Cyclization of 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-1,6-hexodialdo-1,5-pyranose acylhydrazone and semicarbazone

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DOI: http://dx.doi.org/10.3998/ark.5550190.0014.311

Abstract

Cyclization of 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-1,6-hexodialdo-1,5-pyranose benzoylhydrazone using acetylating mixtures led us to the corresponding (2*R*)- and (2*S*)-5-phenyl-1,3,4-oxadiazoline derivatives. The same conditions applied to the semicarbazone produced the 5-methyl-1,3,4-oxadiazoline derivative as the main compound, which is formed with acetylating mixtures even at room temperature. X-Ray analysis and NMR techniques were used to determine the stereochemistry of the new asymmetric centers.

Keywords: Oxadiazolines, sugar heterocycles, semicarbazones, acetylation

Introduction

The synthesis of 3-*N*-acyl-1,3,4-oxadiazolines is a well-known reaction and there is a lot of information on this field, however in recent years the number of publications has increased due to the great potential of this heterocyclic ring as chemotherapeutic agent.[1,2] Nevertheless, some aspects of heterocyclization reaction are not well known.

Looking for new potential biological agents, we studied the differences between heterocyclization of acylhydrazone and semicarbazone obtained from protected carbohydrate derivatives. Also, a hypothesis for their different behavior is proposed.

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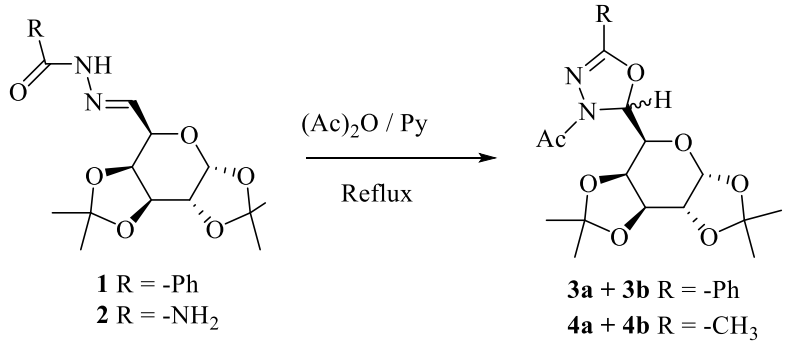
Results and Discussion

In this paper we analyzed the behavior of 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-1,6-hexodialdo-1,5-pyranose benzoylhydrazone (**1**) and 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-1,6-hexodialdo-1,5-pyranose semicarbazone (**2**) under acetylating conditions, in order to obtain the corresponding 3-*N*-acetyl-5-phenyl-2-[5-(1,2:3,4-di-*O*-isopropylidene-α-L-arabino-pyranosyl)]-1,3,4-oxadiazolines (**3**) and 3-*N*-acetyl-5-methyl-2-[5-(1,2:3,4-di-*O*-isopropylidene-α-L-arabinopyranosyl)]-1,3,4-oxadiazolines (**4**). In Scheme 1, we show the acetylation reaction and the obtained products.



1 R = -Ph
2 R = -NH_2

3a + **3b** R = -Ph
4a + **4b** R = -CH_3

Scheme 1. Synthesis of compound **3** and **4**.

Semicarbazone derivative **2** was synthesized by reaction of 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-1,6-hexodialdo-1,5-pyranose with semicarbazide hidrochloride and sodium bicarbonate in ethanolic solution. After removal of salts the crude product was obtained as a syrup, which crystallized from methanol. The ^{1}H NMR analysis performed on the syrup indicated that there is only one isomer, unlike benzoyl hydrazone **1**[3], which was synthesized as a mixture of *anti:syn* isomers in a 3:1 relationship. We performed a single crystal x-ray diffraction analysis of **2** and found an *anti* configuration for the C=N bond, but also presented a deviation respect to the expected zig-zag conformation. This orientation of the carbonyl group relative to the N=C group enables the formation of intermolecular hydrogen bonds, contributing to the ordering of the molecules and subsequent crystallization (Figure 1).

