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Synthesis and Conformational Properties of Sugar Amides and Thioamides

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Abstract: The synthesis of deoxythioformamido and deoxythioacetamido derivatives of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose, 1,2:3,5-di-*O*-isopropylidene-α-D-glucofuranose, and 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose at the primary carbon atom has been effected by thionation of the corresponding sugar amides. Formamides and thioformamides existed as a mixture of the *Z* (major) and *E* (minor) stereomers around the N-C(=X) bond in $CDCl_3$ solutions, while the *Z* rotamer was the sole one detected in the cases of acetamides and thioacetamides.

N-Formyl and *N*-acetyl amino sugars are biologically important compounds which are commonly found as constituents of glycoconjugates, playing an important role in molecular recognition phenomena.[1] A key structural aspect of these molecules is the hindered internal rotation about the carbon-nitrogen amide bond as a consequence of its partial double-bond character.[2] *N*-Thiocarbonyl amino sugars are interesting as close analogues of the natural amido sugars for structure-activity studies and enzymatic tests. The higher volume and polarizability of the sulphur atom and the increased rotational barriers of thioamides[3] as compared to their oxo-counterparts may result in different conformational properties which have been invoked to explain disparities in their biological activities.[4] Thus, the conformational analysis of both series of *N*-carbonyl and *N*-thiocarbonyl amino sugars is not trivial.

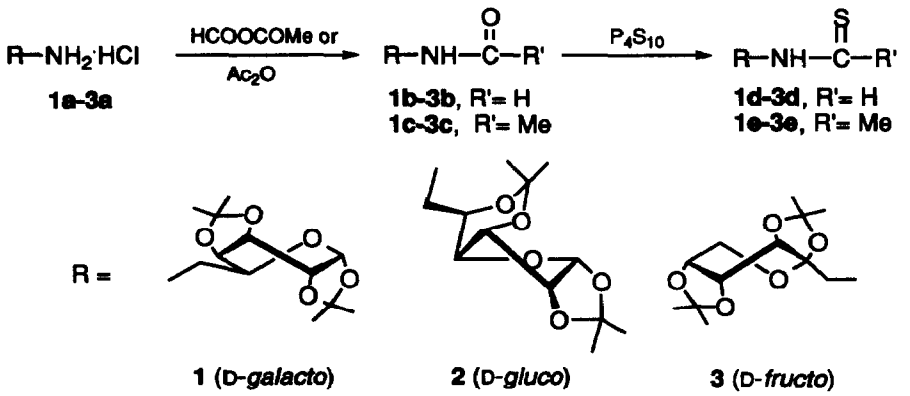
The conformational behaviour of acylated monosaccharides bearing an amido or thioamido group at a secondary carbon atom of a rigid pyranose ring has been regarded to some extent,[5] and the synthesis of fully unprotected sugar thioamides by direct thioacylation of the corresponding amino sugars has been recently achieved.[6] Hitherto, no attention has been directed to their congeners at a primary carbon atom, in spite of the biological significance of the amino sugars precursors; e.g. 6-amino-6-deoxy-D-glucose is a constituent of aminoglycoside antibiotics such as kanamycins, gentamicins, and neamine[7], and 1-amino-1-deoxy-D-fructose is the product of Amadori rearrangement of D-glucosylamine.[8]

We now report the synthesis and conformational properties of some formamido, acetamido, thioformamido, and thioacetamido sugars in which the functional group is linked to a primary carbon atom. Protection of the secondary hydroxyl groups has been effected by acetalation, keeping in mind that

deprotection of the acetal groups can be effected under mild acidic conditions compatible with the above functional groups.[9]

RESULTS AND DISCUSSION

The new sugar formamides (**1b-3b**), acetamides (**3c**), thioformamides (**1d-3d**), and thioacetamides (**1e-3e**) were prepared from the corresponding diisopropylidene amino hexose hydrochlorides[10] (**1a-3a**) by the synthetic pathway shown in Scheme 1. The acetamido derivatives **1c** and **2c** have been previously reported,[11,12] but their NMR data were either not available or not complete. *N*-Thioformamido sugars have been obtained from isothiocyanate precursors by reduction with tributyltin hydride.[13] In our hands, this reaction was unsuccessful when derivatives bearing the isothiocyanato group at a primary carbon atom[14-16] were used as substrates. Nevertheless, thionation[17] of the corresponding formamides afforded the target thioformamido sugars in satisfactory yields.



Scheme 1

The structural study of the *N*-acyl(thioacyl) derivatives **1b-3b**, **1c-3c**, **1d-3d**, and **1e-3e** requires discussion of: (a) the *E,Z* configurational assignment of the amide(thioamide) bond, (b) the preferred conformation about the α-methylene-nitrogen bond, (c) the relative disposition between the sugar ring and the amido- or thioamido-methylene branch, and (d) the conformation of the sugar ring.

