C-6), 111.8 [*C*(CH$_3$)$_2$], 104.1 (C-1), 83.1 (C-2), 82.8 (C-3), 78.7 (C-4), 72.3 (*C*H$_2$C$_6$H$_5$), 60.0 (*C*H$_2$CH$_3$), 27.0, 26.4 [C(*C*H$_3$)$_2$], 14.2 (CH$_2$*C*H$_3$) ppm; IR (neat): $\bar{\nu} = 3{,}241$ (NH), 1,723 (C=O) cm^{-1}.

4-(3-O-Benzyl-1,2-O-isopropylidene-α-D-threo-furanos-4-yl)pyridazin-6-one (**16**, $C_{18}H_{20}N_2O_5$)

The obtained residue was purified by CC eluted with a 1:3 mixture of ethyl acetate:toluene. Syrup; $R_f = 0.22$ (5:1 ethyl acetate:methanol); ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = 12.12$ (br s, H-1), 7.75 (d, $J = 1.9$ Hz, H-3), 7.30–7.06 (m, C$_6$*H*$_5$), 6.89 (s, H-5), 6.09 (d, $J = 3.7$ Hz, H-1′), 5.05 (d, $J = 2.5$ Hz, H-4′), 4.72 (d, $J = 3.7$ Hz, H-2′), 4.56 and 4.34 (AB system, $J = 12.1$ Hz, C*H*$_2$C$_6$H$_5$), 4.29 (d, $J = 2.5$ Hz, H-3′), 1.54 and 1.37 [2 s, C(C*H*$_3$)$_2$] ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 162.0$ (C-6), 142.7 (C-4), 137.0 (C-3), 136.2 (C-1, *C*$_6$H$_5$), 128.6, 128.3, 127.8 (CH, *C*$_6$H$_5$), 126.6 (C-5), 112.3 [*C*(CH$_3$)$_2$], 105.2 (C-1′), 82.4 (C-3′), 82.4 (C-2′), 78.8 (C-4′), 72.1 (*C*H$_2$C$_6$H$_5$), 26.8 and 26.1 [C(*C*H$_3$)$_2$] ppm; IR (neat): $\bar{\nu} = 3{,}241$ (NH), 1,784 (C=O), 1,592 (C=C) cm^{-1}; ESI(+)-HRMS: found 345.1442 (345.1450 calcd for $C_{18}H_{21}N_2O_5$).

Ethyl 4-(3-O-benzyl-1,2-O-isopropylidene-α-D-threo-furanos-4-yl)-1-phenylpyrazole-3-carboxylate (**17**, $C_{26}H_{28}N_2O_6$)

The obtained residue was purified by CC eluted with a 1:20 mixture of ethyl acetate:toluene. Syrup; $R_f = 0.58$ (1:2 ethyl acetate:toluene); ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = 8.12$ (s, H-5), 7.75–7.04 (m, C$_6$*H*$_5$), 6.07 (d, $J = 3.8$ Hz, H-1′), 5.74 (d, $J = 2.9$ Hz, H-4′), 4.74 (d, $J = 3.8$ Hz, H-2′), 4.48 and 4.23 (AB system, $J = 12$ Hz, C*H*$_2$C$_6$H$_5$), 4.36–4.28 (m, H-3′, *C*H$_2$CH$_3$), 1.57 and 1.37 [2 s, C(C*H*$_3$)$_2$], 1.33 (t, $J = 7.2$ Hz, CH$_2$C*H*$_3$) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 162.2$ (*C*O$_2$*Et*), 140.7 (C-4), 139.5 (C-1, C$_6$*H*$_5$-N), 137.2 (C-1, C$_6$*H*$_5$), 129.1 (C-5), 129.4, 128.3, 127.8, 127.7, 127.5, 119.9 (*C*H, C$_6$*H*$_5$), 122.1 (C-3), 111.8 [*C*(CH$_3$)$_2$], 104.5 (C-1′), 83.4 (C-2′), 81.6 (C-3′), 76.0 (C-4′), 72.2 (*C*H$_2$C$_6$H$_5$), 61.1 (*C*H$_2$CH$_3$), 26.9 and 26.3 [C(*C*H$_3$)$_2$], 14.2 (CH$_2$*C*H$_3$) ppm; IR (neat): $\bar{\nu} = 1{,}723$ (C=O), 1,595 (C=C) cm^{-1}; ESI(+)-HRMS: found 465.2008 (465.2026 calcd for $C_{26}H_{29}N_2O_6$).

Ethyl 2-benzoyl-4-(3-O-benzyl-1,2-O-isopropylidene-α-D-threo-furanos-4-yl)-2,3-dihydro-1H-pyrazole-3-carboxylate (**18**, $C_{27}H_{30}N_2O_7$)

A solution of 0.149 g sodium acetate (1.80 mmol) and 2.57 cm^3 acetic anhydride (2.73 mmol) was added dropwise with stirring to a mixture of 0.49 g hydrazone **14** (1.00 mmol) in 2.0 cm^3 dry $CHCl_3$. The mixture was stirred for 4 h at 100°C and then cooled to room temperature. The crude mixture was concentrated in a vacuum and extracted with $CHCl_3$ (3 × 45.0 cm^3). The organic layer was dried and the solvent evaporated. The obtained residue was purified by CC with a 1:10 mixture of ethyl acetate:toluene, and **18** was obtained as syrup. Yield 0.36 g (72%); $R_f = 0.48$ (2:1 ethyl acetate:toluene); ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = 7.75$–7.04 (m, 10H, C_6H_5), 7.03 (s, H-3), 6.12 (d, $J = 3.7$ Hz, H-1′), 5.94 (s, H-5), 5.89 (dd, $J = 4.0$, 2.0 Hz, H-4′), 4.63 (d, $J = 3.7$ Hz, H-2′), 4.50 (d, $J = 4.0$ Hz, H-3′), 4.43 and 4.30 (AB system, $J = 12.2$ Hz, $CH_2C_6H_5$), 4.00–3.95 (m, CH_2CH_3), 1.51 and 1.34 [2 s, $C(CH_3)_2$], 1.22 (t, $J = 7.2$ Hz, CH_2CH_3) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 164.8$ (CO_2Et), 156.5 ($COPh$), 149.2 (C-4), 137.3 (C-1, $CH_2C_6H_5$), 131.9 (C-1, C_6H_5), 131.5, 128.6, 128.2, 128.1, 127.7, 127.2 (CH, C_6H_5), 119.8 (C-5), 112.2 [$C(CH_3)_2$], 104.0 (C-1′), 89.3 (C-3), 83.4 (C-2′), 82.8 (C-3′), 80.1 (C-4′), 72.2 ($CH_2C_6H_5$), 60.7 (CH_2CH_3), 27.3 and 26.7 [$C(CH_3)_2$], 14.1 (CH_2CH_3) ppm; IR (neat): $\bar{\nu} = 3{,}241$ (NH) cm^{-1}.

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