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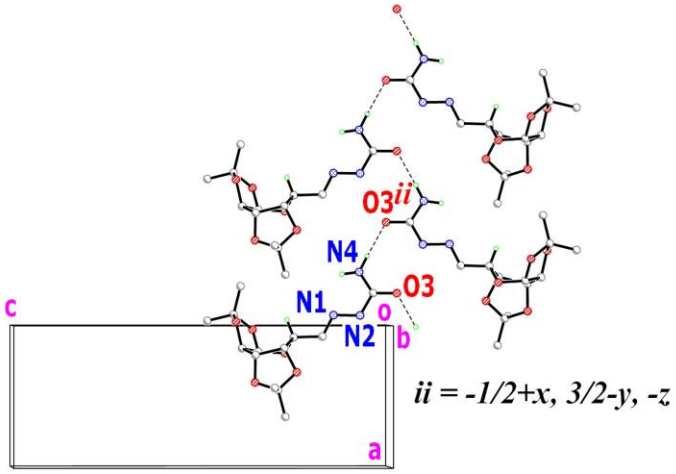

Figure 1. Drawing of the crystal packing of compound **2.**

Acetylation of compound **1** using acetic anhydride in pyridine and reflux, yielded (2*R*)- and (2*S*)-3-*N*-acetyl-5-phenyl-2-[5-(1,2:3,4-di-*O*-isopropylidene-α-L-arabinopyranosyl)]-1,3,4-oxadiazolines **3a** and **3b** in a nearly 1:1 relationship. Once purified, the compound with higher Rf crystallized. After the X-ray analysis, we found *S* stereochemistry for the new asymmetric center. (Figure 2).

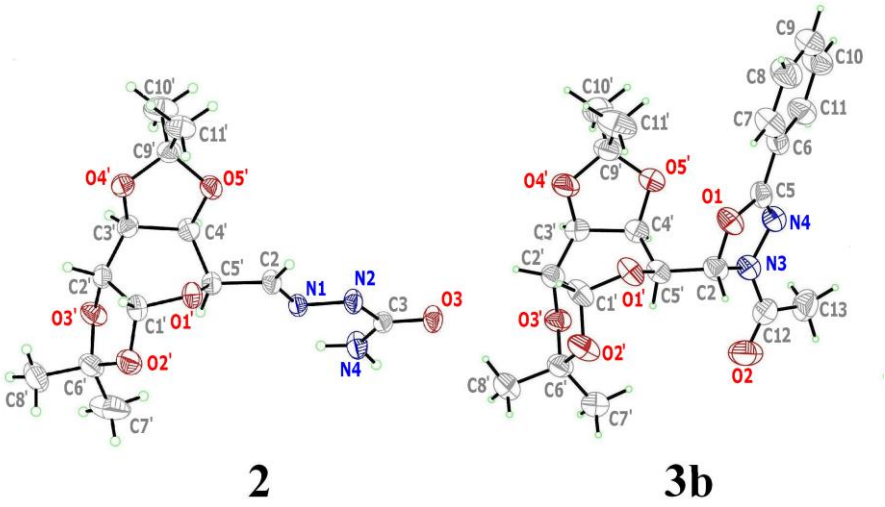

Figure 2. Ellipsoid plots (40% probability level) of compound **2** and **3b**.

Both molecules (**2** and **3b**) share their leftmost part (Figure 2, primed labels), and thus have a number of characteristics in common: in both units the fused dioxolane cycles prevent the pyranose ring from assuming a regular conformation; it exhibits instead a highly distorted twist-

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boat geometry clearly evidenced through the comparison of some selected torsion angles, viz., C2'-C3'-C4'-C5': 12.6(2)º (**3b**) or -3.8 (**2**) (implying that the C2'-C3' and C4'-C5' bonds are nearly eclipsed) vs. C2'-C1'-O1'-C5': 41.3(2)º (in **3b**), 47.4(1)º (in **2**) (showing that the C2'-C1' and O1'-C5' bonds are far from coplanar).