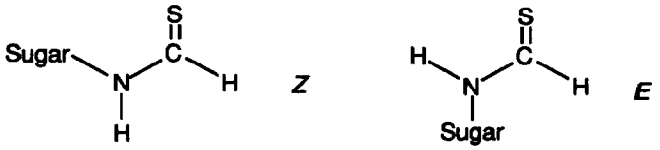
Formamides (**1b-3b**) and thioformamides (**1d-3d**) showed in their ^{1}H (Table 1) and ^{13}C NMR (Table 2 and Experimental) spectra in $CDCl_3$ solution two sets of signals, indicative of an equilibrium mixture of the *Z* and *E* isomers about the amide (thioamide) bond. The configurational assignment of formamido and thioformamido sugars at secondary positions has been previously studied.[5] Some rules have been proposed to distinguish between the *Z* and *E* configurations on the basis of the ^{1}H and ^{13}C chemical shifts of the formyl (thioformyl) group and the α-methylene group, as well as values of $J_{NH,CHO}$ and $J_{NH,CHS}$. All these criteria were of application for the new derivatives at a primary carbon atom, i.e.: $\delta_{\alpha CH2}$ (*Z*) > $\delta_{\alpha CH2}$ (*E*), $\delta_{\alpha CH2}$ (*Z*) < $\delta_{\alpha CH2}$ (*E*), $\delta_{HC(=X)}$ (*Z*) > $\delta_{HC(=X)}$ (*E*), $\delta_{C(=X)}$ (*Z*) < $\delta_{C(=X)}$ (*E*), $J_{NH,CHO}$ = 0.4-1.4 Hz (*Z*), $J_{NH,CHO}$ = 11.8-12.0 Hz (*E*), $J_{NH,CHS}$ = 6.1-6.3 Hz (*Z*), $J_{NH,CHS}$ = 14.5-14.8 Hz (*E*).

Table 1. ^{1}H NMR Data ($CDCl_3$) of Compounds **1b-3b** and **1d-3d**.

Compound	Chemical shifts (δ, ppm)									
	H-1a	H-1b	H-2	H-3	H-4	H-5	H-6a	H-6b	NH	CHS
1b*Z*[a]	—	5.51d	4.31dd	4.60dd	4.21dd	3.90ddd	3.81ddd	3.20ddd	6.10bs	8.19d
1b*E*	—	5.51d	4.32dd	4.62dd	4.21dd	3.76m	←——— 3.44m ------→		6.00bs	8.06d
2b*Z*[a]	—	5.99d	4.57d	4.21d	4.25dd	3.65td	3.73dddd	3.40dddd	5.81bs	8.21d
2b*E*	—	5.99d	4.59d	4.22d	4.25dd	←——— 3.58-3.52m ----→		3.37m	5.81bs	8.07d
3b*Z*[a]	3.70dd	3.55dd	—	4.23d	4.58dd	4.23-4.21m	3.86dd	3.75d	6.15bs	8.19d
3b*E*	←—— 3.46-3.44m ---→		—	4.12d	4.61dd	4.23-4.21m	3.89dd	3.75d	5.85bs	8.03d
1d*Z*[b]	—	5.52d	4.33dd	4.64dd	4.27dd	4.31-4.25m	4.19-4.15m	3.56ddd	8.31bs	9.38d
1d*E*	—	5.53d	4.34dd	4.65dd	4.27dd	3.87ddd	←—— 3.70-3.65m ---→		8.22bs	9.15d
2d*Z*[b]	—	5.97d	4.55d	4.22d	4.28dd	3.82td	4.17dddd	3.75dddd	8.18bs	9.47d
2d*E*	—	5.96d	4.56d	4.22d	4.28dd	←——— 3.83 - 3.50m --------→			8.19bs	9.20d
3d*Z*[a]	4.03ddd	3.90ddd	—	4.28d	4.59dd	4.21ddd	3.87dd	3.73dd	8.18bs	9.59dt
3d*E*	3.67dd	3.63dd	—	4.13d	4.60dd	4.20ddd	3.88dd	3.75dd	8.00bs	9.21d

