Carbohydrate Research 344 (2009) 2113–2119

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Microwave-assisted efficient synthesis of glucose-based 3-acetyl-5-alkyl-2,3-dihydro-1,3,4-oxadiazole derivatives catalyzed by sodium acetate

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ARTICLE INFO

Article history:
Received 14 May 2009
Received in revised form 15 July 2009
Accepted 23 July 2009
Available online 28 July 2009

Keywords:
Carbohydrate
1,3,4-Oxadiazole derivatives
Antitumor activity
Microwave irradiation
Cyclization

ABSTRACT

A novel approach to synthesize glucose-based 3-acetyl-5-alkyl-2,3-dihydro-1,3,4-oxadiazoles with the assistance of microwave irradiation was developed. The effects of different catalysts on the heterocyclization process were investigated, and the reaction conditions were optimized, with NaOAc emerging as the catalyst of choice. Under the optimized conditions, a series of novel 3-acetyl-5-alkyl-2,3-dihydro-1,3,4-oxadiazole derivatives **4** and **5** were successfully synthesized from hydrazones **2** and **3**. The absolute configurations of hydrazones **2**, **3** and oxadiazoles **4**, **5** were confirmed by NMR spectroscopic data. The ratio of the isomers **4** and **5** was ~1:1.

1. Introduction

1,3,4-Oxadiazole compounds have shown a wide array of pharmacological activities, including antibacterial, anti-fungal, analgesic, anti-inflammatory, anti-hypertension, and muscle-relaxing activities. Consequently, they have attracted increasing attention in the field of drug discovery.[1–7] Various modifications of the structure of 1,3,4-oxadiazoles have been carried out,[8–10] to increase their hydrophobicity and bioavailability and transport across the intestinal membrane and the blood–brain barrier.[11–15] 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose has been used in the modification of various bioactive compounds, such as anticancer, antibacterial, immune modulating,[16] and photodynamic therapeutic agents.[17] Previously we have successfully synthesized a fructose-based 3-acetyl-2,3-dihydro-1,3,4-oxadiazole (GLB) and its 5-linear 5-alkyl derivatives; these derivatives showed moderate cytotoxic activities (Scheme 1).[18] A combination of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose and 3-acetyl-2,3-dihydro-1,3,4-oxadiazoles might lead to novel compounds with better bioactivities.[19–21] Therefore, we designed and synthesized a series of glucose-based 1,3,4-oxadiazole derivatives using microwave irradiation. Compared to the general microwave-assisted heterocyclic reactions that last several minutes,[22–26] the preparation of fructose-based 1,3,4-oxadiazole derivatives can only be completed after microwave irradiation for more than 30 min.[18] Apparently, further enhancement of the reaction rate is needed. Therefore, we attempted to improve the conditions of the reaction by the addition of catalysts such as a Lewis acid, a base, and an acetate.[27]

2. Results and discussion

D-Glucose reacted in anhydrous acetone with catalysis by zinc chloride to obtain 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, which was then oxidized by PDC and acetic anhydride to afford 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexos-3-ulose (**1**) in 52.5% yield.[28] Catalyzed by acetic acid, compound **1** reacted with hydrazines in methanol over a range of 12–24 h to give a mixture of *E*/*Z* hydrazones **2** and **3** (~1:1 ratio) in 70–90% yields (Table 1, Scheme 2). The R_f value of isomer **3** was smaller than that of isomer **2**.

The configurations of the hydrazones **2** and **3** were confirmed by their ^{1}H and ^{13}C NMR data. It was found in the ^{1}H NMR spectra that the chemical shifts of H-1, H-2, and H-4 of hydrazone **2** (δ 5.88–5.94, 5.03–5.14, and 4.16–4.25, respectively) were smaller than those of isomer **3** (δ 5.95–6.02, 5.33–5.55, and 4.27–4.32, respectively), and the chemical shift of H-4 of hydrazone **2** (δ 4.99–5.11) was larger than that of isomer **3** (δ 4.76–4.89). In the ^{13}C NMR spectra, both the C-1 and the C-5 of isomer **2** showed smaller chemical shifts than those of isomer **3**, and the chemical shifts of C-2, C-3, C-4, and C-6 of **2** were all larger than those of **3**. Moreover, the NOESY spectrum of isomers **3d** and **3e** showed a correlation between N–H and H-1 or H-2, and showed no correlation between N–H and H-4, indicating a *Z* configuration. The NOESY spectrum of isomers **2d** and **2e** showed a stronger correlation signal between N–H and H-4 than between N–H and H-2; therefore, **2** should be of the *E* configuration.

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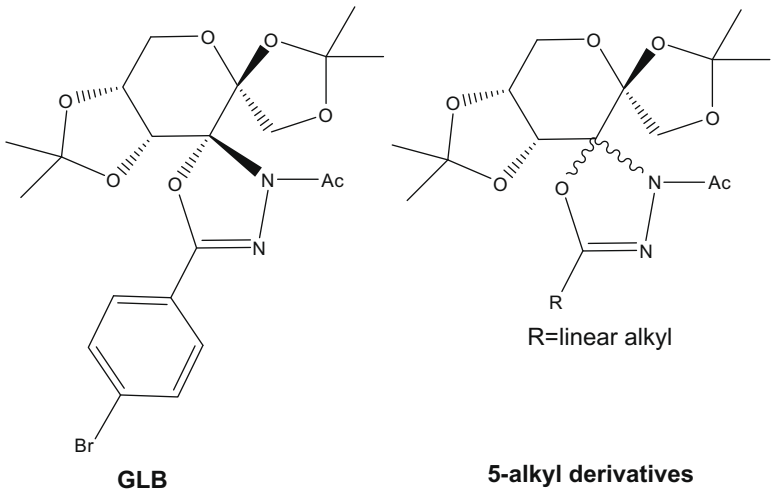
doi:10.1016/j.carres.2009.07.009