The two five membered dioxolane rings exhibit in turn clear envelope conformations with "slap-atoms" O3', O5' in **3b** and O3', C9' in **2** being 0.42(1), 0.35(1), 0.49(1) and 0.48(1) Å, respectively, away from the L.S. planes defined by the remaining four atoms. Differences reside in the rightmost part of the structures.

In the case of **3b** the 1,3,4-oxadiazoline ring is almost planar with only a slight puckering into an envelope shape, atom C2 being 0.14(1) Å away from the plane defined by the remaining four atoms (torsion angle N3-N4-C5-O1: 1.6(1)º)). The terminal phenyl group appears rotated around the C5-C6 bond by 13.0(1)º. The final model ends up having six asymmetric carbon centers, C1', C2', C3', C4', C2, C5'. The absolute configuration (*R* at C1', C2' and *S* at the remaining four asymmetric sites) was figured out from the configuration of carbon centers of known stereochemistry.

Since there are no active N-H or O-H donors in the molecule, no strong H-bonding interactions exist in the structure. There is only a weak non classical C4'-H4'...O1'^{i} contact (H4'…O1'^{i}: 2.50 Å, C4'…O1'^{i}: 3.264(4) Å, C4'-H4'…O1'^{i}: 134º¸ (i): 2-x, 1/2+y, 1-z) generating a weakly linked chain which runs along b, threaded by the monoclinic twofold screw axis. Structure **2** differs from **3b** in that there are no rings in this part of the structure, while there are active N-H donors giving raise to a strong H-bond N4---H4A…O3^{ii} (H4A…O3^{ii}: 2.05 Å, N4…O3^{ii}: 2.958 Å, N4---H4A…O3^{ii}: 167º¸ (ii): -1/2+x,3/2-y,-z) generating a strongly linked chain, also threaded by a twofold screw axis (this time along a).

Compounds **3a** and **3b** were characterized spectroscopically, and a NOESY experiment was performed for **3a**. In this experiment, the most relevant cross peak correlations were H4-H2(Het) and –CH_3(C)-Ph, which confirmed the 2*R* stereochemistry for compound **3a**. The observed correlations are depicted in Figure 3.

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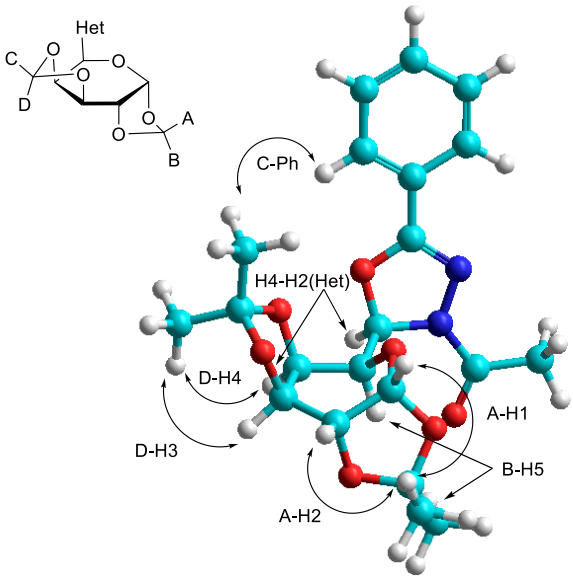

Figure 3. Cross correlations found in the NOESY experiment for compound **3a**.