	Coupling constants (*J*, Hz)															
	$J_{1a,1b}$	$J_{1a,NH}$	$J_{1b,NH}$	$J_{1a,CH}$	$J_{1b,CH}$	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$	$J_{6a,NH}$	$J_{6b,NH}$	$J_{6a,CH}$	$J_{6b,CH}$	$J_{CH,NH}$
1b*Z*	—	—	—	—	—	5.0	2.5	7.9	1.9	3.9	9.1	13.9	8.1	4.1	—	—	1.4
1b*E*	—	—	—	—	—	5.0	2.5	7.9	1.9	—	—	—	—	—	—	—	12.0
2b*Z*	—	—	—	—	—	3.7	0	3.9	6.6	4.7	7.1	13.2	6.1	5.4	0.7	0.4	0.5
2b*E*	—	—	—	—	—	3.7	0	3.9	6.6	—	—	—	—	—	—	—	11.9
3b*Z*	13.7	5.7	5.3	—	—	—	—	3.5	7.9	2.0	0	13.0	—	—	—	—	0.4
3b*Z*	—	—	—	—	—	—	—	2.7	7.9	2.0	0	13.0	—	—	—	—	11.8
1d*Z*	—	—	—	—	—	5.0	2.5	7.9	1.9	3.5	8.7	13.2	—	3.7	0	0	6.1
1d*E*	—	—	—	—	—	5.0	2.5	7.9	1.9	3.5	8.7	13.2	—	3.7	0	0	14.5
2d*Z*	—	—	—	—	—	3.6	0	3.6	6.7	4.2	6.6	12.9	7.4	7.7	1.0	0.8	6.2
2d*E*	—	—	—	—	—	3.6	0	3.6	6.7	—	—	—	—	—	1.0	0.8	14.8
3d*Z*	14.3	4.9	4.9	1.2	1.2	—	—	2.5	7.7	2.1	0.5	12.9	—	—	—	—	6.3
3d*E*	14.3	6.3	4.5	0	0	—	—	2.7	7.7	2.1	0.5	12.9	—	—	—	—	14.8

[a] *At 500 MHz.* [b] *At 300 MHz.*



The *Z* rotamer was found to be the major one in both series of compounds (Table 3). The signals arising from both isomers did not coalesce in the range of the temperatures considered (up to 55°C), nor a significant widening was observed as compared to signals from the solvent, indicative of a high activation energy for the rotation about the N-C(=X) bond with respect to the NMR time scale.

Acetamides (**1c-3c**) and thioacetamides (**1e-3e**) existed in $CDCl_3$ solutions as a single rotameric form, as seen from ^1H (Table 4) and ^{13}C NMR (Table 2 and Experimental) spectra at different temperatures (-40 to 55°C). The *Z* configuration was assigned on the basis of a differential NOE experiment: the irradiation of the CH_3 signal produced an increasing (11-12%) of the corresponding signal for the NH proton.

Table 2. ^{13}C NMR Selected Data of Compounds **1b-e** to **3b-e**.

δ(ppm)	Compound											
	1b	**2b**	**3b**	**1c**	**2c**	**3c**	**1d**	**2d**	**3d**	**1e**	**2e**	**3e**
C=X(*Z*)	161.3	161.0	161.1	171.0	169.8	170.1	189.4	189.3	188.8	200.9	201.2	200.7
C=X(*E*)	164.8	164.7	165.4	—	—	—	192.2	192.4	192.7	—	—	—
αCH$_2$(*Z*)	38.1	40.1	44.6	39.8	41.4	46.9	43.5	45.1	50.6	46.0	48.1	53.4
αCH$_2$(*E*)	41.6	43.7	47.4	—	—	—	49.5	50.8	55.1	—	—	—

Table 3. Relative Proportion of *Z:E* Isomers for Sugar Formamides **1b-3b** and Thioformamides **1d-3d**.

	1b	**2b**	**3b**	**1d**	**2d**	**3d**
Z:E[a]	1:0.13	1:0.38	1:0.45	1:0.13	1:0.19	1:0.05

[a]Values obtained by digital integration of signals arising from formyl (thioformyl) protons.

Theoretical studies have suggested a linear relationship between certain ^{13}C=O chemical shifts and their corresponding ^{13}C=S values.[18] Several equations allowing estimation of $\delta_{C=S}$ from $\delta_{C=O}$ (or vice versa) in homologous substrates have been proposed. Such relationships have never been correlated to the stereochemistry of the amido and thioamido groups. Examination of earlier works revealed that the linear relation of eq (1) was obtained for compounds that existed in the exclusive *Z* configuration,[19] while eq (2) has been proposed for cyclic derivatives having the *E* configuration anchored.[20]

$$\delta_{C=S} = 1.31\ \delta_{C=O} - 22.1 \text{ ppm} \quad (1)$$

$$\delta_{C=S} = 1.45\ \delta_{C=O} - 46.5 \text{ ppm} \quad (2)$$

Accordingly, our data for *Z* formamides and thioformamides conformed to eq (1), while the *E* isomers conformed to eq (2), suggesting that these linear relations are of diagnostic value (Figure 1). Furthermore, data for acetamides (**1c-3c**) and thioacetamides (**1e-3e**) also conformed to eq (1), in agreement with the *Z* configuration supported by NOE data.