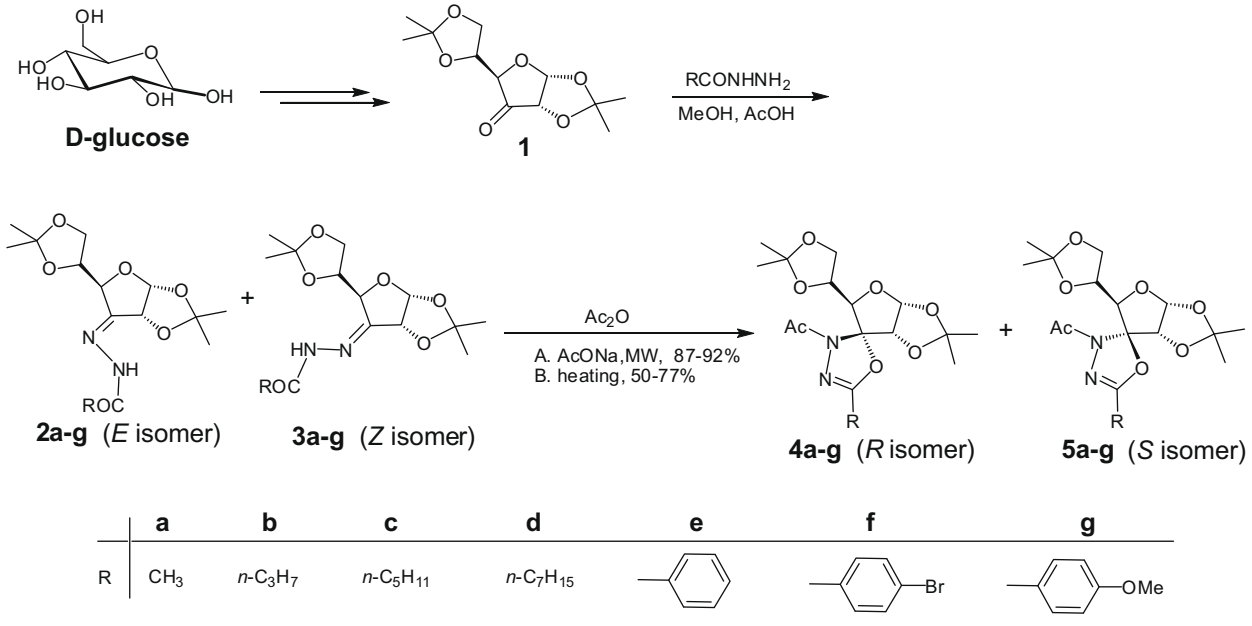


Scheme 1. GLB and its derivatives that have antitumor activity.

Table 1
Synthesis of **4** and **5** under microwave irradiation and with classical heating

	R	2+3		Microwave irradiation			Oil bath heating		
		Yield[a] (%)	Ratio (2:3)[b]	Time (min)	Yield[a] (%)	Ratio (4:5)[b]	Time (h)	Yield[a] (%)	Ratio (4:5)[b]
a	CH_3	92	1:1.1	10	92	1:1.4	24	77	1.5:1
b	n-C_3H_7	80	1:1.2	10	88	1.5:1	48	50	1.3:1
c	n-C_5H_{11}	86	1:1.1	10	91	1.3:1	24	61	1.3:1
d	n-C_7H_{15}	83	1:1.5	10	87	1:1.2	38	53	1.3:1
e	C_6H_5	87	1.4:1	10	90	1.3:1	12	73	1.7:1
f	p-Br–C_6H_4	84	1.2:1	10	91	1:1.3	12	70	1.2:1
g	p-OMe–C_6H_4	79	1.7:1	10	89	1.4:1	12	77	1.2:1

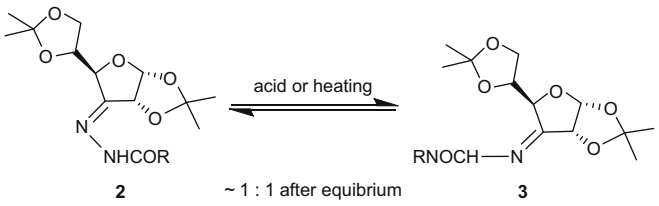
[a] Isolated yield.
[b] Isolated ratio.



Scheme 2. Synthesis of oxadiazoles **4** and **5**.

Equilibration (*syn–anti*) between the isomers **2** and **3** in solution was observed. Detailed investigation found that the equilibrium of **2b** and **3b** could be achieved in less than 5 min by heating (80 °C) or in the presence of acetic acid (<0.1%), the ratio of the isomers was round 1:1 after equilibrium (Scheme 3).

Hydrazones **2** and **3** reacted with acetic anhydride under microwave irradiation above 160 °C to produce the target products **4** and **5**, which were a pair of isomers on the C-3 of the furan ring. Given the high temperature and acidic conditions, the pure isomer of a hydrazone would isomerize (*syn–anti*) to reach equilibrium



Scheme 3. *syn–anti* Equilibration between isomers **2** and **3**.

between the isomers quickly. Therefore, a mixture of isomers **2** and **3** was used for the heterocyclization. Initially, the heterocyclization of **2c** and **3c** was carried out under our previously optimized microwave conditions at 160 °C for 30 min,[18] and oxadiazoles **4c** and **5c** were successfully obtained. In order to further optimize the conditions of the heterocyclization and decrease the reaction time under microwave irradiation, we investigated the effects of different promoters on the rate and yields of the microwave reaction. The results of the optimization are shown in Table 2.

First, we performed the reaction under microwave irradiation at 160 °C for a short time of 5 min to compare the effect of different catalysts. When the heterocyclization of **2c** and **3c** was catalyzed by Lewis acids such as $SnCl_4$, $ZnCl_2$, and $FeCl_3$, the reaction solution turned dark. Even though most of the reactants disappeared, the product yields were very low and large amounts of byproducts were generated. A yield of only 20% was obtained when 0.1 equiv of $FeCl_3$ was used. We presumed that the low yields of products **4c** and **5c** were caused by the Lewis acids, which could lead to the degradation of the reactants, and they showed no positive effects on the heterocyclization of hydrazones **2c** and **3c**.

In the presence of a base like pyridine and DAMP, the yields of heterocyclization increased to around 30% with 10–15% of the reactants still remaining. These results indicated that pyridine and DAMP could not accelerate the heterocyclization of **2c** and **3c**, but catalyzed the degradation of the reactants.

Among the several acetate salts examined as catalysts, the addition of NaOAc afforded the best results. Oxadiazoles **4c** and **5c** were obtained in 45% yields, and 40% of the reactants still remained when reacted at 160 °C for 5 min under microwave conditions. We assumed that NaOAc buffered the acetic acid generated in the reaction process and decreased the amount of acetic acid in the reaction mixture, resulting promotion of the reaction. As a result, byproducts generated by acetic acid decreased, resulting in higher yields of products. Therefore, NaOAc was selected to catalyze the heterocyclization of hydrazones **2** and **3** with the assistance of microwave irradiation.

We then optimized the temperature and time of the heterocyclization with sodium acetate as the catalyst. As shown in Table 2, the optimal conditions of cyclization of hydrazones were at 150 °C for 10 min with NaOAc as the catalyst, giving products up to 92%. Temperatures higher than 150 °C led to a decrease in the yields of products.

Under the optimized conditions of 150 °C for 10 min with the assistance of microwave irradiation, oxadiazoles **4a–g** and **5a–g** were successfully synthesized in excellent yields (Table 1). The ratios of the isomers **4a–g** and **5a–g** were always ~1:1. All of these oxadiazoles **4** and **5** were also synthesized under oil bath heating (no microwave irradiation) to compare the effect of these two methods. The results of the heterocyclization by oil bath heating are summarized in Table 1. Compared with traditional oil bath heating, heterocyclization of oxadiazoles **4** and **5** under microwave irradiation required a much shorter reaction time and produced higher yields of products.

