Synthesis and NMR Analysis of Spiranic Heterocycles from Carbohydrate Derivatives

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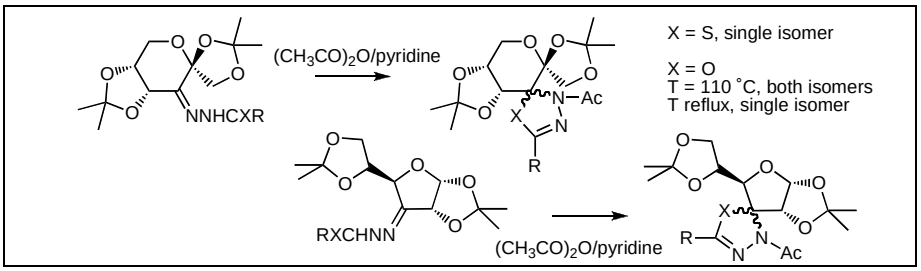

We report the synthesis of some furanose and pyranose acylhydrazones and their heterocyclization products. The new compounds were characterized physically and spectroscopically and the *syn-anti* and (*R*)-(*S*) configuration was determined by NOESY experiments. We discuss the influence of the nucleophile, the temperature and the precursor structure on the heterocyclization products.

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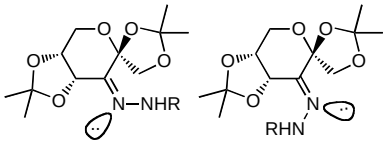
INTRODUCTION

In our previous papers we have reported the synthesis, characterization and bioactivity of some spiranic 1,3,4-thiadiazolines and their thiosemicarbazone precursors [1-4]. In this work we extended this methodology to prepare other spiranic compounds from cyclic ketose derivatives. We thus performed the synthesis of thiosemicarbazone, benzoylhydrazone, and semicarbazone of 1,2:4,5-di-*O*-isopropylidene-β-D-*erythro*-hexo-2,3-diulo-2,6-pyranose. We submitted them to cyclization reaction and the products were physically and spectroscopically characterized.

RESULTS AND DISCUSSION

We synthesized thiosemicarbazone, benzoylhydrazone and semicarbazone from commercial 1,2:4,5-di-*O*-isopropylidene-β-D-*erythro*-hexo-2,3-diulo-2,6-pyranose. In all the cases we obtained a mixture of *syn* and *anti* isomers: 1,2:4,5-di-*O*-isopropylidene-β-D-*erythro*-hexo-2,3-diulo-2,6-pyranose thiosemicarbazone (**1** and **2**), 1,2:4,5-di-*O*-isopropylidene-β-D-*erythro*-hexo-2,3-diulo-2,6-pyranose benzoylhydrazone (**3** and **4**), and 1,2:4,5-di-*O*-isopropylidene-β-D-*erythro*-hexo-2,3-diulo-2,6-pyranose semicarbazone (**5** and **6**) (Scheme I).

Since compounds **5** and **6** displayed different chromatographic behavior it was possible to separate them from the mixture. Pure compounds **5** and **6** were spectroscopically characterized and 2D-NOESY experiments were used to assign them the *syn* or *anti* configuration [5].



Scheme 1

Cross peaks between H-1b and –N*H*CONH$_2$ for compound **5** (higher Rf) and a similar correlation between H-4 and –N*H*CONH$_2$ for isomer **6** indicated that compound **5** had the *syn* configuration while compound **6** had the *anti* configuration. We were able to observe other correlations in both spectra, like those between vicinal protons and those with methyl groups but they were not diagnostic to stereochemistry determination of C=N linkage.

Compounds **1**+**2** and **3**+**4** were characterized as two mixtures using mono- and bidimensional NMR techniques (COSY, HSQC), and, in both cases, we were able to individualize two series of values, one of them showed a very good correlation with compound **5** values, while the other one correlated with displacements of compound **6**.

Taking these facts into account, we assigned the *syn* and *anti* configuration of compounds **1** of **4** (Tables 1-3).

Table 1

^{1}H NMR displacements (δ) for compound **1**-**6** and **10-12**, measured at 500 MHz in deuteriochloroform.