Table 4. ^{1}H NMR Data ($CDCl_3$) of Compounds **1c-3c** and **1e-3e**.

Comp.	Chemical shifts (δ, ppm)								
	H-1a	H-1b	H-2	H-3	H-4	H-5	H-6a	H-6b	NH
1c[a]	—	5.50d	4.29dd	4.57dd	4.18dd	3.87ddd	3.71ddd	3.16ddd	5.93bs
2c[a]	—	6.03d	4.60d	4.22d	4.27dd	3.63td	3.73ddd	3.32ddd	5.94dd
3c[a]	3.62dd	3.54dd	—	4.25d	4.57dd	4.22ddd	3.87dd	3.73dd	6.21bs
1e[a]	—	5.50d	4.33dd	4.63dd	4.26dd	4.24ddd	4.15ddd	3.51ddd	8.34dd
2e[b]	—	6.00d	4.58d	4.23d	4.28dd	3.80td	4.14ddd	3.69ddd	7.51t
3e[a]	3.80d	3.80d	—	4.21d	4.49dd	4.12dd	3.77dd	3.61d	7.97bs

	Coupling constants (*J*, Hz)											
	$J_{1a,1b}$	$J_{1a,NH}$	$J_{1b,NH}$	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$	$J_{6a,NH}$	$J_{6b,NH}$
1c	—	—	—	5.0	2.4	7.9	1.8	3.5	9.0	14.9	7.8	3.8
2c	—	—	—	3.7	0	3.7	7.1	3.5	7.1	13.7	10.0	7.1
3c	13.7	5.1	5.4	—	—	2.6	7.8	1.6	0.5	13.1	—	—
1e	—	—	—	5.0	2.5	7.7	1.8	3.3	8.5	13.6	6.7	4.3
2e	—	—	—	3.7	0	3.8	7.1	7.1	4.6	14.8	7.7	7.7
3e	0	4.7	4.7	—	—	2.6	7.7	2.1	0	13.2	—	—

[a]At 300 MHz. [b]At 500 MHz.

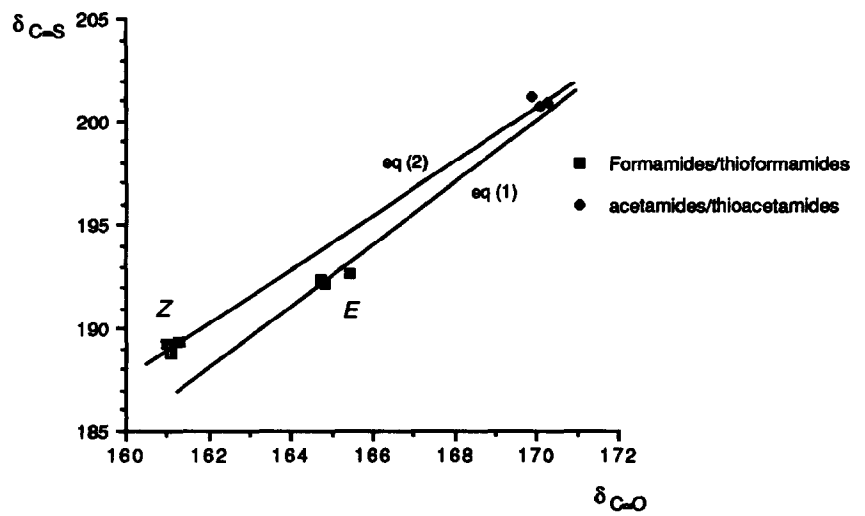
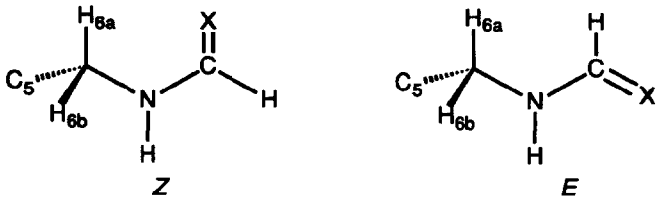
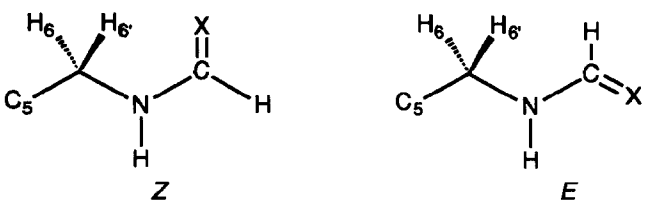


Figure 1. Plot of δ(^{13}C=S) vs δ(^{13}C=O) for compounds **1b-3b/1d-3d** and **1c-3c/1e-3e**.