As shown in Table 1, the ratio of the isomers of the heterocyclization of glucose-based hydrazones was always ~1:1 under both heating and microwave irradiation; therefore, the cyclization showed no stereoselectivity. The stereochemistry of the cyclization should be influenced by the steric hindrance of the two isopropylidene groups. Because the isopropylidene group is far from the C-3 position of the furan ring, the chance for the oxygen atom to attack the C-3 from the top or bottom of the furan rings is essentially the same. Therefore, the ratio of the *S*:*R* configuration of the product is ~1:1. We have reported that the *R* and *S* configurations of the fructose-based 1,3,4-oxadiazoles are determined by the *Z*/*E* configurations of the hydrazones.[18] In this paper, the ratio of isomers of the glucose-based 1,3,4-oxadiazoles **4** and **5** was about the same as the ratio of the isomers of the hydrazones **2** and **3**, which were both ~1:1. These results were in agreement with our previous conclusions.[18]

The configurations of C-3 of compounds **4** and **5** were assigned by their ^{1}H NMR, ^{13}C NMR, and NOESY spectra. It was found in the ^{1}H NMR spectra that the chemical shifts of H-1 and H-2 of all oxadiazoles **4** (δ 5.89–5.98 and 4.36–4.99, respectively) were smaller than those of isomer **5** (δ 5.95–6.22 and 4.72–5.33, respectively), and the chemical shift of H-4 of the hydrazone **4** (δ 5.45–5.68) was larger than that of isomer **5** (δ 4.09–4.76). In the ^{13}C NMR spectra, both the C-1 and the C-5 of isomer **4** showed smaller chemical shifts than those of **5**, and the chemical shifts of C-2, C-3, and C-4 of **4** were all larger than those of **5**. The 1D NOESY spectrum of **4b** and **4g** showed the strongest correlation between NAc and H-4, indicating that the Ac group of the oxadiazole ring is below the furan ring of the glucose; hence, the C-3 should be of the *R* configuration. Moreover, the 1D NOESY spectrum of **5b** and **5g** showed the strongest correlation between NAc and H-2, demonstrating that the Ac group is above the furan ring of glucose; therefore **5** should be of the *S* configuration.

Table 2
Microwave-assisted cyclization of **2c** and **3c** with different promoters

Entry	*T* (°C)	Promoter[a]	Time (min)	Reactant remaining[b] (%)	Yield (%) and ratio (4:5)[c]
1	160	$SnCl_4$	5	—	—
2	160	$ZnCl_2$	5	—	—
3	160	$FeCl_3$	5	—	20(1.1:1)
4	160	Pyridine	5	10	34(1.2:1)
5	160	DMAP	5	15	30(1.1:1)
6	160	NaOAc	5	40	45(1.3:1)
7	160	KOAc	5	45	40(1.2:1)
8	160	$Cu(OAc)_2$	5	—	—
9	160	NaOAc	10	—	80(1.1:1)
10	170	NaOAc	10	—	68(1.2:1)
11	150	NaOAc	10	—	92(1.3:1)
12	140	NaOAc	10	40	44(1.1:1)

[a] The amount of $SnCl_4$, $ZnCl_2$, $FeCl_3$, and DMAP is 0.1 equiv; the amount of NaOAc, KOAc, and $Cu(OAc)_2$ is 2.25 equiv; pyridine is used as a solvent with the same volume (0.5 mL) as Ac_2O.
[b] All reactions were performed with **2c** and **3c** (100 mg) and promoters in 1 mL of solvent under microwave irradiation.
[c] Isolated yield.

3. Conclusions

In summary, a novel approach to synthesize 3-acetyl-1,3,4-oxadiazole derivatives was developed with NaOAc as the catalyst under the assistance of microwave irradiation. Under the optimized conditions, a series of glucose-based 3-acetyl-1,3,4-oxadiazole derivatives **4** and **5** were synthesized from hydrazones **2** and **3** in good yields, and the ratio of the isomers **4** and **5** is ~1:1. The absolute configurations of hydrazones **2**, **3** and oxadiazoles **4**, **5** were confirmed by NMR data.

4. Experimental

4.1. General methods

Unless specified otherwise, all reactants and reagents were purchased commercially and used without further purification. Solvents were purified by standard procedures. Melting points were measured with an X4 melting-point apparatus and are uncorrected. Optical rotations were measured at 25 °C using an Optical Activity AA-10R automatic polarimeter. NMR spectra were recorded on a Jeol-300 instrument and a Varian Inova-500 instrument. Mass spectra were measured on an IBI-MDS Sciexciex Q-star or an FAB-MS mass spectrometer. Elemental analyses were determined on a Perkin–Elmer 240 C instrument. TLC was performed on Silica Gel GF254 plates (Hai Yang Chemical Factory, Qingdao, Shandong, PR China) with detection by UV fluorescence quenching and by spraying with 10% H_2SO_4. Column chromatography was performed on Silica Gel H60 (Hai Yang Chemical Factory, Qingdao, Shandong, PR China). Microwave reactions were conducted using a Biotage-Initiator EXP EO Microwave Synthesizer.

4.2. General procedures for the preparation of compounds 2a–g and 3a–g

AcOH (0.5 mL) was added slowly to a stirred solution of 1,2:4,5-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**1**) (2.0 g, 7.75 mmol) and the appropriate hydrazine (7.75 mmol) in MeOH (40.0 mL) at room temperature (reflux at 60 °C for aromatic substituted compounds). The reaction was monitored by TLC (1:3 petroleum ether–EtOAc) until the reactant disappeared after ~12–24 h; the solvent was then evaporated. The residual foam was separated by column chromatography to obtain hydrazone isomers **2** and **3**, respectively. See Section 4.4 for characterization and physicochemical and spectral data.

4.3. General procedures for the preparation of compounds 4a–g and 5a–g under microwave irradiation

A mixture of **2** and **3** (2.0 mmol) was dissolved in Ac_2O (1.0 mL) and boiled at 150 °C under microwave heating for 10 min in the microwave initiator. The solution was concentrated, and the residual solvent was removed by adding toluene and evaporating under reduced pressure three times. The residual foam was purified by chromatography (1:8 EtOAc–cyclohexane) to afford oxadiazoles **4** and **5**, respectively. See Section 4.4 for characterization and physicochemical and spectral data.

4.4. Compounds 2–5

4.4.1. (*E*)-1,2:5,6-Di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose acetylhydrazone (2a)

Colorless foam; $[\alpha]_D^{25}$ +106.7 (*c* 1.50, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 5.89 (d, 1H, $J_{1,2}$ 4.5 Hz, H-1), 5.03 (d, 1H, H-2), 5.00 (d, 1H, H-4), 4.17 (m, 1H, H-5), 4.04 (m, 1H, H-6a), 3.80 (m, 1H, H-6b), 2.08 (s, 3H, CH_3CO), 1.41–1.24 (m, 12H, $CH_3 \times 4$); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 172.3 (C=O), 151.2 (C-3), 112.8, 109.8 (CMe_2), 103.3 (C-1), 79.5 (C-2), 76.9 (C-5), 75.4 (C-4), 66.3 (C-6), 27.5, 26.0, 25.1, 21.6 20.0 ($C(CH_3)_2$, $COCH_3$); HRESIMS: Calcd for $C_{14}H_{22}N_2O_6$: 315.1551 $[M+H]^+$. Found: 315.1546 $[M+H]^+$.