Compound	H-1a	H-1b	H-4	H-5	H-6a	H-6b
1	4.13	4.13	4.72	4.46	3.79	3.72
3	4.26	4.22	5.13	4.47	3.82	3.77
5	4.15	4.11	4.73	4.43	3.81	3.73
10	4.14	4.11	4.75	4.46	3.80	3.74
2	4.69	4.04	5.03	4.33	4.26	4.08
4	5.07	4.12	5.13	4.39	4.32	4.10
6	4.69	4.08	5.00	4.33	4.26	4.07
11	4.75	4.05	4.96	4.31	4.26	4.06
12	4.64	4.13	4.72	4.38	4.21	3.99

Table 2

Coupling constant (Hz) for compounds **1**-**6** and **10-12**, measured at 500 MHz in deuteriochloroform.

Compound	$J_{1a,1b}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
1	0	8.0	0	1.5	13.5
3	10.0	7.5	0	1.5	13.0
5	9.6	7.6	1.1	1.7	13.4
10	9.7	7.7	0	1.7	13.2
2	9.0	5.5	2.0	0	13.5
4	[a]	4.0	0	0	13.3
6	9.1	5.0	2.2	1.1	13.4
11	9.0	5.6	2.2	2.0	13.2
12	9.3	6.2	2.3	0.7	13.1

[a] Not measurable by signal superposition.

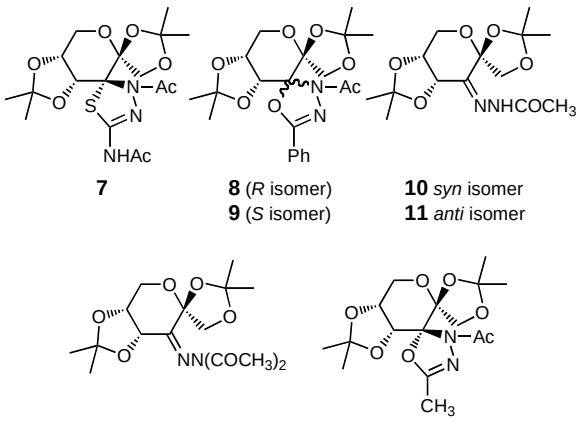
Table 3

^{13}C NMR displacements (δ) for compound **1**-**6** and **10-12**, measured at 125 MHz in deuteriochloroform.

Compound	C-1	C-2	C-3	C-4	C-5	C-6
1	74.2	103.3	139.9	75.8	74.5	64.8
3	74.3	103.4	145.2	76.0	74.4	65.0
5	73.7	103.2	137.5	76.0	74.3	64.7
10	74.1	103.2	139.1	76.1	74.4	64.8
2	71.5	103.7	142.2	72.2	74.4	59.3
4	71.3	104.0	145.2	72.9	74.7	58.9
6	71.9	103.8	139.9	71.4	74.1	59.3
11	71.1	103.9	141.1	71.6	74.2	59.2
12	72.5	104.4	169.6	72.1	75.5	61.9

As we have previously described, the cyclization of some aldose thiosemicarbazones is not selective, and both possible thiadiazolines can be obtained [6-8]. On the other hand, when we used thiosemicarbazones of chiral cyclic ketone as starting material, the cyclization took place by a preferential side, and a single spiranic compound was obtained. This behavior was typical of thiosemicarbazones derived from camphor, fenchone, menthone [2], and 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose [1].

In this work we analyzed the cyclization reaction products of compounds **1**-**6**, under standard conditions (Procedure I, see Experimental), and the obtained products are shown in Scheme II.



7 **8** (*R* isomer) **9** (*S* isomer) **10** *syn* isomer **11** *anti* isomer

12 **13**

Scheme II

Cyclization of thiosemicarbazone derivatives (**1**+**2**) gave (3*R*)-2'-acetamido-4'-*N*-acetyl-1,2:4,5-di-*O*-isopropylidenespiro[3-deoxy-β-D-*erythro*-hexopyranose-3,5'-[1,3,4]thiadiazoline] (**7**) as the only spiranic heterocycle.

The (3*R*)- and (3*S*)-4'-*N*-acetyl-1,2:4,5-di-*O*-isopropylidene-2'-phenylspiro[3-deoxy-β-D-*erythro*-hexopyranose-3,5´-[1,3,4]oxadiazoline] (**8**+**9**) were obtained from benzoylhydrazones (**3**+**4**) using Procedure I.

