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Oxidative cyclization of D-fructose thiosemicarbazones to 2-amino-5-(D-*arabino*-1,2,3,4-tetrahydroxybut-1-yl)-1,3,4-thiadiazoles through carbon-carbon bond cleavage of the sugar chain

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Received September 25, 2002, accepted December 13, 2002

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Pharmazie 58: 367–371 (2003)

Condensation of D-fructose (**1**) with thiosemicarbazide or 4-phenylthiosemicarbazide gave the corresponding D-fructose thiosemicarbazones (**3a** and **3b**). The latter compounds underwent oxidative cyclization with 10% ethanolic ferric chloride to give mixtures of 2-amino-5-(D-*arabino*-1,2,3,4-tetrahydroxybut-1-yl)-1,3,4-thiadiazole (**6a**) and 2-amino-5-hydroxymethyl-1,3,4-thiadiazole (**5a**) from **3a** and the corresponding 2-phenylamino compounds **6b** and **5b** from **3b**. These products were formed as a result of cyclization of the thiosemicarbazone entity accompanied by C-1–C-2 or C-2–C-3 bond cleavage of the sugar chain. Structures of the 1,3,4-thiadiazole acyclo *C*-nucleosides **6a** and **5b** were confirmed by comparison with the unequivocally prepared compounds obtained by the dehydrogenative cyclization of D-arabinose thiosemicarbazones **11a** and **11b** with ethanolic ferric chloride. Structures of the 5-hydroxymethyl-1,3,4-thiadiazoles **5a** and **5b** were also confirmed by comparison with **5a** and **5b** unequivocally prepared by periodate cleavage of the alditolyl chain of **6a** and **6b** followed by reduction of the resulting aldehydes **8a** and **8b** with sodium borohydride. Compounds **6a** and **6b** were further characterized as their acetates **7a** and **7b** and were found to exist in the extended planar zizag conformation **13**. Condensative cyclization of the D-arabinose thiosemicarbazones **11a** and **11b** by boiling with acetic anhydride afforded the 1,3,4-thiadiazoline acyclo *C*-nucleoside acetates **9a** and **9b** which exist in the sickle (bent) conformation **14**. De-*N*- and de-*O*-acetylation with concomitant aromatization of **9a** and **9b** with 10% ethanolic $FeCl_3$ gave the 1,3,4-thiadiazole acyclo *C*-nucleosides **6a** and **6b**. The assigned structures were corroborated by 2D ^1H-^1H HOMCOR and 2D ^1H-^{13}C HETCOR NMR spectroscopy.

1. Introduction

We have been studying different routes for the synthesis of 1,3,4-thiadiazole [1–4] and 1,3,4-thiadiazoline [1, 5] acyclo *C*-nucleosides because of their valuable antimicrobial activities [1–5]. 1,3,4-Thiadiazole acyclo *C*-nucleosides were synthesized by oxidative cyclization of aldose sugar thiosemicarbazones [6–8] and *S*-alkylhydrazonecarbodithioates [4] as well as by dehydrative cyclization of 1-(poly-*O*-acetyl-aldonoyl)thiosemicarbazides [3], poly-*O*-acetylaldaric acids bis (thiosemicarbazides) [3] and poly-*O*-acetylaldaric acids bis (*S*-alkyldithiocarbohydrazides) [9, 10]. 1,3,4-Thiadiazoline acyclo *C*-nucleosides were prepared by condensative cyclization of aldose sugar thiosemicarbazones [11] and *S*-alkyl-hydrazonecarbodithioates [5] as well as by cyclocondensation of aldoses with thiobenzoylhydrazine [12–16].

Ketose monosaccharides, in contrast to their aldose congeners, are scarcely utilized in the synthesis of acyclo *C*-nucleosides [1, 2]. Lichtenthaler [17] attributed the modest utilization of ketoses as inexpensive raw materials in organic synthesis as being due to the more uncertain and less well understood chemistry of ketoses in comparison with that of aldoses. This led us to focus our attention on the utilization of ketose hydrazones in the synthesis of acyclo *C*-nucleosides. We also envisaged that cyclization of ketose hydrazones would be of academic interest because, for a fruitful cyclization to occur, it should involve concurrent carbon-carbon bond cleavage of the sugar chain with formation of more than one cyclization product.