4.4.2. (*Z*)-1,2:5,6-Di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose acetylhydrazone (3a)

Colorless foam; $[\alpha]_D^{26}$ +237.8 (*c* 0.74, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 10.60 (s, 1H, NH), 5.96 (d, 1H, $J_{1,2}$ 4.2 Hz, H-1), 5.35 (d, 1H, H-2), 4.79 (d, 1H, H-4), 4.29 (m, 1H, H-5), 4.02 (m, 1H, H-6a), 3.98 (m, 1H, H-6b), 2.05 (s, 3H, CH_3CO), 1.46–1.04 (m, 12H, $CH_3 \times 4$); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 172.4 (C=O), 152.9 (C-3), 112.7, 108.8 (CMe_2), 104.5 (C-1), 78.1 (C-2), 77.1 (C-5), 74.0 (C-4), 63.5 (C-6), 27.2, 26.1, 25.1, 21.5, 20.2 ($C(CH_3)_2$, $COCH_3$); HRESIMS: Calcd for $C_{14}H_{22}N_2O_6$: 315.1551 $[M+H]^+$. Found: 315.1545 $[M+H]^+$.

4.4.3. (*E*)-1,2:5,6-Di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose butyrylhydrazone (2b)

Colorless foam; $[\alpha]_D^{25}$ −85.7 (*c* 0.98, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 5.88 (d, 1H, $J_{1,2}$ 3.3 Hz, H-1), 5.04 (d, 1H, H-2), 4.99 (d, 1H, H-4), 4.16 (m, 1H, H-5), 4.01 (m, 1H, H-6a), 3.84 (m, 1H, H-6b), 2.15 (t, 2H, CH_2CO), 1.56–0.84 (m, 17H, $CH_3 \times 4$, C_2H_5); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 174.6 (C=O), 153.8 (C-3), 112.7, 109.8 (CMe_2), 103.3 (C-1), 79.5 (C-2), 76.9 (C-5), 75.0 (C-4), 66.3 (C-6), 33.5, 27.3, 26.6, 26.0, 25.2, 17.5, 13.7 ($C(CH_3)_2$), C_3H_7); HRESIMS: Calcd for $C_{16}H_{26}N_2O_6$: 343.1864 $[M+H]^+$. Found: 343.1863 $[M+H]^+$.

4.4.4. (*Z*)-1,2:5,6-Di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose butyrylhydrazone (3b)

Colorless foam, $[\alpha]_D^{25}$ −125.7 (*c* 1.40, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 5.98 (d, 1H, $J_{1,2}$ 4.5 Hz, H-1), 5.34 (d, 1H, H-2), 4.78 (d, 1H, H-4), 4.28 (m, 1H, H-5), 4.02 (m, 1H, H-6a), 3.97 (m, 1H, H-6b), 2.24 (t, 2H, CH_2CO), 1.58–0.86 (m, 17H, $CH_3 \times 4$, C_2H_5); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 174.6 (C=O), 153.0 (C-3), 112.7, 108.9 (CMe_2), 104.5 (C-1), 78.4 (C-2), 77.2 (C-5), 74.0 (C-4), 63.7 (C-6), 33.8, 27.2, 27.0, 26.0, 25.3, 18.5, 13.8 ($C(CH_3)_2$, C_3H_7); HRESIMS: Calcd for $C_{16}H_{26}N_2O_6$: 343.1864 $[M+H]^+$. Found: 343.1867 $[M+H]^+$.

4.4.5. (*E*)-1,2:5,6-Di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose hexanoylhydrazone (2c)

Colorless foam; $[\alpha]_D^{25}$ +166.0 (*c* 1.03, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 10.29 (s, 1H, NH), 5.88 (d, 1H, $J_{1,2}$ 4.2 Hz, H-1), 5.04 (d, 1H, H-2), 5.00 (d, 1H, H-4), 4.18 (m, 1H, H-5), 4.04 (m, 1H, H-6a), 3.79 (m, 1H, H-6b), 2.16 (t, 2H, CH_2CO), 1.53–0.83 (m, 21H, $CH_3 \times 4$, C_4H_9); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 153.8 (C-3), 112.7, 109.8 (CMe_2), 103.3 (C-1), 79.5 (C-2), 76.9 (C-5), 75.0 (C-4), 66.2 (C-6), 31.5, 30.9, 27.5, 27.3, 26.0, 25.2, 23.8, 22.0, 13.9 ($C(CH_3)_2$, C_5H_{11}); HRESIMS: Calcd for $C_{18}H_{30}N_2O_6$: 371.2177 $[M+H]^+$. Found: 371.2171 $[M+H]^+$.

4.4.6. (*Z*)-1,2:5,6-Di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose hexanoylhydrazone (3c)

Colorless foam; $[\alpha]_D^{25}$ +212.0 (*c* 1.17, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 10.51 (s, 1H, NH), 5.96 (d, 1H, $J_{1,2}$ 4.8 Hz, H-1), 5.34 (d, 1H, H-2), 4.78 (d, 1H, H-4), 4.28 (m, 1H, H-5), 3.96–3.82 (m, 2H, H-6a, H-6b), 2.25 (t, 2H, CH_2CO), 1.55–0.82 (m, 21H, $CH_3 \times 4$, C_4H_9); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 150.1 (C-3), 112.7, 108.9 (CMe_2), 104.5 (C-1), 78.4 (C-2), 77.2 (C-5), 74.0 (C-4), 63.7 (C-6), 31.8, 31.0, 27.3, 27.1, 26.1, 25.1, 24.0, 22.0, 13.9 ($C(CH_3)_2$, C_5H_{11}); HRESIMS: Calcd for $C_{18}H_{30}N_2O_6$: 371.2177 $[M+H]^+$. Found: 371.2175 $[M+H]^+$.

4.4.7. (*E*)-1,2:5,6-Di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose octanoylhydrazone (2d)

Colorless foam; $[\alpha]_D^{25}$ +137.3 (*c* 1.02, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 10.29 (s, 1H, NH), 5.88 (d, 1H, $J_{1,2}$ 4.2 Hz, H-1), 5.04 (d, 1H, H-2), 5.02 (d, 1H, H-4, *J* 3.6 Hz), 4.16 (m, 1H, H-5), 4.04 (m, 1H, H-6a), 3.77 (m, 1H, H-6b), 2.17 (t, 2H, CH_2CO), 1.53–0.82 (m, 25H, $CH_3 \times 4$, C_6H_{13}). HRESIMS: Calcd for $C_{20}H_{34}N_2O_6$: 399.2490 $[M+H]^+$. Found: 399.2490 $[M+H]^+$.

4.4.8. (*Z*)-1,2:5,6-Di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose octanoylhydrazone (3d)

Colorless foam; $[\alpha]_D^{25}$ −140.9 (*c* 1.02, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 10.50 (s, 1H, NH), 5.95 (d, 1H, $J_{1,2}$ 5.4 Hz, H-1), 5.33 (d, 1H, H-2), 4.76 (d, 1H, H-4), 4.27 (d, 1H, H-5), 3.92–3.81 (m, 2H, H-6), 2.24 (m, 2H, CH_2CO), 1.51–0.83 (m, 25H, $CH_3 \times 4$, C_6H_{13}); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 150.1 (C-3), 112.7, 108.9 (*C*Me$_2$), 104.5 (C-1), 78.4 (C-2), 77.2 (C-5), 74.0 (C-4), 63.8 (C-6), 33.7, 31.8, 31.2, 28.5, 27.3, 27.0, 26.1, 25.3, 24.3, 22.1, 14.0 (C(*C*H$_3$)$_2$, C_7H_{15}); HRESIMS: Calcd for $C_{20}H_{34}N_2O_6$: 399.2490 $[M+H]^+$. Found: 399.2492 $[M+H]^+$.