Semicarbazones **5** and **6** (as a mixture), treated in a similar way, did not yield spiranic derivatives, and we isolated degradation products, which were characterized as *syn*- and *anti*-1,2:4,5-di-*O*-isopropylidene-β-D-*erythro*-hexo-2,3-diulo-2,6-pyranose acetylhydrazone (**10** and **11**), and 1,2:4,5-di-*O*-isopropylidene-β-D-*erythro*-hexo-2,3-diulo-2,6-pyranose diacetylhydrazone (**12**, Tables 1-3). This degradative process had already been observed in other thiosemicarbazone [2] and semicarbazone [8] cyclization.

L. Somogyi has reported that acetylhydrazones are capable of yielding methyl-1,3,4-oxadiazolines [8] with more drastic conditions, therefore we treated mixture **10**+**11** using Procedure II (see Experimental), and obtained (3*R*)-4'-*N*-acetyl-1,2:4,5-di-*O*-isopropylidene-2'-methylspiro[3-deoxi-β-D-*erythro*-hexopyranose-3,5´-[1,3,4]oxadiazoline] (**13**) as the main product (Scheme II). The same treatment on **5**+**6** mixture as starting material led us to similar results.

According to these facts, we performed the cyclization on the mixture of benzoylhydrazones **3**+**4** using Procedure II, and found only compound **8**. Compounds **7**-**9** and **13** were spectroscopically characterized and their assignments are shown in Tables 4-6.

The stereochemistry of compound **8** was determined by NOESY experiments (see Experimental). We identified all methyl groups, and found a correlation between methyl-(d) group and the aromatic signals, which indicated that the cyclization took place by the α side (Figure 1).

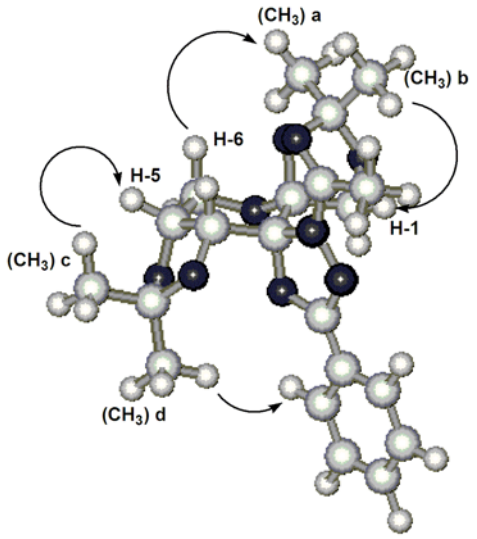
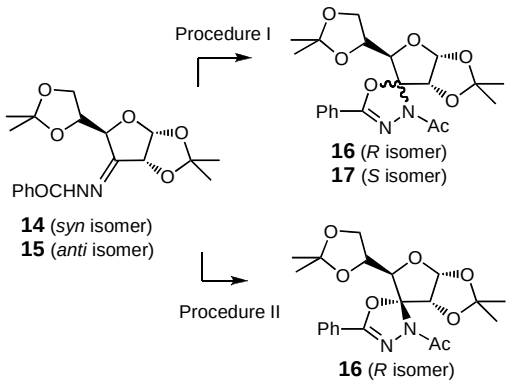


Figure 1



16 (*R* isomer) **17** (*S* isomer)

14 (*syn* isomer) **15** (*anti* isomer)

16 (*R* isomer)

Scheme III

Displacements of compounds **7** and **13** had a good correlation with compound **8**, and then we propose that they have the same stereochemistry at C-3. The presence of sulfur instead of oxygen in compound **7** is responsible for the slight differences.

From the analysis of heterocyclization products of pyranose derivatives, we concluded that the nature of the nucleophile determined the facial selectivity of the heterocyclization.

To evaluate the behavior of an acylhydrazone of a furanose ring derivative we synthesized the *syn* and *anti*-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose benzoylhydrazone (**14** and **15**), and submitted them to Procedures I and II (Scheme III).

Procedure I gave a mixture of (3*R*)- and (3*S*)-4'-*N*-acetyl-1,2:4,5-di-*O*-isopropylidene-2'-phenylspiro[3-deoxy-α-D-*ribo*-hexofuranose-3,5'-[1,3,4]oxadiazoline] which were isolated and separately characterized (**16** and **17**) (Tables 7-9). Procedure II afforded compound **16** as a main product.