The conformational analysis about the α-methylene-nitrogen bond can be undertaken on the basis of the $J_{CH2,NH}$ values, which could be generally measured for the major *Z* isomers of formamides (**1b-3b**) and thioformamides (**1d-3d**). The D-*galacto* derivative **1b** (*Z*) showed $J_{6,NH}$ and $J_{6',NH}$ values compatible with *antiperiplanar* and *gauche* dispositions, respectively. This conformation implies a parallel arrangement betweeen H-6 and the carbonyl oxygen atom, which is in agreement with the strong downfield shift observed for the corresponding resonance as compared with the *E* isomer ($\Delta\delta_{H\text{-}6',E\rightarrow Z} \approx 0.4$ ppm). A similar effect was observed in the ^{1}H NMR spectrum of **1d**, supporting the same preferred conformation.

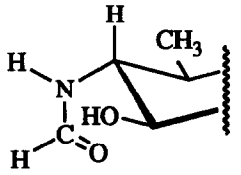


In the cases of D-*gluco* (**2b,d**) and D-*fructo* (**3b,d**) derivatives, both $^3J_{H,H}$ coupling constant values between the α-methylene and the NH protons were very close, and both methylene protons were deshielded in the *Z* isomer as compared to the *E* isomer, in agreement with an *antiperiplanar* disposition between the carbonyl (thiocarbonyl) group and the sugar ring, with both methylene protons in the vicinity of the oxygen (sulphur) atom. Nevertheless, the downfield shift is more pronounced for H-6 than for H-6', suggesting a conformational equilibrium between the *anti* and the above mentioned *gauche* conformations.



Although only a few $J_{CH2,NH}$ coupling constants could be measured for the minor *E* isomers (Table 1), the obtained values suggested that the relative configuration about the amide or thioamide bond does not have much influence on the conformation about the adjacent CH_2-NH bond.

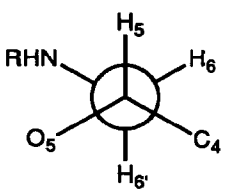
The ^{1}H NMR spectra of **2b**(*Z*), **2c**(*Z* and *E*), and **3c**(*Z*) showed long range coupling constants between the formyl or thioformyl proton and the α-methylene protons ($J_{CH2,HC(=X)}$ = 0.4-1.2 Hz). The existence of an analogous $^4J_{H,H}$ coupling constant in 4-formamidopyranoses (**4**) has been invoked to support a W arrangement in a *synperiplanar* conformation.[21] In our case, this feature appears simultaneously in the signals of both methylene protons, which is not consistent with this interpretation. Most probably, they are pseudoallylic coupling constants due to the partial double-bond character of the amide(thioamide) bond.



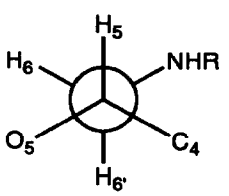
4

The values of $J_{CH2,NH}$ in acetamides (**1c-3c**) and thioacetamides (**1e-3e**), as well as the corresponding ^1H chemical shifts, were very close to those for the homologous *Z*-formamides and *Z*-thioformamides. This was indicative of equivalent magnetic environments and was in further support of the *Z*-configuration for these derivatives. Replacement of hydrogen by methyl in **1b-3b** and **1d-3d** did not have appreciable consequences in the preferred conformation about the CH_2-NH bond albeit its drastic effect on the *Z*/*E* ratio.

The relative disposition between the sugar ring and the amido(thioamido)methylene residue in these compounds could not be conclusively established from NMR data. For D-*galacto* (**1b-e**) and D-*gluco* (**2b-c**) derivatives, the values of $J_{5,6}$ and $J_{5,6'}$ were indicative of *gauche* and *anti* dispositions, respectively, and were compatible with the staggered conformations A and B. Taking into consideration that *gauche* interactions involving carbon substituents are unfavourable as compared to *gauche* interactions with oxygen,[22] conformer A, in which the amido(thioamido) group is *antiperiplanar* to C-4, should be favoured.



A



B

Finally, the vicinal coupling constants around the sugar ring agreed with reported data for 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose,[23] 1,2:3,5-di-*O*-isopropylidene-α-D-glucofuranose,[24] and 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose[25] derivatives, supporting the $^{O}S_2$ (D), $^{3}T_2$ (D), and $^{3}S_O$ (D) conformation, respectively, for **1a-e**, **2a-e**, and **3a-e** (Scheme 1).