4.4.9. (*E*)-1,2:5,6-Di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose benzoylhydrazone (2e)

White amorphous solid; mp 188–190 °C; $[\alpha]_D^{25}$ +130.0 (*c* 0.77, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 10.93 (s, 1H, NH), 7.82 (d, 2H, H-2′, H-6′), 7.62 (dd, 1H, H-4′), 7.55 (d, 2H, H-3′, H-5′), 5.94 (d, 1H, $J_{1,2}$ 3.9 Hz, 1H), 5.14 (d, 1H, H-2), 5.10 (m, 1H, H-4), 4.22 (m, 1H, H-5), 4.12 (t, 1H, H-6a), 3.89 (t, 1H, H-6b), 1.24–1.39 (m, 12H, $CH_3 \times 4$); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 163.4 (C=O), 155.8 (C-3), 133.2 (C-1′), 132.2 (C-4′), 128.6 (C-3′, C-5′), 127.5 (C-2′, C-6′), 112.8, 110.2 (*C*Me$_2$), 103.2 (C-1), 79.9 (C-2), 77.4 (C-4), 74.8 (C-5), 66.8 (C-6), 27.5, 27.2, 26.0, 25.3 (C(*C*H$_3$)$_2$). HRESIMS: Calcd for $C_{19}H_{24}N_2O_6$: 377.1707 $[M+H]^+$. Found: 377.1702 $[M+H]^+$.

4.4.10. (*Z*)-1,2:5,6-Di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose benzoylhydrazone (3e)

White amorphous solid; mp 165–166 °C; $[\alpha]_D^{25}$ +177.1 (*c* 0.70, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 11.05 (s, 1H, NH), 7.78 (d, 2H, H-2′, H-6′), 7.57–7.52 (m, 3H, H-3′, H-4′, H-5′), 5.99 (s, 1H, $J_{1,2}$ 4.5 Hz, H-1), 5.53 (s, 1H, H-2), 4.86 (s, 1H, H-4), 4.30 (m, 1H, H-5), 3.96 (m, 1H, H-6a), 3.87 (m, 1H, H-6b), 1.37–1.25 (m, 12H, $CH_3 \times 4$); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 156.6 (C-3), 133.3 (C-1′), 132.0 (C-4′), 128.5 (C-3′, C-5′), 128.0 (C-2′, C-6′), 112.8, 109.0 (*C*Me$_2$), 104.6 (C-1), 78.8 (C-2), 77.4 (C-4), 75.0 (C-5), 63.6 (C-6), 27.4, 27.0, 26.1, 25.1 (C(*C*H$_3$)$_2$); HRESIMS: Calcd for $C_{19}H_{24}N_2O_6$: 377.1707 $[M+H]^+$. Found: 377.1705 $[M+H]^+$.

4.4.11. (*E*)-1,2:5,6-Di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose *p*-bromobenzoylhydrazone (2f)

White amorphous solid; mp 220–221 °C; $[\alpha]_D^{25}$ +133.3 (*c* 0.48, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 10.92 (s, 1H, NH), 7.78 (s, 4H, H-2′, H-3′, H-5′, H-6′), 5.94 (d, 1H, $J_{1,2}$ 4.2 Hz, H-1), 5.14 (1H, H-2), 5.11 (1H, H-4), 4.25 (m, 1H, H-5), 4.11 (dd, 1H, H-6a), 3.87 (dd, 1H, H-6b), 1.25–1.39 (m, 12H, $CH_3 \times 4$); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 162.5 (C=O), 156.5 (C-3), 132.2 (C-1′), 131.7 (C-3′, C-5′), 129.6 (C-2′, C-6′), 125.9 (C-4′), 112.8, 110.2 (*C*Me$_2$), 103.2 (C-1), 79.8 (C-2), 77.4 (C-4), 74.8 (C-5), 66.7 (C-6), 27.5, 27.3, 26.1, 25.3 (C(*C*H$_3$)$_2$); HRESIMS: Calcd for $C_{19}H_{23}BrN_2O_6$: 455.0812 $[M+H]^+$. Found: 455.0806 $[M+H]^+$.

4.4.12. (*Z*)-1,2:5,6-Di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose *p*-bromobenzoylhydrazone (3f)

White amorphous solid; mp 141–142 °C; $[\alpha]_D^{25}$ +196.9 (*c* 0.65, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 11.18 (s, 1H, NH), 7.76 (s, 4H, H-2′, H-3′, H-5′,H-6′), 6.02 (d, 1H, $J_{1,2}$ 4.5 Hz, H-1), 5.52 (s, 1H, H-2), 4.89 (s, 1H, H-4), 4.32 (m, 1H, H-5), 3.98, 3.88 (m, 2H, H-6), 1.26–1.38 (m, 12H, $CH_3 \times 4$); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 162.8 (C=O), 157.0 (C-3), 132.4 (C-1′), 131.5 (C-3′, C-5′), 130.0 (C-2′, C-6′), 125.7 (C-4′), 112.8, 109.0 (*C*Me$_2$), 104.5 (C-1), 78.8 (C-2), 77.3 (C-4), 74.9 (C-5), 63.6 (C-6), 27.4, 27.0, 26.1, 25.1 (C(*C*H$_3$)$_2$); HRESIMS: Calcd for $C_{19}H_{23}BrN_2O_6$: 455.0812 $[M+H]^+$. Found: 455.0805 $[M+H]^+$.

4.4.13. (*E*)-1,2:5,6-Di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose *p*-methoxylbenzoylhydrazone (2g)

White amorphous solid; mp 162–163 °C; $[\alpha]_D^{25}$ −102.4 (*c* 1.25, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 10.81 (s, 1H, NH), 7.78 (d, 2H, H-2′, H-6′), 7.05 (d, 2H, H-3′, H-5′), 5.91 (d, 1H, $J_{1,2}$ 3.9 Hz, H-1), 5.11 (d, 1H, H-2), 5.05 (d, 1H, *J* 8.1 Hz, H-4), 4.23 (m, 1H, H-5), 4.10 (m, 1H, H-6a), 3.90 (m, 1H, H-6b), 3.88 (s, 3H, OCH_3), 1.38–1.25 (m, 12H, $CH_3 \times 4$); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 162.4 (C=O), 155.0 (C-3), 129.6 (C-1′), 125.0 (C-3′, C-5′), 113.9 (C-2′, C-6′), 112.8 (C-4′), 110.3 (*C*Me$_2$), 103.2 (C-1), 100.2, 80.0 (C-2), 77.5 (C-4), 74.9 (C-5), 66.9 (C-6), 55.6 (OCH_3), 27.6, 27.3, 26.2, 25.5 (C(*C*H$_3$)$_2$); HRESIMS: Calcd for $C_{20}H_{26}N_2O_7$: 407.1813 $[M+H]^+$. Found: 407.1811 $[M+H]^+$.