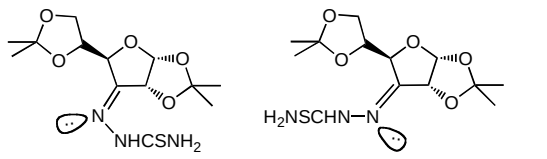
The C-3 configuration of both isomers was assigned by NOESY experiments on compound **17**, as it is shown on Figure 2.

The meticulous analysis of the NMR assignments of compounds **1**-**6**, **10**, **11**, **14**, and **15** (Tables 3 and 9) showed that the C-2 displacements of all *syn* isomers (**1**, **3**, **5**, **10**, and **14**) were lower than the C-2 values for the corresponding *anti* isomers (**2**, **4**, **6**, **11** and **15**). The C-4 values, showed the opposite relationship.

Karabatsos and Taller [9] have reported that the substituent placed on the same side of –NHR group must be the most deshielded. Since this asseveration disagrees with our present observations, so we reinvestigated our *syn-anti* assignations for 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose thiosemicarbazone (**18** and **19**) [1] (previously made using Karabatsos and Taller's supposition). We performed the corresponding NOESY experiments and found that compound with $[\alpha]_D$ = +335.1° (assigned as *anti* isomer), showed a correlation between H-2 and –N*H*CSNH$_2$, which is present only in a *syn* structure (**18**, Scheme IV).

According to this result we had to rectify the former assignation: thiosemicarbazone having $[\alpha]_D$ = +335.1° (**18**) has the *syn* configuration and the stereoisomer with $[\alpha]_D$ = +270.8° has the *anti* configuration (**19**).

Based on our experimental data we concluded that the nature of the nucleophile determined the facial selectivity of cyclization in sterically hindered ulose acylhydrazones,



Scheme IV

Table 4

^{1}H NMR displacements (δ) for compounds **7**-**9** and **13** measured at 500 MHz.

Compound	H-1a	H-1b	H-4	H-5	H-6a	H-6b
7 [a]	4.17	4.14	6.43	4.44	4.28	4.08
8 [b]	3.98	3.92	5.94	4.52	4.30	4.16
9 [b]	4.85	3.79	4.80	4.65	4.41	3.78
13 [a]	4.03	3.95	5.94	4.35	4.32	4.18

[a] deuteriochloroform, [b] acetone-d_6

Table 5

Coupling constant (Hz) for compounds **7**-**9** and **13**, measured at 500 MHz.

Compound	$J_{1,1b}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
7 [a]	9.5	6.5	4.4	0	13.5
8 [b]	9.2	6.2	3.2	0.7	13.7
9 [b]	10.1	7.1	3.1	0.5	12.8
13 [a]	9.2	6.0	3.0	0	13.4

[a] deuteriochloroform, [b] acetone-d_6

Table 6

^{13}C NMR displacements (δ) for compound **7**-**9** and **13**, measured at 125 MHz.

Compound	C-1	C-2	C-3	C-4	C-5	C-6
7 [a]	72.0	107.1	85.8	70.2	72.2	60.7
8 [b]	71.6	105.9	98.6	69.1	72.3	60.4
9 [b]	73.2	105.2	101.2	76.2	76.8	66.6
13 [a]	71.7	105.2	97.0	68.3	72.5	59.6

[a] deuteriochloroform, [b] acetone-d_6

Table 7

^{1}H NMR displacements (δ) for compound **14**-**17**, measured at 500 MHz in deuteriochloroform.

Compound	H-1	H-2	H-4	H-5	H-6a	H-6b
14	6.09	5.17	4.86	4.39	4.03	4.03
15	5.86	5.14	4.64	4.14	4.24	4.17
16	6.21	4.86	4.22	4.08	4.11	4.04
17	5.98	4.49	5.67	4.27	4.10	4.10

Table 8

Coupling constant (Hz) for compounds **14**-**17**, measured at 500 MHz in deuteriochloroform.

Compound	$J_{1,2}$	$J_{2,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
14	4.8	1.0	2.0	7.0	7.0	0
15	4.0	1.2	9.0	6.0	5.5	9.0
16	3.8	-	8.7	2.0	5.5	8.0
17	4.2	-	8.0	5.8	5.8	0

Table 9

^{13}C NMR displacements (δ) for compound **14-17**, measured at 125 MHz in deuteriochloroform.