When compound **2** was subjected to the same reaction conditions methyloxadiazolines **4a** (*R*) and **4b** (*S*) were obtained, although some byproducts were also detected. In order to perform a cleaner reaction, we carried out a microwave assisted synthesis, using the same reagents and heating at 140 °C during 60 minutes and we obtained **4a** and **4b** with better yields. Stereochemistry of compound **4a** and **4b** were determined by comparison with NMR data of compounds **3a** and **3b**. Conditions, yields, and *R*:*S* relationship for compounds **3** and **4** are shown on Table 1. After 15 min of irradiation, we observed the formation of both oxadiazolines (**4a** and **4b**) and the presence of a third compound (**5**), which disappears after 60 min of irradiation. The chromatographic behavior of **5** is similar to that observed for the main byproduct of the thermal treatment. Once isolated, compound **5** was identified as 4-*N*-acetyl-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-1,6-hexodialdo-1,5-pyranose semicarbazone.

Table 1. Conditions for synthesis of compounds **3** and **4**, yield, and *R*:*S* relationship.

Compound	Method	Heating	Yield	R:S
3a and **3b**	Thermal	1 h	94 %	1.1:1
4a and **4b**	Thermal	3 h	52 %	1.3:1
4a and **4b**	μwave	1 h	68 %	1:1.1

Hang *et al.*[4] proposed a mechanism for acylhydrazone cyclization via two different pathways, the direct and the indirect one. This latter route would generate the methyloxadiazoline as results of prolonged heating. When we treated semicarbazone **2** with acetic anhydride and pyridine at reflux, the product of direct cyclization was not observed and the main products were methyloxadiazolines (**4a** and **4b**). When the same reaction was carried out at room temperature,

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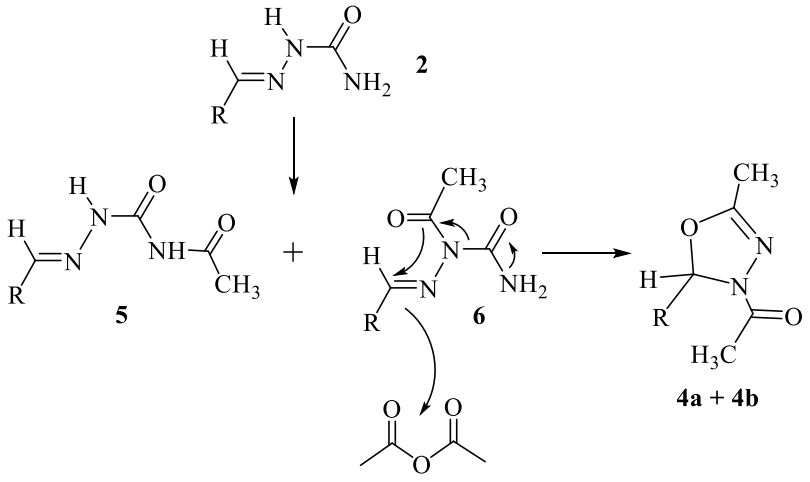
the formation of compound **5** and **4b** was observed within two hours of reaction. After 60 hs the reaction was stopped and we could isolate the oxadiazoline **4b** (6%) along with traces of **4a**, compound **5** (13%)**,** and the unreacted compound **2** (35%); meanwhile *N*2-acetyl or *N*2,*N*4-diacetyl derivatives were not detected.

These results demonstrated that the formation of methyloxadiazoline could not be attributed exclusively to the reaction temperature. Under these conditions, *N*4 would be the first acetylated nitrogen, since it is not sterically hindered, giving compound **5**. The proposed reaction mechanism[4] (Scheme 2) starts with a *N*2 acylation, followed by a cyclization assisted by acetic anhydride. Based on this hypothesis, we propose that, if some of *N*2 acetylation takes place, this derivative (**6**) can rearrange assisted by the *N*4 electron pair, and undergo cyclization at low temperature. If we assume that the mechanism is similar to the one proposed for thiosemicarbazones cyclization, *via* carbocation intermediate[5] the result is the same.