EXPERIMENTAL SECTION

General methods. Melting points were determined with a Gallenkamp apparatus and are uncorrected. A Perkin-Elmer Model 141 MC polarimeter and 1 cm cells were used for measurement of specific rotations at room temperature. UV spectra were obtained on a Philips PU 8710 spectrophotometer in $CHCl_3$ solutions. IR spectra were recorded on a Bomem Michelson MB-120 FTIR spectrophotometer. ^1H NMR (and ^{13}C NMR)

spectra were recorded at 500 and 300 (75.5) MHz with, respectively, Bruker 500 AMX and 300 AMX spectrometers. Chemical shifts are given in ppm, and tetramethylsilane was the internal standard. Temperature measurements were based on the chemical shift separation of the protons of a methanol sample and the use of known temperature-shift correlations.[26] The samples were thermically equilibrated at the corresponding temperature before measurement. Mass spectra were taken on a Kratos MS-80 RFA instrument in the EI mode. TLC was performed with E. Merck precoated TLC plates, silica gel 30F-245, with visualization by UV light and by charring wiht 10% sulfuric acid. Flash and column chromatography were carried out with silica gel 60 (E. Merck, 230-400 mesh).

Solvents were comercial-grade and were used as supplied, with the following exceptions. DMF was distilled from BaO. Dioxane and toluene were distilled from metallic sodium. Methanol was distilled from magnesium turnings and iodine. Pyridine was distilled from KOH. Acetic anhydride was distilled from freshly melted sodium acetate.

Materials. 6-Amino-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**1a**), 6-amino-6-deoxy-1,2:3,5-di-*O*-isopropylidene-α-D-glucofuranose (**2a**), and 1-amino-1-deoxy-2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**3a**) hydrochlorides,[10] were prepared from, respectively, 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose,[27] commercial-grade 1,2-*O*-isopropylidene-α-D-glucofuranose, and 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose[28] in three steps as reported previously for related compounds.[15]

General procedure for preparation of the *N*-formylamino sugars 1b-3b. To a suspension of the corresponding amino sugar hydrochloride **1a-3a** (0.5 g, 1.69 mmol) in dry DMF (0.5 mL) and dry diethyl ether (5 mL) was added acetic-formic anhydride (6.95 g, 5 mL, 78 mmol). The amine was liberated by dropwise addition of pyridine under stirring. After 30 min at room temperature the solution was made alkaline with 2 M sodium hydroxide, and then concentrated. The residue was extracted with CH_2Cl_2 (3 x 15 mL). The combined extracts were dried ($MgSO_4$) and evaporated to dryness. Column chromatography (2:3 ethyl acetate-petroleum ether) of the crude product gave **1b-3b**.

6-Deoxy-6-formamido-1,2:3,4-di-O-*isopropylidene-α-D-galactopyranose* (**1b**). Yield 0.47 g (97%), mp 100-101°C (from ethyl acetate-petroleum ether), $[\alpha]_D$ -9 (*c* 1, CH_2Cl_2); ν_{max} 3318, 1676, and 1535 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): Table 1 and δ 1.48, 1.44, 1.33, 1.12 (4 s, 12 H, 4 Me). ^{13}C NMR: Table 2 and δ 108.9, 108.3 (2 CMe_2 *Z,E*), 95.8 (C-1 *Z,E*), 71.1 (C-4 *Z*), 70.6 (C-4 *E*), 70.3 (C-3 *Z,E*), 70.0 (C-2 *Z*), 69.9 (C-2 *E*), 67.0 (C-5 *E*), 66.0 (C-5 *Z*), 25.6, 25.5, 24.5, and 23.8 (4 Me *Z,E*). EIMS: *m/z* 272 (55%, M^+-$Me^·$), 229 (20, M^+-$CH_2NHCHO^·$), 171 (25, 229-Me_2CO), 113 (45, 4-methylidene-2,2-dimethyl-*m*-dioxolene cation), 100 (100, 2,2-dimethyl-*m*-dioxolene cation), and 85 (40, 2-methyl-*m*-dioxolenium cation). *Anal.* Calcd for $C_{13}H_{21}NO_6$: C, 54.34; H, 7.36; N, 4.87. Found: C, 54.40; H, 7.13; N, 4.71.