Compound	C-1	C-2	C-3	C-4	C-5	C-6
14	105.0	76.6	152.7	79.7	77.8	64.3
15	102.8	81.0	152.7	77.9	74.3	68.0
16	106.2	82.8	104.5	82.0	74.0	67.4
17	103.9	83.2	103.6	72.9	72.9	67.4

while the ring size of the carbohydrate derivatives did not have any influence on the selectivity of the oxygen attack. These cyclizations led to one or both isomers depending on the reaction temperature.

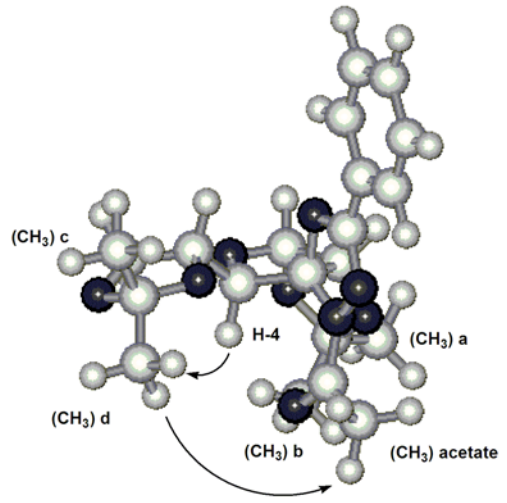


Figure 2

EXPERIMENTAL

General Methods. Optical rotations were recorded at 20 °C on a Perkin Elmer 343 polarimeter, and the melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz, respectively on a Bruker AVANCE II 500. Elemental analyses were performed by UMYMFOR, CONICET- University of Buenos Aires, Argentina. 2D homonuclear shift correlations were made using gradient pulses for selection, COSYGPQF AVANCE version (00/04/28). For 2D H-1/C correlation *via* double inept transfer were made using sensitivity improvement, HSQCETGPSI2 AVANCE version (05//10/28) [10-12]. Thin layer chromatography (tlc) was carried out on 60F254 silica plates (Merck) and visualization was made by UV light and ethanol/sulfuric acid (10:1), followed by heating. Chromatographic purification was performed on silica gel G (Merck) using mixtures of cyclohexane and acetone as eluent.

General procedure for synthesis of acylhydrazones. The corresponding ulose was dissolved in ethanol and heated with a small excess of thiosemicarbazide or benzoylhydrazide. The semicarbazone was synthesized in a similar way using semicarbazide hydrochloride/sodium carbonate. The reaction was monitored by tlc until no starting material was observed. The reaction medium was evaporated and the residue purified by flash chromatography.

General procedure for synthesis of spiro heterocylces. Acylhydrazones were dissolved in pyridine and acetic anhydride was added. The mixture was heated at 110 ±5 ºC (Procedure **I**) or at reflux (Procedure **II**), and the reaction was monitored by tlc. The reaction was left at room temperature and then stopped by adding some ethanol. The reaction medium was evaporated using some toluene to eliminate the residues of acetic acid. The residue was purified using flash chromatography.

***Syn*- and *anti*-1,2:4,5-di-*O*-isopropylidene-β-D-*erythro*-hexo-2,3-diulo-2,6-pyranose thiosemicarbazones (1 and 2).** Title compound was synthesized using the general procedure for acylhydrazones from 1,2:4,5-di-*O*-isopropylidene-β-D-*erythro*-2,3-hexodiulo-2,6-pyranose (515 mg, 2.0 mmol) and thiosemicarbazide (222 mg, 2.4 mmol). After purification, the mixture of *syn* (**1**) and *anti* (**2**) isomers was obtained as colorless syrup (**1**:**2** ratio 1:3.4, determined by ^{1}H NMR of crude material) (567 mg, 85.6%). ^{1}H NMR (deuteriochloroform): δ 1.34, 1.36, 1.42, 1.44, 1.49, 1.53, 1.76 (7s, -CH_3), 6.95, 6.99, 7.23 (3s, -NH_2), 10.65, 10.64 (2s, -NH-CS-); ^{13}C NMR (deutériochloroform): δ 25.10, 25.89, 25.96, 26.12, 26.33, 26.61, 26.67, 26.92 (8s, -CH_3), 110.04, 110.90, 112.96, 113.25 (4s, isopropylidene groups), 139.94, 142.24 (2s, C=N), 179.51, 179.72 (2s, C=S). *Anal*. Calcd. for $C_{13}H_{21}N_3O_5S$: C, 47.13; H 6.34. Found: C, 47.10; H 6.36.