Scheme 2. Proposed cylization mechanism for semicarbazones

According to our previous experiences on cyclization of sterically hindered thiosemicarbazones and acylhydrazones,[6] the stereochemistry of the molecule can rule the side of attack of sulfur atom, but this influence was not observed for oxygenated derivatives. Other authors reported that predominance of *R* or *S* oxadiazoline isomer is a direct consequence of the acylhydrazone *syn*:*anti* relationship,[4,7] but no *R*:*S* selectivity was observed for the oxadiazoline derivative because *syn* and *anti* isomers can be equilibrated by temperature or the presence of acetic acid.

During cyclization of **2** at room temperature, acetic anhydride with excess of pyridine was used, so, isomerization of *anti* form of **2** could not take place, and the main heterocyclic compound obtained was **4b**. Taking into account that the starting material was a single isomer we can conclude that the preferential formation of **4b** is a consequence of the stereochemistry of C=N bond on compound **2**. On the other hand, some calculations using molecular mechanics,[8]

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showed that compound **4a** is about 6 Kcal/mol more stable than **4b**, so **4b** must be a kinetic product meanwhile **4a** must be the thermodynamic one.

Conclusions

Taking into account our experimental results, we can conclude that the cyclization of benzoylhydrazone **1** using acetic anhydride and pyridine at reflux, yielded 1,3,4-oxadiazoline derivatives (**3a** and **3b**) as a mixture of *syn*:*anti* isomers. Under the same conditions, the semicarbazone **2** yields the methyloxadiazoline instead of the product of direct cyclization. This fact can be explained by the presence of the *N*4 electron pair, which promotes the loss of the carbamoyl group. Also, we performed the acetylation of compound **2** at room temperature and found that the cyclization takes place yielding preferentially **4b**, which would be the kinetic reaction product.

Experimental Section

General. Elemental analysis was performed on an Exeter Analytical CE-440 elemental analyzer. Optical rotations were recorded at 20 °C on a Perkin Elmer 343 polarimeter. ^{1}H, ^{13}C NMR spectra were recorded on solution of $CDCl_3$ on a Bruker AC-200 spectrometer, operating at 200, 50 MHz respectively; or a Bruker AMX-500 spectrometer, operating at 500, 125 MHz respectively. Assignments of the ^{1}H and ^{13}C NMR spectra were confirmed with the aid of two dimensional techniques ^{1}H, ^{13}C (COSY, HSQC).
Microwave-assisted synthesis was performed on an Anton Paar Monowave 300 microwave reactor with external surface sensor in a sealed reaction vessel. Chromatographic purifications were performed by flash column with Merck silica gel 60. The chemicals used in this work purchased from Aldrich and were used without further purification.
X-ray data was collected on an Oxford Diffraction Gemini CCD S Ultra single crystal diffractometer using Mo Ka radiation (λ = 0.71073 Å).[9] A multi-scan absorption correction was applied.[10] The structure was solved by direct methods and refined by full-matrix least squares against F2 using all data.[11] All non-H atoms were refined anisotropically, while H atoms were located at idealized positions with their displacement parameters riding on the values of their parent atoms. The general-purpose crystallographic program PLATON[12] was used for the structure analysis and presentation of the results. The figures were drawn with XP.[11]

1,2:3,4-Di-*O*-isopropylidene-α-D-*galacto*-1,6-hexodialdo-1,5-pyranose semicarbazone (2). To 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-1,6-hexodialdo-1,5-pyranose 0.56 g (2.2 mmol) dissolved in 25 mL of ethanol, semicarbazide hydrochloride (0.27 g, 2.4 mmol) and sodium bicarbonate (0.20 g, 2.4 mmol) were added. The mixture was heated with magnetic stirring for 2