In 1956 Holmberg [6] reported the oxidative cyclization of D-fructose thiosemicarbazone (**3a**) with $FeCl_3$ to 2-amino-5-(D-*arabino*-1,2,3,4-tetrahydroxybut-1-yl)-1,3,4-thiadiazole hydrochloride (**6a** · HCl). Structure **6a** was indirectly assigned [6] on the basis of possessing the same melting point and equal magnitude, but opposite sign, of optical rotation as 2-amino-(L-*arabino*-1,2,3,4-tetrahy-

droxybut-1-yl)-1,3,4-thiadiazole hydrochloride obtained by a similar oxidative cyclization of L-arabinose thiosemicarbazone [6]. Oxidative cyclization of **3a** to **6a** must have taken place with concomittant C-1−C-2 cleavage of **3a**. However, no explanation was offered [6] as to why 2-amino-5-hydroxymethyl-1,3,4-thiadiazole (**5a**), the other possible product emanating from the alternative cyclization accompanied by C-2−C-3 bond cleavage of **3a**, was not obtained.

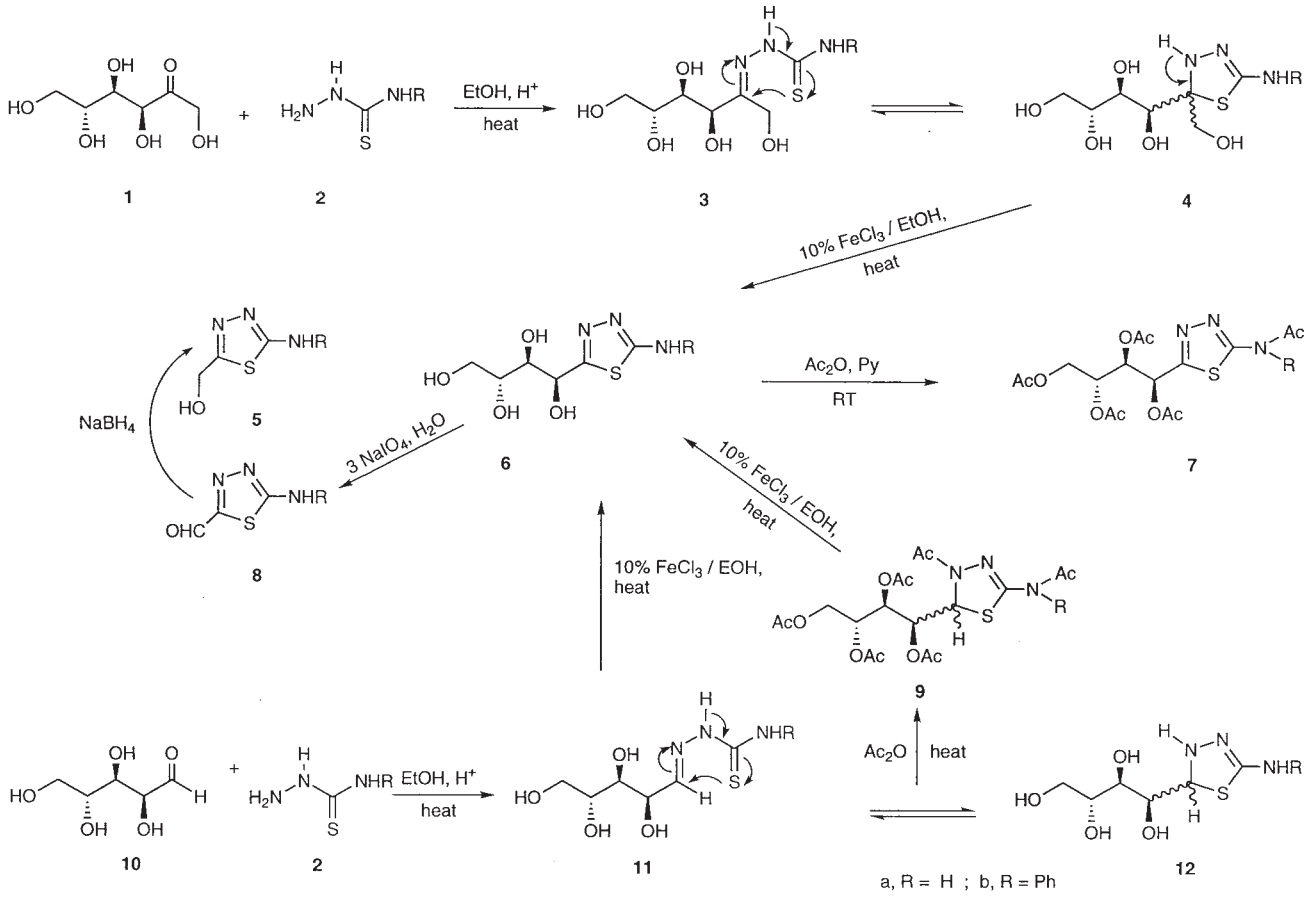
As a part of our studies on the utilization of sugar hydrazones for the synthesis of acyclo *C*-nucleosides [3–5, 18], this article describes the results obtained from extending these studies to ketose hydrazones and from reinvestigating the aforementioned cyclization of D-fructose thiosemicarbazones to 1,3,4-thiadiazole acyclo *C*-nucleosides. Also described are the results obtained on the condensative cyclization of D-fructose thiosemicarbazones to 1,3,4-thiadiazoline acyclo *C*-nucleosides.