***Syn*- and *anti*-1,2:4,5-di-*O*-isopropylidene-β-D-*erythro*-hexo-2,3-diulo-2,6-pyranose benzoylhydrazones (3 and 4).** Title compound was synthesized using the general procedure for acylhydrazones from the 1,2:4,5-di-*O*-isopropylidene-β-D-*erythro*-2,3-hexodiulo-2,6-pyranose (500 mg, 1.9 mmol) and benzoylhydrazide (350 mg, 2.6 mmol). After purification, colorless syrup was obtained as a mixture of *syn* (**3**) and *anti* (**4**) isomers (**3**:**4** ratio 1:4.8 determined by ^{1}H NMR of crude material) (535 mg, 73.5%). ^{1}H NMR (deuteriochloroform): δ 1.35, 1.39, 1.41, 1.43, 1.46, 1.51, 1.52, 1.56 (8s, -CH_3), 7.37-7.89 (m, aromatics), 10.98, 11.55 (2s, -NH-CO-); ^{13}C NMR (deuteriochloroform): δ 24.97, 25.56, 26.08, 26.62, 26.84, 27.15 (6s, -CH_3), 110.57, 110.62, 112.25, 112.97 (4s, isopropylidene groups), 127.07-132.84 (aromatics), 145.17, 145.21 (2s, C=N), 163.036 (s, C=O). *Anal*. Calcd. for $C_{19}H_{24}N_2O_6$: C, 60.64; H 6.38. Found: C, 60.59; H 6.36.

***Syn*- and *anti*-1,2:4,5-di-*O*-isopropylidene-β-D-*erythro*-hexo-2,3-diulo-2,6-pyranose semicarbazones (5 and 6).** Title compound was synthesized using the general procedure for acylhydrazones from the 1,2:4,5-di-*O*-isopropylidene-β-D-*erythro*-2,3-hexodiulo-2,6-pyranose (465 mg, 1.8 mmol), semicarbazide hydrochloride (226 mg, 2.0 mmol) and sodium carbonate (124 mg, 1.2 mmol). After purification, compounds **5** (*syn*) and **6** (*anti*) were separately obtained as colorless syrups (471 mg, 82.9%, **5**:**6** ratio 1:2.6 determined by ^{1}H NMR of crude material).

Compound 5 (*Syn* isomer): $[\alpha]_D$ -163.1 (*c* 0.98, $CHCl_3$); ^{1}H NMR (deuteriochloroform): δ 1.36, 1.49, 1.53, 1.66 (4s, -CH_3), 5.70 (s broad, -NH_2), 9.30 (s, -NH-CO-); ^{13}C NMR (deuteriochloroform): δ 25.10, 25.99, 26.16, 26.79 (4s, -CH_3), 110.50, 112.49 (2s, isopropylidene groups), 137.48 (s, C=N), 155.97 (s, C=O).

Compound 6 (*Anti* isomer): $[\alpha]_D$ -256.9 (*c* 1.14, $CHCl_3$); ^{1}H NMR (deuteriochloroform): δ 1.38, 1.39, 1.41, 1.50 (4s, -CH_3), 5.60 (s, broad -NH_2), 9.54 (s, -NH-CO-); ^{13}C NMR (deuteriochloroform): δ 25.99, 26.35, 26.60, 26.76 (4s, -CH_3), 110.66, 112.95 (2s, isopropylidene groups), 139.91 (s, C=N), 156.51 (s, C=O). *Anal*. Calcd. for $C_{13}H_{21}N_3O_6$: C, 49.52; H 6.66. Found: C, 49.48; H 6.69.