6-Deoxy-6-formamido-1,2:3,5-di-O-*isopropylidene-α-D-glucofuranose* (**2b**). Yield 0.46 g (95%), syrup, $[\alpha]_D$ +26.0 (*c* 1, CH_2Cl_2); ν_{max} 3274, 1688, and 1547 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): Table 1 and δ 1.48, 1.35, 1.34, 1.32 (4 s, 12 H, 4 Me). ^{13}C NMR: Table 2 and δ 112.1 (CMe_2 dioxolane *Z,E*), 106.2 (C-1 *Z,E*), 100.8 (CMe_2 dioxane *Z,E*), 83.7 (C-2 *E*), 83.6 (C-2 *Z*), 80.5 (C-4 *Z*), 79.6 (C-4 *E*), 74.7 (C-3 *Z,E*), 71.5 (C-5 *E*), 70.4 (C-5 *Z*), 26.9, 26.3, 23.8, and 23.7 (4 Me *Z,E*). EIMS: *m/z* 286 (2%, M^+-$H^·$), 272 (20, M^+-$Me^·$), 229 (20, M^+-$CH_2NHCHO^·$), 214 (10, 272-Me_2CO), 171 (18, 229-Me_2CO), 113 (100, 2,2-dimethyl-*m*-dioxenium cation), 100 (20, 2,2-dimethyl-*m*-dioxolene cation), 85 (20, 2-methyl-*m*-dioxolenium cation). *Anal.* Calcd for $C_{13}H_{21}NO_6$: C, 54.34; H, 7.36; N, 4.87. Found: C, 54.28; H, 7.38; N, 4.83.

1-Deoxy-1-formamido-2,3:4,5-di-O-*isopropylidene-β-D-fructopyranose* (**3b**). Yield 0.43 g (90%), syrup, $[\alpha]_D$ -18.0 (*c* 1, CH_2Cl_2); ν_{max} 3343, 1694, and 1532 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): Table 1 and δ 1.53, 1.51, 1.39, 1.36 (4 s, 12 H, 4 Me). ^{13}C NMR: Table 2 and δ 108.5, 107.9 (2 *C*Me_2 *Z,E*), 101.9 (C-2 *Z*), 101.3 (C-2 *E*), 71.6 (C-3 *Z*), 70.5 (C-3 *E*), 70.1 (C-5 *E*), 69.9 (C-5 *Z*), 69.5 (C-4 *Z*), 69.4 (C-4 *E*), 60.9 (C-6 *E*), 60.7 (C-6 *Z*), 25.7, 25.4, 24.4, and 23.4 (4 Me *Z,E*). EIMS: *m/z* 287 (5, $M^{+\cdot}$), 272 (20, M^+-Me$^\cdot$), 229 (95, M^+-$CH_2NHCHO^\cdot$), 171 (98, 229-Me_2CO), 113 (35, 4-methylidene-2,2-dimethyl-*m*-dioxolene cation), 100 (100, 2,2-dimethyl-*m*-dioxolene cation), 85 (50, 2-methyl-*m*-dioxolenium cation). *Anal.* Calcd for $C_{13}H_{21}NO_6$: C, 54.34; H, 7.36; N, 4.87. Found: C, 54.37; H, 7.25; N, 4.70.

General procedure for the preparation of *N*-acetylamino sugars 1c-3c. To a solution of the corresponding amino sugar hydrochloride **1a-3a** (0.53g, 1.79 mmol) in pyridine (2.65 mL), Ac_2O (2.65 mL, 28.09 mmol) was added. The mixture was kept at room temperature for 2 h, and then poured into ice-water. The aqueous solution was extracted with CH_2Cl_2, washed with 2 N H_2SO_4, then with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated.

6-Acetamido-6-deoxy-1,2:3,4-di-O-*isopropylidene-α-D-galactopyranose*[11] (**1c**). ^1H NMR (300 MHz, $CDCl_3$): Table 4 and δ 1.52, 1.48, 1.35, 1.34 (4 s, 12 H, 4 Me). ^{13}C NMR: Table 2 and δ 95.9 (C-1), 71.2 (C-4), 70.2 (C-3), 70.0 (C-2), 66.1 (C-5), 25.9 (*Me*CO).

6-Acetamido-6-deoxy-1,2:3,5-di-O-*isopropylidene-α-D-glucofuranose*[12] (**2c**). ^1H NMR (300 MHz, $CDCl_3$): Table 4 and δ 1.48, 1.38, 1.35, 1.31 (4 s, 12 H, 4 Me). ^{13}C NMR: Table 2 and δ 106.3 (C-1), 83.9 (C-2), 80.7 (C-4), 74.9 (C-3), 70.6 (C-5), 26.4 (*Me*CO).