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hs, filtered to eliminate the salt and evaporated. Te residue was suspended in dichloromethane, filtered, evaporated and dissolved in methanol. From this solution crystallizes compound **2**. Colourless crystals, yield 75%, 0.520 mg; mp 221-223 °C; CCDC 894994; Rf: 0.42 in ethyl acetate; $[\alpha]_D^{20}$ -1.5 (*c* 0.95, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δH 1.36, 1.37, 1.49, 1.58 (12 H, four s, -C(C<u>H</u>$_3$)$_2$), 4.34 (1H, dd, $^3J_{HH}$ 2.1 Hz, $^3J_{HH}$ 7.9 Hz, H-4), 4.36 (1H, dd, $^3J_{HH}$ 2.5 Hz, $^3J_{HH}$ 5.0 Hz, H-2), 4.39 (1H, dd, $^3J_{HH}$ 1.9 Hz, $^3J_{HH}$ 6.0 Hz, H-5), 4.66 (1H, dd, $^3J_{HH}$ 2.5 Hz, $^3J_{HH}$ 7.9 Hz, H-3), 5.33 and 5.85 (2H, two broad s, -CON<u>H</u>$_2$), 5.58 (1H, d, $^3J_{HH}$ 5.0 Hz, H-1), 8.95 (1H, s, -CON<u>H</u>-); ^{13}C NMR (125 MHz, $CDCl_3$) δC 24.3, 24.9, 25.9, 26.2 (-C(<u>C</u>H$_3$)$_2$), 68.4 (C-5), 70.3 (C-2), 70.6 (C-3), 73.0 (C-4), 96.2 (C-1) 108.9, 109.7 (-<u>C</u>(CH$_3$)$_2$), 141.1 (C-6), 157.4 (C=O); Anal. calcd. for $C_{13}H_{21}N_3O_6$: %C, 49.52; %H, 6.71; %N, 13.33. Found %C, 49.33; %H, 6.92; %N, 13.21.

General synthetic procedure for thermal cyclization of compound 1 and 2. Compound **1** (0.352 g, 0.9 mmol) or **2** (0.399 g, 1.3 mmol) were dissolved in pyridine (2.5 mL) and acetic anhydride (2.5 mL). The resulting mixture was refluxed (see Table 1) and then was left to reach room temperature. Once cold, some ethanol was added and the reaction medium was evaporated at reduced pressure, giving a glassy residue. The residue was purified using flash dry column on Silicagel G with mixtures of cyclohexane/acetone and obtained compounds **3a** and **3b** or **4a** and **4b**.

(2*R*)-3-*N*-Acetyl-5-phenyl-2-[5-(1,2:3,4-di-*O*-isopropylidene-α-L-arabinopyranosyl)]-1,3,4-oxadiazoline 3a. Colorless syrup, Rf: 0.52 in 40% ethyl acetate/cyclohexane; $[\alpha]_D^{20}$ 0.82 (*c* 1.03, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δH 1.29 1.41, 1.48, 1.54 (12 H, four s, -C(C<u>H</u>$_3$)$_2$), 2.34 (3H, s, -NCOC<u>H</u>$_3$), 4.34 (1H, dd, $^3J_{HH}$ 2.6 and $^3J_{HH}$ 4.9 Hz, H-2) 4.44 (1H, broad s, H-5), 4.55 (1H, dd, $^3J_{HH}$ 2.0 Hz and $^3J_{HH}$ 7.8 Hz, H-4), 4.69 (1H, dd, $^3J_{HH}$ 2.6 Hz and $^3J_{HH}$ 7.8 Hz, H-3), 5.49 (1H, d, $^3J_{HH}$ 4.9 Hz, H-1), 6.43 (1H, broad s, HetH-2); ^{13}C NMR (125 MHz, $CDCl_3$) δC 21.4 (-N<u>C</u>H$_3$), 24.9, 25.0, 25.9, 26.2 (-C(<u>C</u>H$_3$)$_2$), 66.3 (C-5), 70.7 (C-2), 71.1 (C-3), 71.5 (C-4), 90.6 (HetC-2), 96.5 (C-1), 109.2, 110.2 (-<u>C</u>(CH$_3$)$_2$), 124.7-131.3 (aromatics), 156.9 (C=N), 167.7 (C=O). Anal. calcd. for $C_{21}H_{26}N_2O_7$: %C, 60.28; %H, 6.26; %N, 6.69. Found %C, 59.93; %H, 6.60; %N, 6.50.