(3*R*)-2'-acetamido-4'-*N*-acetyl-1,2:4,5-di-*O*-isopropylidene-spiro[3-deoxy-β-D-*erythro*-hexopyranose-3,5´-[1,3,4]thiadiazoline] (7). Thiadiazoline **7** was synthesized using Procedure I, from mixture of thiosemicarbazones **1** and **2** (337 mg, 1.0 mmol) and acetic anhydride (3 mL), in pyridine (3 mL). After purification, compound **7** was obtained as a single isomer (249 mg, 58.9%): amorphous solid mp 130-131 ºC; $[\alpha]_D$ +104.8 (*c* 0.82, $CHCl_3$); ^{1}H NMR (deuteriochloroform): δ 1.36, 1.37, 1.48, 1.73 (4s, -CH_3); 2.19, 2.22 (2s, -$COCH_3$); 9.38 (s, -NH-); ^{13}C NMR (deuteriochloroform): δ 23.03, 25.17, 25.28, 25.60, 25.91, 26.20 (6s, -$COCH_3$ and -CH_3), 109.84, 113.74 (2s, isopropylidene groups), 144.92 (s, C=N), 169.06, 170.71 (2s, C=O). *Anal*. Calcd. for $C_{17}H_{25}N_3O_7S.C_4H_8O_2$: C, 50.10; H 6.56. Found: C, 50.08; H 6.40.

(3*R*)- and (3*S*)-4'-*N*-acetyl-1,2:4,5-di-*O*-isopropylidene-2'-phenylspiro[3-deoxy-β-D-*erythro*-hexopyranose-3,5´-[1,3,4]-oxadiazoline] (8 and 9). Oxadiazolines **8** and **9** were synthesized by Procedure I, from a mixture of benzoylhydrazones **3** and **4** (350 mg, 0.9 mmol) and acetic anhydride (3 mL), in pyridine (3 mL). After purification, compounds **8** and **9** were obtained as colorless syrup (309 mg, 79.4%, **8**:**9** 1.4:1, as determined by ^{1}H NMR of crude material). The reaction performed under Procedure II (289 mg, 0.8 mmol) afforded, after purification, compound **8** (*R* configuration) as a single isomer (174 mg, 54.2%). ^{1}H NMR (acetone-d_6): δ 1.25, 1.31, 1.32, 1.33, 1.37, 1.46 (6s -CH_3), 2.29, 2.32 (2s, -$COCH_3$), 7.43-7.95 (m, aromatics); ^{13}C NMR (acetone-d_6): δ 23.88, 24.01 (2s, -$COCH_3$), 25.41, 25.62, 25.78, 25.93, 26.02, 26.34, 26.53, 26.66 (8s, -CH_3), 110.10, 111.05, 111.64, 114.28 (4s, isopropylidene groups), 124.72-138.38 (aromatics), 154.08, 154.40 (2s, C=N), 168.02 (s, C=O).

Compound 8: amorphous solid mp 173-175 ºC; $[\alpha]_D$ +105.9 (*c* 0.94, $CHCl_3$); ^{1}H NMR (acetone-d_6): δ 1.31, 1.33, 1.37, 1.46 (4s, -CH_3), 2.32 (s, -$COCH_3$), 7.43-7.91 (m, aromatics); ^{13}C NMR (acetone-d_6): δ 24.01 (s, -$COCH_3$), 25.41, 25.62, 26.34, 26.53 (4s, -CH_3), 110.10, 114.28 (2s, isopropylidene groups), 124.72-132.38 (aromatics) 154.40 (s, C=N), 168.02 (s, C=O). *Anal*. Calcd. for $C_{21}H_{26}N_2O_7$: C, 60.29; H 6.22. Found: C, 60.28; H, 6.41.

(3*R*)-4'-*N*-acetyl-1,2:4,5-di-*O*-isopropylidene-2'-methyl-spiro[3-deoxy-β-D-*erythro*-hexopyranose-3,5´-[1,3,4]oxa-diazoline] (13). Oxadiazoline **13** was synthesized using Procedure II from a mixture of semicarbazones **5** and **6** (273 mg, 0.9 mmol) and acetic anhydride (2 mL), in pyridine (2 mL). After purification, compound **13** was obtained as a single isomer (white amorphous solid, 129 mg, 41.4%): $[\alpha]_D^{20}$ -15.4 (*c* 0.77, $CHCl_3$); ^{1}H NMR (deuteriochloroform): δ 1.37, 1.38, 1.52, 1.57 (4s, -CH_3), 2.06 (s, heterocyclic -CH_3), 2.25 (s, -$COCH_3$); ^{13}C NMR (deuteriochloroform): δ 11.33 (s, heterocyclic -CH_3), 23.89 (s, -$COCH_3$), 25.60, 25.64, 25.88, 26.39 (4s, -CH_3), 109.74, 114.15 (2s, isopropylidene groups), 153.96 (s, C=N), 168.25 (s, C=O). *Anal*. Calcd. for $C_{16}H_{24}N_2O_7$: C, 53.93; H 6.74. Found: C, 54.19; H 7.04.