4.4.14. (*Z*)-1,2:5,6-Di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose *p*-methoxylbenzoylhydrazone (3g)

White amorphous solid; mp 161–162 °C; $[\alpha]_D^{25}$ −230.3 (*c* 0.66, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 10.89 (s, 1H, NH), 7.81 (d, 2H, H-2′, H-6′), 7.06 (d, 2H, H-3′, H-5′), 6.01 (d, 1H, $J_{1,2}$ 4.5 Hz, H-1), 5.55 (d, 1H, H-2), 4.86 (s, 1H, H-4), 4.30 (m, 1H, H-5), 3.98, 3.96 (m, 2H, H-6a, H-6b), 3.88 (s, 3H, OCH_3), 1.38–1.27 (m, 12H, $CH_3 \times 4$); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 130.1, 125.3 (C-4′), 113.7, 112.7 (*C*Me$_2$), 108.9 (C-1), 104.4, 94.6, 78.7 (C-2), 77.3 (C-4), 74.8 (C-5), 63.6 (C-6), 55.4 (OCH_3), 27.4, 26.9, 26.1, 25.1 (C(*C*H$_3$)$_2$); HRESIMS: Calcd for $C_{20}H_{26}N_2O_7$: 407.1813 $[M+H]^+$. Found: 407.1811 $[M+H]^+$.

4.4.15. (3*R*)-4′-*N*-Acetyl-1,2:4,5-di-*O*-isopropylidene-2′-methyl-*spiro*-[3-deoxy-α-D-*ribo*-hexofuranos-3-*C*-3-yl-3,5′-[1,3,4]-oxadiazoline] (4a)

Colorless foam; $[\alpha]_D^{25}$ −55.4 (*c* 0.65, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 5.89 (d, 1H, $J_{1,2}$ 3.9 Hz, H-1), 5.57 (d, 1H, H-2), 4.39 (d, 1H, H-4), 4.18–4.01 (m, 3H, H-5, H-6), 2.21 (s, 3H, CH_3C=N), 2.05 (s, 3H, CH_3CO), 1.64–1.24 (m, 12H, $CH_3 \times 4$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 168.4 (C=O), 153.0 (C=N), 114.1, 109.6 (*C*Me$_2$), 103.8 (C-1), 103.1 (C-3), 83.2 (C-2), 72.9 (C-4), 72.5 (C-5), 67.4 (C-6), 26.9, 26.2, 26.0, 25.2, 23.4, 11.1 (C(*C*H$_3$)$_2$, CO*C*H$_3$); HRESIMS: Calcd for $C_{16}H_{24}N_2O_7$: 357.1656 $[M+H]^+$. Found: 357.1657 $[M+H]^+$.

4.4.16. (3*S*)-4′-*N*-Acetyl-1,2:4,5-di-*O*-isopropylidene-2′-methyl-*spiro*-[3-deoxy-α-D-*ribo*-hexofuranos-3-*C*-3-yl-3,5′-[1,3,4]-oxadiazoline] (5a)

Colorless foam; $[\alpha]_D^{25}$ −11.6 (*c* 1.03, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 6.18 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 4.80 (d, 1H, H-2), 4.10 (d, 1H, H-4), 4.09–3.99 (m, 3H, H-5, H-6), 2.27 (s, 3H, CH_3C=N), 2.02 (s, 3H, CH_3CO), 1.62–1.24 (m, 12H, $CH_3 \times 4$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 167.4 (C=O), 155.2 (C=N), 113.3, 109.5 (*C*Me$_2$), 106.1 (C-1), 103.8 (C-3), 82.7 (C-2), 81.7 (C-4), 73.8 (C-5), 67.4 (C-6), 27.0, 26.6, 25.1, 22.0, 11.3 (C(*C*H$_3$)$_2$, CO*C*H$_3$); HRESIMS: Calcd for $C_{16}H_{24}N_2O_7$: 357.1656 $[M+H]^+$. Found: 357.1658 $[M+H]^+$.

4.4.17. (3*R*)-4′-*N*-Acetyl-1,2:4,5-di-*O*-isopropylidene-2′-propyl-*spiro*-[3-deoxy-α-D-*ribo*-hexofuranos-3-*C*-3-yl-3,5′-[1,3,4]-oxadiazoline] (4b)

Colorless foam; $[\alpha]_D^{25}$ −57.1 (*c* 0.63, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 5.89 (d, 1H, $J_{1,2}$ 3.9 Hz, H-1), 5.58 (d, 1H, H-4), 4.38 (d, 1H, H-2), 4.37–4.01 (m, 3H, H-5, H-6), 2.36 (m, 2H, CH_2C=N), 2.24 (s, 3H, CH_3CO), 1.67–0.94 (m, 17H, $CH_3 \times 4$, C_2H_5); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 168.6 (C=O), 155.8 (C=N), 114.0, 109.6

(*C*Me$_2$), 103.9 (C-1), 103.1 (C-3), 83.1 (C-2), 72.8 (C-4), 72.6 (C-5), 67.4 (C-6), 27.2, 26.6, 26.3, 26.0, 25.2, 23.5, 13.3 (C(*C*H$_3$)$_2$, *C*OC$_3$H$_7$); HRESIMS: Calcd for $C_{18}H_{28}N_2O_7$: 385.1969 [M+H]$^+$. Found: 385.1968 [M+H]$^+$.

4.4.18. (3*S*)-4′-*N*-Acetyl-1,2:4,5-di-*O*-isopropylidene-2′-propyl-*spiro*-[3-deoxy-α-D-*ribo*-hexofuranos-3-*C*-3-yl-3,5′-[1,3,4]-oxadiazoline] (5b)

Colorless foam; $[\alpha]_D^{25}$ −33.8 (*c* 1.30, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 6.10 (d, 1H, $J_{1,2}$ 3.9 Hz, H-1), 4.72 (d, 1H, H-2), 4.03∼3.94 (m, 4H, H-4, H-5, H-6), 2.26 (m, 2H, *J* 7.5 Hz, $CH_2C{=}N$), 2.20 (s, 3H, CH_3CO), 1.65–0.93 (m, 17H, $CH_3 \times 4$, C_2H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.5 (C=O), 158.1 (C=N), 113.3, 109.6 (*C*Me$_2$), 106.1 (C-1), 103.6 (C-3), 82.8 (C-2), 82.0 (C-4), 73.7 (C-5), 67.5 (C-6), 27.4, 27.0, 26.9, 26.7, 25.2, 22.1, 18.8, 13.7 (C(*C*H$_3$)$_2$, *C*OC$_3$H$_7$); HRESIMS: Calcd for $C_{18}H_{28}N_2O_7$: 385.1969 [M+H]$^+$. Found: 385.1965 [M+H]$^+$.