2. Investigations, results and discussion

Condensation of D-fructose (**1**) with thiosemicarbazide (**2a**) or 4-phenylthiosemicarbazide (**2b**) gave D-fructose thiosemicarbazone (**3a**) and 4-phenylthiosemicarbazone (**3b**), respectively (Scheme). D-Arabinose thiosemicarbazone (**11a**) and D-arabinose 4-phenyl-thiosemicarbazone (**11b**) were similarly prepared from D-arabinose (**10**) by reaction with **2a** and **2b** respectively. Compounds **3a, 3b, 11a** and **11b** showed the expected OH, NH, and C=N IR absorptions.

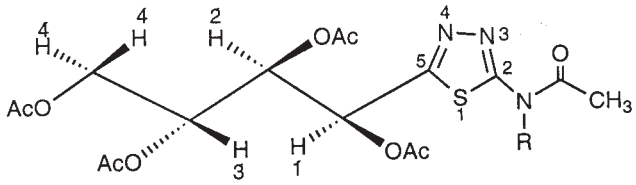
Treatment of **3a** with 10% ethanolic $FeCl_3$ solution gave two products, the first of which directly crystallized from the reaction mixture in 46% yield and was analyzed as $C_6H_{11}N_3O_4S$; CH_4O less than the starting thiosemicarbazone **3a**. It showed IR absorptions characteristic of OH, NH, and C=N groups and its ^1H NMR spectrum revealed proton signals of an amino group (2 N*H)*, and a tetrahydroxybutyl moiety (4 O*H*, and 5 C*H)*. These data are in agreement with the 2-amino-5-(D-*arabino*-1,2,3,4-tetrahydroxybut-1-yl)-1,3,4-thiadiazole structure **6a**. This result is in agreement with Holmberg's finding [6], although we have been able to isolate only **6a** rather than its hydrochloride (**6a** · HCl) [5]. Formation of **6a** from **3a** must have taken place through the cyclic 1,3,4-thiadiazoline tautomeric structure **4a** by cleavage of the C-5−CH_2OH bond (C-1−C-2 bond of the sugar chain of **3a**) and elimination of a methanol molecule. Corroboration of the assigned structure was achieved by direct comparison with a sample of **6a** unequivocally prepared by dehydrogenative cyclization of D-arabinose thiosemicarbazone **11a** with 10% ethanolic $FeCl_3$. Both products were found to be identical. The mother liquor, after the separation of **6a**, gave another product in 38% yield which was analyzed as $C_3H_5N_3OS$. The latter product was found to be identical with 2-amino-5-hydroxymethyl-1,3,4-thiadiazole (**5a**) unequivocally prepared from **6a** by sodium periodate oxidation followed by borohydride reduction of the obtained 2-amino-5-formyl-1,3,4-thiadiazole (**8a**). Formation of **5a** from **3a** must have taken place through the tautomeric 1,3,4-thiadiazoline structure **4a** by cleavage of the thiadiazoline C-5-tetrahydroxybutyl C-1′ bond (C-2−C-3 bond of the sugar chain of **3a**) and elimination of the tetrahydroxybutyl chain.