***Syn* and *anti*-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexo-furanos-3-ulose benzoylhydrazone (14 and 15).** Title compounds were synthesized using the general procedure for acylhydrazones from 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-1,5-hexofuranos-3-ulose (600 mg, 2.3 mmol) and benzoylhydrazide (380 mg, 2.8 mmol). After purification, compounds **14** and **15** were obtained as colorless syrup (510 mg, 58.3%, **14**:**15** 1:1.5, as determined by ^{1}H NMR of crude material), and compound **15** was isolated. ^{1}H NMR (deuteriochloroform): δ 1.32, 1.35, 1.40,

1.44, 1.49, 1.54 (6s -CH_3), 7.44-7.87 (m, aromatics), 10.16, 11.32 (2s, -NHCOPh); ^{13}C NMR (deuteriochloroform): δ 25.50, 26.23, 26.59, 26.94, 27.15, 27.50, 27.69 (7s, -CH_3), 109.87, 111.43,113.70, 114.61 (4s, isopropylidene groups), 127.71-133.29 (aromatics) 156.65, 156.47 (2s, C=N), 164.68 (s, C=O).

Compound 15 (*Anti* isomer): white needles mp 186-188 ºC; $[\alpha]_D^{20}$ +244.2 (*c* 1.11, $CHCl_3$); ^{1}H NMR (deuteriochloroform): δ 1.32, 1.40, 1.44, 1.54 (4s, -CH_3), 7.44-7.87 (m, aromatics), 11.33 (s, -NHCOPh); ^{13}C NMR (deuteriochloroform): δ 25.49, 26.20, 26.95, 27.51 (4s, -CH_3), 109.87, 113.70 (2s, isopropylidene groups), 127.75-132.29 (aromatics) 156.65 (s, C=N), 164.68 (s, C=O). *Anal*. Calcd. for $C_{19}H_{24}N_2O_6$: C, 60.64; H 6.38. Found: C, 60.55; H 6.42.

(3*R*)- and (3*S*) -4'-*N*-acetyl-1,2:4,5-di-*O*-isopropylidene-2'-phenylspiro[3-deoxi-α-D-*ribo*-hexofuranose-3,5´-[1,3,4]oxadiazoline] (16 and 17). Oxadiazolines **16** and **17** were synthesized using Procedure I from the mixture of benzoylhydrazones **14** and **15** (165 mg, 0.44 mmol) and acetic anhydride (3 mL), in pyridine (3 mL). After purification, compounds **16** and **17** were obtained as colorless syrups (132 mg, 72.1%, **16**:**17** 1,1:1, isolated mass). The same reaction performed by Procedure II (128 mg, 0.3 mmol) afforded, after purification, compound **16** (3´*R* isomer) as the main compound (89 mg, 62.7%).

Compound 16: $[\alpha]_D^{20}$ -11.0 (*c* 1.02, $CHCl_3$); ^{1}H NMR (deuteriochloroform): δ 1.13, 1.19, 1.40, 1.68 (4s, -CH_3), 2.40 (s, -$COCH_3$), 7.43-7.88 (m, aromatics); ^{13}C NMR (deuteriochloroform): δ 22.15 (s, -$COCH_3$) 25.14, 26.88, 27.01, 27.07 (4s, -CH_3), 109.60, 113.35 (2s, isopropylidene groups), 124.28-131.56 (aromatics) 154.73 (s, C=N), 167.89 (s, C=O).

Compound 17: $[\alpha]_D^{20}$ -69.5 (*c* 0.84, $CHCl_3$); ^{1}H NMR (deuteriochloroform): δ 1.24, 1.35, 1.37, 1.69 (4s, -CH_3), 2.36 (s, -$COCH_3$), 7.45-7.55 (m, aromatics); ^{13}C NMR (deuteriochloroform): δ 23.48 (s, -$COCH_3$) 25.22, 26.09, 26.31, 26.92, (4s, -CH_3), 109.75, 114.34 (2s, isopropylidene groups), 124.25-131.64 (aromatics) 152.94 (C=N), 168.92 (s, C=O). *Anal*. Calcd. for $C_{21}H_{26}N_2O_7$: C, 60.29; H 6.22. Found: C, 60.32; H 6.45.

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