4.4.19. (3*R*)-4′-*N*-Acetyl-1,2:4,5-di-*O*-isopropylidene-2′-pentyl-*spiro*-[3-deoxy-α-D-*ribo*-hexofuranos-3-*C*-3-yl-3,5′-[1,3,4]-oxadiazoline] (4c)

Colorless foam; $[\alpha]_D^{25}$ −32.8 (*c* 1.34, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 5.97 (d, 1H, $J_{1,2}$ 4.2 Hz, H-1), 5.45 (d, 1H, H-4), 4.47 (d, 1H, H-2), 4.12 (m, 1H, H-5), 4.08 (m, 1H, H-6a), 4.03 (m, 1H, H-6b), 2.36 (t, 2H, $CH_2C{=}N$), 2.05 (s, 3H, CH_3CO), 1.58–0.85 (m, 21H, $CH_3 \times 4$, C_4H_9); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 167.2 (C=O), 156.1 (C=N), 112.6, 108.7 (*C*Me$_2$), 103.4 (C-1), 102.1 (C-3), 82.1 (C-2), 82.8 (C-4), 72.1 (C-5), 66.2 (C-6), 30.2, 26.6, 25.9, 25.8, 24.8, 24.5, 23.2, 21.7, 13.8 (C(*C*H$_3$)$_2$, *C*OC$_5$H$_{11}$); HRESIMS: Calcd for $C_{20}H_{32}N_2O_7$: 413.2282 [M+H]$^+$. Found: 413.2278 [M+H].

4.4.20. (3*S*)-4′-*N*-Acetyl-1,2:4,5-di-*O*-isopropylidene-2′-pentyl-*spiro*-[3-deoxy-α-D-*ribo*-hexofuranos-3-*C*-3-yl-3,5′-[1,3,4]-oxadiazoline] (5c)

Colorless foam; $[\alpha]_D^{25}$ −18.2 (*c* 1.10, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 6.16 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 4.78 (d, 1H, H-2), 4.09–4.01 (m, 4H, H-4, H-5, H-6), 2.36 (t, 2H, $CH_2C{=}N$), 2.30 (s, 3H, CH_3CO), 1.68–0.90 (m, 21H, $CH_3 \times 4$, C_4H_9; ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 158.4 (C=N), 113.3, 109.6 (*C*Me$_2$), 106.0 (C-1), 103.6 (C-3), 82.7 (C-2), 81.9 (C-4), 73.7 (C-5), 67.4 (C-6), 31.2, 27.0, 26.7, 25.5, 25.2, 25.0, 22.2, 22.1, 13.9 (C(*C*H$_3$)$_2$, *C*OC$_5$H$_{11}$); HRESIMS: Calcd for $C_{20}H_{32}N_2O_7$: 413.2282 [M+H]$^+$. Found: 413.2278 [M+H]$^+$.

4.4.21. (3*R*)-4′-*N*-Acetyl-1,2:4,5-di-*O*-isopropylidene-2′-heptyl-*spiro*-[3-deoxy-α-D-*ribo*-hexofuranos-3-*C*-3-yl-3,5′-[1,3,4]-oxadiazoline] (4d)

Colorless foam; $[\alpha]_D^{25}$ +7.62 (*c* 1.05, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 5.89 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 5.59 (d, 1H, H-4), 4.36 (d, 1H, H-2), 4.13–4.02 (m, 3H, H-5, H-6), 2.36 (t, 2H, $CH_2C{=}N$), 2.20 (s, 3H, CH_3CO), 1.64–0.88 (m, 27H, $CH_3 \times 4$, C_6H_{13}); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 168.6 (C=O), 156.0 (C=N), 114.1, 109.6 (*C*Me$_2$), 103.7 (C-1), 102.9 (C-3), 83.2 (C-2), 72.9 (C-4), 72.6 (C-5), 67.5 (C-6), 31.6, 29.0, 28.7, 27.0, 26.3, 26.1, 25.3, 25.2, 24.3, 22.5, 14.0 (C(*C*H$_3$)$_2$, *C*OC$_7$H$_{15}$); HRESIMS: Calcd for $C_{22}H_{36}N_2O_7$: 441.2595 [M+H]$^+$. Found: 441.2592 [M+H]$^+$.

4.4.22. (3*S*)-4′-*N*-Acetyl-1,2:4,5-di-*O*-isopropylidene-2′-heptyl-*spiro*-[3-deoxy-α-D-*ribo*-hexofuranos-3-*C*-3-yl-3,5′-[1,3,4]-oxadiazoline] (5d)

Colorless foam; $[\alpha]_D^{25}$ −7.62 (*c* 1.05, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 5.90 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 5.60 (d, 1H, H-2), 4.37 (d, 1H, H-4), 4.16–4.00 (m, 3H, H-5, H-6), 2.35 (t, 2H, $CH_2C{=}N$), 2.21 (s, 3H, CH_3CO), 1.65–0.85 (m, 27H, $CH_3 \times 4$, C_6H_{13}); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 167.5 (C=O), 158.4 (C=N), 113.3, 109.6 (*C*Me$_2$), 106.0 (C-1), 103.6 (C-3), 82.7 (C-2), 82.0 (C-4), 73.7 (C-5), 67.5 (C-6), 31.7, 29.1, 28.7, 26.9, 26.3, 26.2, 25.4, 25.3, 24.4, 22.5, 14.0 (C(*C*H$_3$)$_2$, *C*OC$_7$H$_{15}$); HRESIMS: Calcd for $C_{22}H_{36}N_2O_7$: 441.2595 [M+H]$^+$. Found: 441.2599 [M+H]$^+$.

4.4.23. (3*R*)-4′-*N*-Acetyl-1,2:4,5-di-*O*-isopropylidene-2′-phenyl-*spiro*-[3-deoxy-α-D-*ribo*-hexofuranos-3-*C*-3-yl-3,5′-[1,3,4]-oxadiazoline] (4e)

Colorless foam; $[\alpha]_D^{25}$ −58.3 (*c* 0.96, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.82 (dd, 2H, H-2′, H-6′), 7.52 (m, 3H, H-3′, H-4′, H-5′), 5.98 (d, $J_{1,2}$ 4.2 Hz, 1H, H-1), 5.68 (d, 1H, H-4), 4.49 (d, 1H, H-2), 4.26 (m, 1H, H-5), 4.13 (m, 2H, H-6), 2.35 (s, 3H, CH_3CO), 1.67–1.21 (m, 12H, $CH_3 \times 4$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 168.7 (C=O), 152.8 (C=N), 131.6 (C-4′), 128.7 (C-1′), 126.7 (C-2′, C-6′), 124.3 (C-3′, C-5′), 114.2, 109.7 (*C*Me$_2$), 103.8 (C-1), 103.6 (C-3), 83.1 (C-2), 76.5 (C-4), 72.9 (C-5), 67.2 (C-6), 27.0, 26.1, 25.2, 22.7 (C(*C*H$_3$)$_2$); HRESIMS: Calcd for $C_{21}H_{26}N_2O_7$: 419.1813 [M+H]$^+$. Found: 419.1804 [M+H]$^+$.

4.4.24. (3*S*)-4′-*N*-Acetyl-1,2:4,5-di-*O*-isopropylidene-2′-phenyl-*spiro*-[3-deoxy-α-D-*ribo*-hexofuranos-3-*C*-3-yl-3,5′-[1,3,4]-oxadiazoline] (5e)

Colorless foam; $[\alpha]_D^{25}$ −59.1 (*c* 1.10, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.86 (dd, 2H, H-2′, H-6′), 7.47 (m, 3H, H-3′, H-4′, H-5′), 6.22 (d, 1H, $J_{1,2}$ 3.9 Hz, H-1), 4.87 (d, 1H, H-2), 4.24–4.03 (m, 3H, H-4, H-5, H-6), 2.36 (s, 3H, CH_3CO), 1.67–1.22 (m, 2H, $CH_3 \times 4$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 167.0 (C=O), 153.3 (C=N), 131.9 (C-4′), 129.0 (C-1′), 126.4 (C-2′, C-6′), 123.7 (C-3′, C-5′), 112.6, 108.8 (*C*Me$_2$), 105.5 (C-1), 104.0 (C-3), 81.9 (C-2), 81.4 (C-4) 73.4 (C-5), 66.6 (C-6), 26.9, 26.1, 25.1, 21.9 (C(*C*H$_3$)$_2$); HRESIMS: Calcd for $C_{21}H_{26}N_2O_7$: 419.1813 [M+H]$^+$. Found: 419.1803 [M+H]$^+$.