Scheme



A similar oxidative cyclization of D-fructose 4-phenylthiosemicarbazone (**3b**) with $FeCl_3$ gave 2-(D-*arabino*-1,2,3,4-tetrahydroxybut-1-yl)-5-phenylamino-1,3,4-thiadiazole (**6b**) and 2-hydroxymethyl-5-phenylamino-1,3,4-thiadiazole (**5b**). Compound **6b** showed ^{1}H NMR proton signals of an N*H*, a phenyl group (5H), and a tetrahydroxybutyl chain (4 O*H* and 5 C*H*) and its ^{13}C NMR spectrum displayed signals of the thiadiazole ring (2 C), the phenyl group (6 C), and the tetrahydroxybutyl chain carbons (4 C). The ^{1}H NMR spectrum of **5b** showed N*H*, phenyl group (5 H), and hydroxymethyl group (O*H* and CH_2) proton signals. Compound **6b** was found to be identical with that unequivocally prepared by dehydrogenative cyclization of D-arabinose 4-phenylthiosemicarbazone (**11b**). In addition, **5b** was found to be identical with a sample unambiguously prepared from **6b** by periodate oxidation followed by borohydride reduction of the obtained 2-formyl-5-phenylamino-1,3,4-thiadiazole **8**b. The two 1,3,4-thiadiazole acyclo *C*-nucleosides **6a** and **6b** were further characterized by acetylation with acetic anhydride in the presence of pyridine at ambient temperature to give the 2-acetamido- and 2-(acetylphenyl)amino-5-(D-*arabino*-1,2,3,4-tetraacetoxybut-1-yl)-1,3,4-thiadiazoles **7a** and **7b** respectively. Both compounds exhibited ^{1}H NMR signals of the tetraacetoxybutyl chain (5 C*H* and 4 OCOCH_3) and the acetamido group (NCOCH_3) protons. Compound **7a** showed, in addition, an exchangeable NH while **7b** showed proton signals of the phenyl group (5 H). ^{13}C NMR of **7b** revealed five *C*OCH$_3$ carbons at δ 168.78–167.41, the two thiadiazole ring carbons at δ 159.77 and 137.15 [19], the phenyl group (6 C) at δ 128.55–116.92, the tetraacetoxybutyl chain (4 C) at δ 68.79–66.5, and five COCH_3 carbons at δ 21.42–18.79 ppm. Assignment of these signals has been pinpointed by 2D ^{1}H-^{1}H HOMCOR and 2D ^{1}H-^{13}C HETCOR measurements. The coupling constants of the tetraacetoxybutyl chain CH protons of **7a** and **7b** were amenable for analysis as a tool for deducing their in-solution, most abundantly populated conformations at ambient temperature. The pattern of the coupling constants of **7a** and **7b** (see sections 3.11 and 3.12) is: $J_{1',2'} < 4$ Hz, $J_{2',3'} > 7$ Hz, $J_{3',4'} < 4$ Hz, and $J_{3'',4''} > 7$ Hz. Comparing these values with < 4 Hz and > 7 Hz established [20–24] for vicinal CH protons in gauch orientation (dihedral angle 60°) or antiparallel orientation (dihedral angle 180°) respectively, it is evident that the tetraacetoxybutyl chains H-1′–H-2′ and H-3′– H-4′ are in gauch orientations while H-2′–H-3′ and H-3′–H-4″ are in antiparallel orientations. These orientations indicate that compounds **7a** and **7b** exist preponderantly in the extended planar zigzag conformation **13a** and **13b** free from unfavourable 1,3-eclipsed interactions.

Heating D-arabinose thiosemicarbazone (**11a**) and 4-phenylthiosemicarbazone (**11b**) with acetic anhydride effected their cyclization with concurrent *N*- and *O*-acetylation to give 2-acetamido-5-(D-*arabino*-1,2,3,4-tetraacetoxybut-1-yl)-4-acetyl-4,5-dihydro-1,3,4-thiadiazole (**9a**) and 4-acetyl-2-(acetylphenyl)amino-5-(D-*arabino*-1,2,3,4-tetraacetoxybut-1-yl)-4,5-dihydro-1,3,4-thiadiazole (**9b**). Transformation of **11** to **9** occurred as a result of fixing the tautomeric 1,3,4-thiadiazoline structure **12** of **11** through *N*-acetylation of the thiadiazoline ring C2–NH and N4–H and *O*-acetylation of the tetrahydroxybutyl chain. Compounds **9a** and **9b** showed IR absorptions of OAc, NAc, and C=N functions. The ^{1}H NMR spectrum of **9a** displayed proton signals of the N*H*, thiadiazoline C-5–*H* and N4–COCH_3, the tetraacetoxybutyl group (5 C*H* and 4 OCOCH_3). The coupling constants pattern of the vicinal



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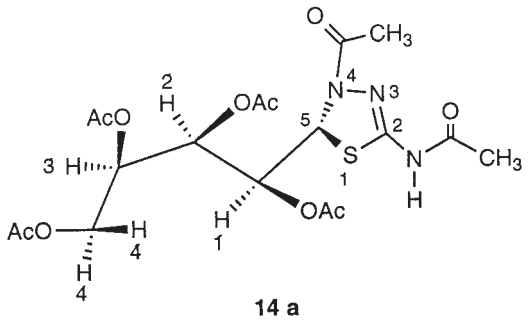
CH protons of **9a** (see section 3.13) is: $J_{5,1'} < 4$ Hz, $J_{1',2'} > 7$ Hz, $J_{2',3'} > 7$ Hz, $J_{3',4'} < 4$ Hz, and $J_{3',4''} > 7$ Hz. This pattern indicated that H-5–H-1′ and H-3′–H-4′ are in gauch orientations while H-1′–H-2′, H-2′–H-3′, and H-3′–H-4″ are in antiparallel orientations. Thus, in contrast to **7a** and **7b**, these orientations indicate the presence of **9a** most abundantly in the sickle (bend) conformation **14a**. The latter conformation derives from the corresponding extended palnar zigzag conformation such as **13a** by 180° rotation around the C-2′–C-3′ bond to alleviate adverse 1,3-eclipsed interactions. It is interesting that although both **7** and **9** possess the same D-*arabino* configuration of their tetraacetoxybutyl chain, yet they are preponderantly in different conformations. Molecular models showed that the N4-Ac group in **9** caused restriction of rotation of the substituted 1,3,4-thiadiazoline ring about the C-5–C-1′ bond in the extended planar zigzag conformation; to mitigate such adverse steric interaction, compound **9a** acquires the sickle conformation **14a**.