(2*S*)-3-*N*-Acetyl-5-phenyl-2-[5-(1,2:3,4-di-*O*-isopropylidene-α-L-arabinopyranosyl)]-1,3,4-oxadiazoline 3b: White solid, mp 142-145 °C; CCDC 892324; Rf: 0.62 in 40% ethyl acetate/cyclohexane; $[\alpha]_D^{20}$ -1.51 (*c* 0.84, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δH 1.17, 1.26, 1.33, 1.57 (12 H, four s, -C(C<u>H</u>$_3$)$_2$), 2.35 (3H, s, -NCOC<u>H</u>$_3$), 4.31 (1H, broad d, $^3J_{HH}$ 2.6 Hz, H-5) 4.36 (1H, dd, $^3J_{HH}$ 2.5, and $^3J_{HH}$ 4.9 Hz, H-2), 4.37 (1H, dd, $^3J_{HH}$ 1.8 Hz and $^3J_{HH}$ 6.4 Hz, H-4), 4.61 (1H, dd, $^3J_{HH}$ 2.4 Hz and $^3J_{HH}$ 7.8 Hz, H-3), 5.67 (1H, d, $^3J_{HH}$ 4.9 Hz, H-1), 6.52 (1H, d, $^3J_{HH}$ 4.3 Hz, HetH-2); ^{13}C NMR (125 MHz, $CDCl_3$) δC 21.4 (-N<u>C</u>H$_3$), 24.3, 25.0, 25.9, 26.1 (-C(<u>C</u>H$_3$)$_2$), 65.5 (C-5), 70.0 (C-4), 71.0 (C-2 and C-3), 90.43 (HetC-2), 96.8 (C-1), 109.2, 109.8 (-<u>C</u>(CH$_3$)$_2$), 124.8-131.5 (aromatics), 157.4 (C=N), 168.4 (C=O). Anal. calcd. for $C_{21}H_{26}N_2O_7$: %C, 60.28; %H, 6.26; %N, 6.69. Found %C, 60.03; %H, 6.56; %N, 6.65.

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(2*R*)-3-*N*-Acetyl-5-methyl-2-[5-(1,2:3,4-di-*O*-isopropylidene-α-L-arabinopyranosyl)]-1,3,4-oxadiazoline 4a: Light brown syrup, Rf: 0.32 in 40% ethyl acetate/cyclohexane; $[\alpha]_D^{20}$ 1.82 (*c* 0.96, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δH 1.30, 1.38, 1.48, 1.49 (12 H, four s, -C(C$\underline{H}_3$)$_2$), 2.04 (3H, s, HetC$\underline{H}_3$), 2.23 (3H, s, -NCOC$\underline{H}_3$), 4.31 (1H, dd, $^3J_{HH}$ 2.0 Hz and $^3J_{HH}$ 1.0 Hz, H-5), 4.33 (1H, dd, $^3J_{HH}$ 2.6, and $^3J_{HH}$ 5.0 Hz, H-2), 4.45 (1H, dd, $^3J_{HH}$ 1.8 Hz and $^3J_{HH}$ 7.9 Hz, H-4), 4.64 (1H, dd, $^3J_{HH}$ 2.4 Hz and $^3J_{HH}$ 7.8 Hz, H-3), 5.52 (1H, d, $^3J_{HH}$ 4.8 Hz, H-1), 6.24 (1H, d, $^3J_{HH}$ 1.0 Hz, HetH-2); ^{13}C NMR (50 MHz, $CDCl_3$) δC 11.3 (Het$\underline{C}H_3$), 21.3 (N-$\underline{C}H_3$), 24.9, 25.0, 25.9 (-C($\underline{C}H_3$)$_2$), 66.3 (C-5), 70.8 (C-2), 71.0 (C-3), 71.5 (C-4), 90.0 (HetC-2), 96.5 (C-1), 109.3, 110.3 (-$\underline{C}$(CH$_3$)$_2$), 157.3 (C=N), 167.3 (C=O). Anal. calcd. for $C_{16}H_{24}N_2O_7$: %C, 53.92; %H, 6.79; %N, 7.86. Found %C, 53.85; %H, 6.82; %N, 7.77.