4.4.25. (3*R*)-4′-*N*-Acetyl-1,2:4,5-di-*O*-isopropylidene-2′-*p*-bromophenyl-*spiro*-[3-deoxy-α-D-*ribo*-hexofuranos-3-*C*-3-yl-3,5′-[1,3,4]-oxadiazoline] (4f)

White amorphous solid; mp 220–221 °C; $[\alpha]_D^{25}$ +118.9 (*c* 0.74, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.69 (dd, 2H, H-2′, H-6′), 7.58 (dd, 2H, H-3′, H-5′), 5.98 (d, 1H, $J_{1,2}$ 4.2 Hz, H-1), 5.64 (d, 1H, H-4), 4.48 (d, 1H, H-2), 4.22 (m, 1H, H-5), 4.10 (m, 2H, H-6), 2.32 (s, 3H, CH_3CO), 1.67, 1.33, 1.20 (m, 12H, $CH_3 \times 4$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 168.7 (C=O), 152.0 (C=N), 132.0 (C-3′, C-5′), 128.1 (C-2′, C-6′), 126.1 (C-1′), 123.2 (C-4′), 114.2, 109.7 (*C*Me$_2$), 103.9 (C-1), 103.8 (C-3), 83.1 (C-2), 76.5 (C-4), 72.8 (C-5), 67.3 (C-6), 26.9, 26.2, 25.2, 23.5 (C(*C*H$_3$)$_2$); HRESIMS: Calcd for $C_{21}H_{25}BrN_2O_7$: 497.0918 [M+H]$^+$. Found: 497.0928 [M+H]$^+$.

4.4.26. (3*S*)-4′-*N*-acetyl-1,2:4,5-di-*O*-isopropylidene-2′-*p*-bromophenyl-*spiro*-[3-deoxy-α-D-*ribo*-hexofuranos-3-*C*-3-yl-3,5′-[1,3,4]-oxadiazoline] (5f)

Colorless foam; $[\alpha]_D^{25}$ +32.0 (*c* 1.00, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.74 (d, 2H, H-2′, H-6′), 7.58 (dd, 2H, H-3′, H-5′), 6.20 (d, 1H, $J_{1,2}$ 3.9 Hz, H-1), 4.86 (d, 1H, H-2), 4.20 (m, 1H, H-4), 4.11 (m, 1H, H-5), 4.06, 4.04 (m, 2H, H-6), 2.37 (s, 3H, CH_3CO), 1.66, 1.38, 1.17, 1.11 (m, 12H, $CH_3 \times 4$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 167.9 (C=O), 153.9 (C=N), 131.9 (C-3′, C-5′), 128.3 (C-2′, C-6′), 126.1 (C-1′), 123.2 (C-4′), 113.4, 109.6 (*C*Me$_2$), 106.1 (C-1), 104.7 (C-3), 82.7 (C-2), 81.9 (C-4), 73.9 (C-5), 67.3 (C-6), 27.0, 26.8, 25.1, 22.1 (C(*C*H$_3$)$_2$); HRESIMS: Calcd for $C_{21}H_{25}BrN_2O_7$: 497.0918 [M+H]$^+$. Found: 497.0920 [M+H]$^+$.

4.4.27. (3*R*)-4′-*N*-Acetyl-1,2:4,5-di-*O*-isopropylidene-2′-*p*-methoxylphenyl-*spiro*-[3-deoxy-α-D-*ribo*-hexofuranos-3-*C*-3-yl-3,5′-[1,3,4]-oxadiazoline] (4g)

White amorphous solid; mp 153–154 °C; $[\alpha]_D^{25}$ −52.7 (*c* 0.91, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.76 (dd, 2H, H-2′, H-6′), 6.94 (dd, 2H, H-3′, H-5′), 5.98 (d, 1H, $J_{1,2}$ 4.2 Hz, H-1), 5.68 (d, 1H, H-4), 4.48 (d, 1H, H-2), 4.25 (m, 1H, H-5), 4.09 (dd, 2H, H-6), 3.87 (s, 3H, OCH_3), 2.32 (s, 3H, CH_3CO), 1.67–1.22 (m, 12H, $CH_3 \times 4$);

^{13}C NMR (75 MHz, $CDCl_3$): δ_C 168.6 (C=O), 162.3 (C-4′), 152.8 (C=N), 128.5 (C-3′, C-5′), 116.5 (C-2′, C-6′), 114.1, 109.6 (CMe_2), 103.9 (C-1), 103.3 (C-3), 83.1 (C-2), 77.4 (C-4), 72.9 (C-5), 67.1 (C-6), 55.4 (OCH_3), 27.0, 26.3, 25.2, 23.4 ($C(CH_3)_2$); HRESIMS: Calcd for $C_{22}H_{28}N_2O_8$: 449.1918 $[M+H]^+$. Found: 449.1919 $[M+H]^+$.

4.4.28. (3*S*)-4′-*N*-acetyl-1,2:4,5-di-*O*-isopropylidene-2′-*p*-methoxylphenyl-*spiro*-[3-deoxy-α-D-*ribo*-hexofuranos-3-*C*-3-yl-3,5′-[1,3,4]-oxadiazoline] (5g)

White solid; mp 152–153 °C; $[\alpha]_D^{25}$ −50.8 (*c* 0.63, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.80 (dd, 2H, H-2′, H-6′), 6.94 (dd, 2H, H-3′, H-5′), 6.21 (d, 1H, $J_{1,2}$ 3.9 Hz, H-1), 4.87 (d, 1H, H-2), 4.21 (d, 1H, H-4), 4.13–4.00 (m, 3H, H-5, H-6), 3.84 (s, 3H, OCH_3), 2.38 (s, 3H, CH_3CO), 1.66–1.14 (m, 12H, $CH_3 \times 4$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 167.7 (C=O), 162.1 (C-4′), 154.7 (C=N), 128.7 (C-3′, C-5′), 116.5 (C-2′, C-6′), 114.0, 109.6 (CMe_2), 106.1 (C-1), 104.1 (C-3), 82.8 (C-2), 81.8 (C-4), 73.9 (C-5), 67.3 (C-6), 55.3 (OCH_3), 27.0, 26.8, 25.1, 22.1 ($C(CH_3)_2$); HRESIMS: Calcd for $C_{22}H_{28}N_2O_8$: 449.1918 $[M+H]^+$. Found: 449.1916 $[M+H]^+$.

Acknowledgment

This work was supported by the National Natural Science Foundation of China (20732001, 30672525).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2009.07.009.

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