14 a

Finally, it was interesting to find out that treatment of **9a** and **9b** with 10% ethanolic $FeCl_3$ solution caused their transformation to the free acyclo *C*-nucleosides **6a** and **6b** respectively. This reaction involved de-*O*-acetylation of the tetraacetoxybutyl chain with concurrent de-*N*-acetylation and aromatization of the thiadiazoline nucleus.

3. Experimental

Melting points were determined on a MEL-TEMP II melting point apparatus in open glass capillaries and are uncorrected. The IR spectra were recorded for KBr discs on a Pye-Unicam SP1025 spectrophotometer. NMR spectra were carried out at ambient temperature (~25 °C) with a Brucker AC-250 Cryospec (250 MHz) or Brucker MW (300 MHz) spectrometer using TMS as an internal standard. Homogeneity of the products and follow up of the reactions were checked by TLC on precoated silica gel G plates (E. Merck; layer thickness 0.25 mm). Solvent systems: V/V; the distance of solvent travel was 5 cm and the spots were visualized by iodine vapour. Elemental microanalyses were performed at the Microanalytical Unit, Cairo University, Cairo, Egypt. The compounds prepared gave satisfactory elemental analyses to (+/–) 0.3%.

3.1. D-Fructose thiosemicarbazone (3a)

A solution of thiosemicarbazide (**2a**, 11 mmol) in EtOH (30 ml) was added to a solution of D-fructose (**1**, 11 mmol) in H_2O (5 ml) containing 2 drops of acetic acid and the mixture was heated under reflux for 4 h. The product which separated after attaining room temperature was filtered and crystallized from H_2O/EtOH to give **3a** as colorless crystals (82%); m.p.:

122–124 °C; TLC in 1:2 $CHCl_3$/MeOH, R_f: 0.5; IR: 3335, 3236 (OH), 3195 (NH), and 1617 cm^{-1} (C=N).
$C_7H_{15}N_3O_5S$ (253)

3.2. D-Fructose 4-phenylthiosemicarbazone (3b)

The title compound was prepared from 4-phenylthiosemicarbazide (**2b**, 10 mmol) and **1** (10 mmol) as described above for the preparation of **3a**. It crystallized from H_2O/EtOH to give **3b** as colorless crystals; m.p.: 129–130 °C; TLC in 1:2 $CHCl_3$/MeOH, R_f: 0.50; IR: 3414, 3303 (OH), 3168 (NH), and 1638 cm^{-1} (C=N).
$C_{13}H_{19}N_3O_5S$ (329)

3.3. D-Arabinose thiosemicarbazone (11a)

A solution of **2a** (11 mmol) in ethanol (30 ml) was added to a solution of D-arabinose (**10**, 11 mmol) in H_2O (5 ml) containing 2 drops of acetic acid and the mixture was heated under reflux for 30 min. The product which separated after attaining room temperature was filtered and cystallized from H_2O/EtOH to give **11a** as colorless crystals (88%); m.p.: 161 °C, Lit. [25], m.p.: 151–152 °C; TLC in 1:1 $CHCl_3$/MeOH, R_f: 0.52; IR: 3265 (OH), 3181 (NH), and 1645 cm^{-1} (C=N).
$C_6H_{13}N_3O_4S$ (223)

3.4. D-Arabinose 4-phenylthiosemicarbazone (11b)

The title compound was prepared from **2b** (12 mmol) and **10** (12 mmol) as described above for the preparation of **11a**. It crystallized from H_2O/EtOH to give **11b** as colorless crystals (83%), m.p.: 110–112 °C; TLC in 1:1 $CHCl_3$/MeOH, R_f: 0.59; IR: 3415, 3346 (OH), 3174 (NH), and 1617 cm^{-1} (C=N).
$C_{12}H_{17}N_3O_4S$ (299)

3.5. Oxidative cyclization of 3a to 2-amino-(5-D-arabino-1,2,3,4-tetrahydroxybut-1-yl)-1,3,4-thiadiazole (6a) and 2-amino-5-hydroxymethyl-1,3,4-thiadiazole (5a)