(2*S*)-3-*N*-Acetyl-5-methyl-2-[5-(1,2:3,4-di-*O*-isopropylidene-α-L-arabinopyranosyl)]-1,3,4-oxadiazoline 4b: Light brown syrup, Rf: 0.45 in 40% ethyl acetate/cyclohexane; $[\alpha]_D^{20}$ -2.38 (*c* 0.91, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δH 1.32, 1.33, 1.47, 1.56 (12 H, four s, -C(C$\underline{H}_3$)$_2$), 2.03 (3H, s, HetC$\underline{H}_3$), 2.23 (3H, s, -NCO$\underline{C}H_3$), 4.21 (1H, dd, $^3J_{HH}$ 1.6 and $^3J_{HH}$ 4.0 Hz, H-5) 4.30 (1H, dd, $^3J_{HH}$ 1.6 and $^3J_{HH}$ 8.1, H-4), 4.32 (1H, dd, $^3J_{HH}$ 2.4 Hz and $^3J_{HH}$ 4.8 Hz, H-2), 4.59 (1H, dd, $^3J_{HH}$ 2.4 Hz and $^3J_{HH}$ 8.1 Hz, H-3), 5.62 (1H, d, $^3J_{HH}$ 5.0 Hz, H-1), 6.30 (1H, d, $^3J_{HH}$ 4.0 Hz, HetH-2); ^{13}C NMR (200 MHz, $CDCl_3$) δC 11.5 (Het$\underline{C}H_3$), 21.3 (-NCO$\underline{C}H_3$), 24.3, 25.0, 25.9, 26.1 (-C($\underline{C}H_3$)$_2$), 65.3 (C-5), 69.8 (C-4), 71.0 (C-2 and C-3), 89.9 (HetC-2), 96.8 (C-1), 109.2, 109.7 (-$\underline{C}$(CH$_3$)$_2$), 157.9 (C=N), 167.9 (C=O). Anal. calcd. for $C_{16}H_{24}N_2O_7$: %C, 53.92; %H, 6.79; %N, 7.86. Found %C, 53.79; %H, 6.86; %N, 7.65.

Microwave-assisted synthesis of compounds 4a and 4b. Compound **2** (0.4245 g, 1.3 mmol) were dissolved in pyridine (3.0 mL) in a microwave vessel and acetic anhydride (2.5 mL) was added. The sealed vessel with the mixture was heated at 140 °C with stirring (900 rpm) and the temperature was held for 60 min. Once cold, the mixture was transferred to a round bottom flask, some ethanol was added and the reaction medium was evaporated at reduced pressure, giving a glassy residue. The residue was purified as described previously and compounds **4a** and **4b** were obtained in a 68% yield (0.321 mg).

Acknowledgements

The authors thank the Universidad de Buenos Aires (N° 20020100100142), ANPCyT (PICT-BID 2007-00291), and CONICET (PIP 112-200801-0064) for financial support and Mr. Bruno Cetrángolo for his invaluable help. They also acknowledge ANPCyT (project N°. PME 2006-01113) for the purchase of the Oxford Gemini CCD diffractometer and the Spanish Research Council (CSIC) for provision of a free-of-charge license to the Cambridge Structural Database (Allen, 2002). N. B. D. is member of the Research Career from CONICET.

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