A solution of **3a** (8 mmol) in EtOH (50 ml) was gradually treated with a 10% ethanolic solution of $FeCl_3$ (10 ml) and heated under reflux for 30 min on a boiling waterbath. The product which separated after attaining room temperature was filtered and crystallized from H_2O/EtOH to give **6a** as colorless crystals (46%); m.p.: 198 °C, Lit. [6], m.p. of 6a · HCl: 198–200 °C; mixed m.p. with **6a** unequivocally prepared (section 3.7): 198 °C; TLC in 1:1 $CHCl_3$/MeOH, R_f: 0.61; IR: 3380 (OH), 3265 (NH), and 1626 cm^{-1} (C=N); ^1H NMR $[(CD_3)_2SO]_2$: δ 5.04 (s, 2 H, exchangeable, NH_2) and 3.70–3.40 ppm (m, 9 H, tetrahydroxybutyl 5 H + 4 OH).
$C_6H_{11}N_3O_4S$ (221)
Keeping the mother liquor after the separation of **6a** at room temperature for 2 days yielded a second product which was filtered and crystallized from EtOH to give **5a** as pale yellow crystals (38%); m.p. and mixed m.p. with unequivocally prepared **5a** (section 3.9): 110 °C, TLC in 9:1 $CHCl_3$/MeOH, R_f: 0.52; IR: 3414 (OH), 3265 (NH), and 1625 cm^{-1} (C=N).
$C_3H_5N_3OS$ (131)

3.6. Oxidative cyclization of 3b to 2-(D-arabino-1,2,3,4-tetrahydroxybut-1-yl)-5-phenylamino-1,3,4-thiadiazole (6b) and 2-hydroxymethyl-5-phenylamino-1,3,4-thiadiazole (5b)

A solution of **3b** (6 mmol) in EtOH (50 ml) was cyclized with a 10% ethanolic solution of iron(III) chloride (10 ml) as described for the preparation of **6a**. The separated product was crystallized from H_2O/EtOH to give **6b** as colorless crystals (44%); m.p. and mixed m.p. with the unequivocally prepared **6b** (section 3.8): 233–235 °C; TLC in 1:1 $CHCl_3$/MeOH, R_f: 0.63; IR: 3413 (OH), 3297 (NH), and 1605 cm^{-1} (C=N); ^1H NMR $[(CD_3)_2SO]$: δ 10.16 (s, 1 H, exchangeable, NH), 7.50 (d, 2 H, phenyl H-2 and H-6, $J_{2,3}$ 7.70 Hz), 7.35 (t, 2 H, phenyl H-3 and H-5, $J_{3,4}$ 7.40 Hz), 6.97 (t, 1 H, phenyl H-4, $J_{4,3}$ 7.40 Hz), 5.11 (d, 1 H, tetrahydroxybutyl H-1′, $J_{1',2'}$ 1.40 Hz), 4.46–3.77 (broad, 4 H, exchangeable, 4 OH), 3.62–3.39 ppm (m, 4 H, tetrahydroxybutyl H-2′, H-3′, H-4′ and H-4″); ^{13}C NMR $[(CD_3)_2SO]$: δ 166.73 (thiadiazolyl C-2). 166.57 (thiadiazolyl C-5), 143.00 (phenyl C-1), 131.03 phenyl C-3 and C-5), 123.48 (phenyl C-4), 119.19 (phenyl C-2 and C-6), 75.73 and 72.84 (tetrahydroxybutyl C-2′ and C-3′), 70.31, and 65.38 ppm (tetrahydroxybutyl C-1′ and C-4′respectively).
$C_{12}H_{15}N_3O_4S$ (297)
Keeping the mother liquor after the separation of **6b** at room temperature for 2 days yielded a second product which was filtered and crystallized from EtOH to give **5b** as pale yellow crystals (32%); m.p. and mixed m.p. with the unequivocally prepared **5b** (section 3.10): 168 °C; TLC in 9:1 $CHCl_3$/MeOH, R_f: 0.54; IR: 3414 (OH), 3225 (NH), and 1608 cm^{-1} (C=N); ^1H NMR $[(CD_3)_2SO]$: δ 10.30 (s, 1 H, exchangeable, NH), 7.60 (d, 2 H, phenyl H-2 and H-6, $J_{2,3}$ 7.70 Hz), 7.35 (t, 2 H, phenyl H-3 and H-5, $J_{3,4}$ 7.40 Hz), 6.99 (t, 1 H, phenyl H-4, $J_{4,3}$ 7.40 Hz), 6.00 (s, exchangeable, OH), and 4.73 ppm (s, 2 H, CH_2).
$C_9H_9N_3OS$ (207)

3.7. Unequivocal synthesis of 6a from 11a

Dehydrogenative cyclization of **11a** (9 mmol) with a 10% ethanolic solution of $FeCl_3$ (10 ml) as described in section 3.5, gave **6a** (61%); m.p.: 198 °C; TLC in 1:1 $CHCl_3$/MeOH, R_f: 0.61; IR: 3380 (OH), 3265 (NH), and 1626 cm^{-1} (C=N).

3.8. Unequivocal synthesis of 6b from 11b

Dehydrogenative cyclization of **11** (7 mmol) with a 10% ethanolic solution of $FeCl_3$ (10 ml) as described in section 3.5, gave **6b** (64%), m.p.: 233–235 °C; TLC in 1:1 $CHCl_3$/MeOH, R_f: 0.63; IR: 3413 (OH), 3297 (NH), and 1605 cm^{-1} (C=N).

3.9. Unequivocal synthesis of 5a

3.9.1. 2-Amino-5-formyl-1,3,4-thiadiazole (8a)

A suspension of the unequivocally prepared **6a** (section 3.7, 5 mmol) in H_2O (15 ml) was treated with a solution of sodium metaperiodate (13 mmol) in H_2O (25 ml) and stirred for 1 h at room temperature. The product was filtered, washed with H_2O, 10% $Na_2S_2O_3$ solution and H_2O, and crystallized from EtOH to give **8a** as yellow crystals (52%); m.p.: 135 °C; TLC in 9:1 $CHCl_3$/MeOH, R_f: 0.57; IR: 3348 (NH_2), 1684 (CHO), 1550 cm^{-1} (C=N).
$C_3H_3N_3OS$ (129)

3.9.2. Reduction of 8a to 5a

A solution of sodlium borohydride (8 mmol) in H_2O (15 ml) was added dropwise to a suspension of **8a** (8 mmol) in H_2O (15 ml) while stirring. The mixture was kept at room temperature for 24 h and then treated with a few drops of acetic acid. The product obtained was filtered, washed with H_2O, and crystallized from EtOH to give **5a** (60%); m.p. 110 °C. in 9:1 $CHCl_3$/MeOH, R_f: 0.52, IR: 3414 (OH), 3265 (NH), and 1625 cm^{-1} (C=N).

3.10. Unequivocal synthesis of 5b

3.10.1. 2-Formyl-5-phenylamino-1,3,4-thiadiazole (8b)

Oxidation of the unequivocally prepared **6b** (section 3.8, 4 mmol) with sodium metaperiodate (10 ml) as described for the preparation of **8a** and crystallization of the obtained product from EtOH gave **5b** as yellow crystals (58%); m.p.: 184–186 °C; TLC in 9:1 $CHCl_3$/MeOH, R_f: 0.59; IR: 3248 (NH), 1681 (CHO), and 1619 cm^{-1} (C=N).
$C_9H_7N_3OS$ (205)

3.10.2. Reduction of 8b to 5b

Reduction of **8b** (5 mmol) with sodium borohydride (5 mmol) as described for the reduction of **8a** (Section 3.9.2) and crystallization of the obtained product from EtOH gave **5b** (62%); m.p.: 168 °C. TLC in 9:1 $CHCl_3$/MeOH, R_f: 0.54; IR: 3414 (OH), 3225 (NH), and 1608 cm^{-1} (C=N).

3.11. 2-Acetamido-5-(D-arabino-1,2,3,4-tetraacetoxybut-1-yl)-1,3,4-thiadiazole (7a)

A mixture of **6a** (5 mmol), pyridine (5 ml) and acetic anhydride (25 ml) was stirred at room temperature for 24 h and then evaporated. The residue obtained was crystallized from EtOH to give **7a** as colorless crystals (60%); m.p.: 88–90 °C; TLC in 9:1 $CHCl_3$/MeOH, R_f: 0.69; IR: 3168 (NH), 1759 (OAc), 1708 (NAc), and 1553 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 13.35 (s, 1 H, exchangeable, NH), 6.49 (d, 1 H, tetraacetoxybutyl H-1′, $J_{1',2'} < 4$ Hz), 5.69 (dd, 1 H, tetraacetoxybutyl H-2′, $J_{2',3'}$ 8 Hz), 5.36–5.26 (m, 1 H, tetraacetoxybutyl, H-3′), 4.30, 4.15 (2 dd, 1 H, each, tetraacetoxybutyl H-4′ and H-4′, $J_{3',4'}$ 3 Hz, $J_{3',4''}$ 10 Hz), 2.49 (s, 3 H, NAc), 2.16, 2.10 (2 s, 3 H, each, 2 OAc), and 2.02 ppm (s, 6 H, 2 OAc).
$C_{16}H_{21}N_3O_9S$ (431)

3.12. 2-(D-Arabino-1,2,3,4-tetraacetoxybut-1-yl)-5-(acetylphenyl)amino-1,3,4-thiadiazole (7b)

A mixture of **6b** (5 mmol) with pyridine (5 ml) and acetic anhydride (25 ml) was stirred at room temperature for 24 h and then evaporated. The residue obtained was crystallized from EtOH to give **7b** as colorless crystals (62%); m.p.: 118–120 °C; TLC in 9:1 $CHCl_3$/MeOH, R_f: 0.71; IR: 1754 (OAc), 1685 (NAc), and 1595 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 7.60–7.50 (m, 3 H, phenyl protons), 7.34–7.25 (m, 2 H, phenyl protons), 6.49 (d, 1 H, tetraacetoxybutyl H-1′, $J_{1',2'}$ 3 Hz), 5.65 (dd, 1 H, tetraacetoxybutyl H-2′, $J_{2',3'}$ 8 Hz), 5.31–5.26 (m, 1 H, tetraacetoxybutyl H-3′), 4.28, 4.15 (2 dd, 1 H each, tetraacetoxybutyl H-4′ and H-4″, $J_{3',4'}$ 3 Hz, $J_{3',4''}$ 12 Hz), 2.15 (s, 3 H, NAc), 2.08, 2.07, 2.06, and 2.04 ppm (4 s, 3 H each, 4 OAc); ^{13}C NMR ($CDCl_3$): δ 168.78, 168.12, 167.98, 167.52 (4-O−$COCH_3$), 167.41 ($NCOCH_3$), 159.77 (thiadiazolyl C-2), 137.15 (thidiazolyl C-5), 128.55, 128.04, 127.87, 126.75 (phenyl carbons), 68.79, 66.70, 66.59, 59.95 (tetraacetoxybutyl C-2′, C-1′, C-3′, and C-4′ respec-

tively), 21.42 (N−$COCH_3$), 19.00, 18.97, 18.89, 18.79 ppm (4 O−$COCH_3$). $C_{22}H_{25}N_3O_9S$ (507)

3.13. 2-Acetamido-4-acetyl-5-(D-arabino-1,2,3,4-tetraacetoxybut-1-yl)-4,5-dihydro-1,3,4-thiadiazole (**9a**)

A mixture of **11a** (9 mmol) and acetic anhydride (50 ml) was heated under reflux for 4 h and then evaporated to dryness. A solution of the syrup obtained in chloroform (30 ml) was stirred with silica gel for 5 min, filtered and evaporated to give **9a** as a colorless syrup; TLC in 9 : 1 $CHCl_3$/MeOH, R_f: 0.60; IR: 3262 (NH), 1752 (OAc), 1646 (NAc), and 1613 cm^{-1} (C=N); ^1H NMR [$(CD_3)_2SO$]: δ 11.62 (s, 1 H, exchangeable, AcNH), 6.05 (d, 1 H, thiadiazoline H, $J_{5,1'}$ 2 Hz), 5.93 (d, 1 H, tetraacetoxybutyl H-1′, $J_{1',2'}$ 8 Hz), 5.74 (dd, 1 H, tetraacetoxybutyl H-2′, $J_{2',3'}$ 14 Hz), 5.49–5.47 (m, 1 H, tetraacetoxybutyl H-3), 5.37, 5.25 (2 dd, 1 H each, tetraacetoxybutyl H-4′and H-4″, $J_{3',4'}$ 2 Hz, $J_{3',4''}$ 8 Hz), 2.11 (s, 3 H each, 2 NAc), 2.05, 2.04, 2.03, and 2.01 ppm (4 s, 3 H each, 4 OAc). $C_{18}H_{25}N_3O_{10}S$ (475)

3.14. 4-Acetyl-2-(acetylphenyl)amino-5-(D-arabino-1,2,3,4-tetraacetoxybut-1-yl)-4,5-dihydro-1,3,4-thiadiazole (**9b**)

The title compound was prepared from **11b** (7 mmol) and acetic anhydride (50 ml) as described above for the preparation of **9a**. It was crystallized from ethanol to give **9b** as colorless crystals (74%); m.p.: 118–119 °C; TLC in 9 : 1 $CHCl_3$/MeOH, R_f: 0.61; IR: 1751 (OAc), 1691 (NAc), and 1597 cm^{-1} (C=N).
$C_{24}H_{29}N_3O_{10}S$ (509)

3.15. Conversion of **9a** *to* **6a**

A solution of **9a** (4 mmol) in EtOH (25 ml) was treated with a 10% ethanolic solution of $FeCl_3$ (10 ml) and heated on a water bath for 30 min. The product obtained after attaining ambient temperature was filtered and crystallized from H_2O/EtOH to give **6a** (61%); m.p. and mixed m.p.: 198 °C; TLC and IR data are identical to those of the unequivocally prepared **6a** (section 3.7)

3.16. Conversion of **9b** *to* **6b**

Treatment of **9b** (4 mmol) with a 10% ethanolic solution of $FeCl_3$ (10 ml) as described above in section 3.15, gave **6b** (60%); m.p. and mixed m.p.: 235–238 °C, TLC, IR data are identical to those of the unequivocally prepared **6b** (section 3.8).

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