1-Acetamido-1-deoxy-2,3:4,5-di-O-*isopropylidene-β-D-fructopyranose* (**3c**). Yield 0.53 g (95%), mp 105-106°C (from ethyl acetate-hexane), $[\alpha]_D$ -24.0 (*c* 1, CH_2Cl_2); ν_{max} 3305, 1539, and 1077 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): Table 4 and δ 1.53, 1.42, 1.39, 1.37 (4 s, 12 H, 4 Me). ^{13}C NMR: Table 2 and δ 108.9, 108.5 (2 *C*Me_2 *Z,E*), 102.4 (C-2 *Z,E*), 71.9 (C-3 *Z,E*), 70.3 (C-5 *Z,E*), 70.0 (C-4 *Z,E*), 61.2 (C-6 *Z,E*), 25.9 (*Me*CO). EIMS: *m/z* 301 (5%, $M^{+\cdot}$), 286 (30, M^+-Me$^\cdot$), 229 (90, M^+-$CH_2NHCOMe^\cdot$), 171 (100, 229-Me_2CO), 113 (40, 4-methylidene-2,2-dimethyl-*m*-dioxolene cation), 100 (15, 2,2-dimethyl-*m*-dioxolene cation), 85 (40, 2-methyl-*m*-dioxolenium cation). *Anal.* Calcd for $C_{14}H_{23}NO_6$: C, 55.80; H, 7.69; N, 4.65. Found: C, 55.69; H, 7.79; N, 4.59.

General procedure for the preparation of *N*-thioamido sugars 1d-3d and 1e-3e. To a solution of the corresponding *N*-acylamino sugar **1b-3b** (0.4 g, 1.39 mmol) or **1c-3c** (0.4 g, 1.78 mmol) in anhydrous THF (13 mL), P_4S_{10} (0.22 g, 1 mmol) was added and the reaction mixture was irradiated with an ultrasonic apparatus until disappearance of the starting formamide (1 h, ethyl acetate-petroleum ether 1:1). The solvent was evaporated and the residue was extracted with CH_2Cl_2 (2 x 2 mL). The combined extracts were evaporated to dryness and the residue purified by column chromatography (1:1 ethyl acetate-petroleum ether).

6-Deoxy-1,2:3,4-di-O-*isopropylidene-6-thioformamido-α-D-galactopyranose* (**1d**). Yield 0.32 g (76%), syrup, $[\alpha]_D$ +24.0 (*c* 1, CH_2Cl_2), λ_{max} 265 nm (ε_{mM} 15.6); ν_{max} 3306, 1528, and 1069 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): Table 1 and δ 1.50, 1.48, 1.37, 1.34 (4 s, 12 H, 4 Me). ^{13}C NMR: Table 2 and δ 109.4, 108.8 (2 *C*Me_2 *Z,E*), 96.0 (C-1 *Z,E*), 71.4 (C-4 *Z*), 71.2 (C-4 *E*), 70.6 (C-3 *Z,E*), 70.4 (C-2 *Z*), 70.1 (C-2 *E*), 66.0 (C-5 *E*), 65.0 (C-5 *Z*), 25.9, 25.5, 24.5, and 23.8 (4 Me *Z,E*). EIMS: *m/z* 303 (45%, $M^{+\cdot}$), 288 (40, M^+-Me$^\cdot$), 227 (25, 228-NH_2CHS), 169 (98, 227-Me_2CO), 113 (30, 4-methylidene-2,2-dimethyl-*m*-dioxolene cation), 100 (45, 2,2-dimethyl-*m*-dioxolene cation), 85 (45, 2-methyl-*m*-dioxolenium cation). *Anal.* Calcd for $C_{13}H_{21}NO_5S$: C, 51.48; H, 6.98; N, 4.62; S, 10.55. Found: C, 51.49; H, 6.91; N, 4.62; S, 10.50.

6-Deoxy-1,2:3,5-di-O-isopropylidene-6-thioformamido-α-D-glucofuranose (**2d**). Yield 0.30 g (75%), mp 157-158°C (from ethyl acetate-hexane), $[\alpha]_D$ +14.0 (*c* 1, CH_2Cl_2), λ_{max} 268 nm (ε_{mM} 7.2); ν_{max} 3300, 1537, and 1068 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): Table 1 and δ 1.48, 1.37, 1.35, 1.32 (4 s, 12 H, 4 Me). ^{13}C NMR : Table 2 and δ 112.0 (*C*Me$_2$ dioxolane *Z,E*), 106.1 (C-1 *Z,E*), 100.7 (*C*Me$_2$ dioxane *Z,E*), 83.8 (C-2 *E*), 83.7 (C-2 *Z*), 80.4 (C-4 *Z*), 79.4 (C-4 *E*), 74.8 (C-3 *E*), 74.7 (C-3 *Z*), 70.8 (C-5 *E*), 69.3 (C-5 *Z*), 26.8, 26.2, 23.8, and 23.6 (4 Me *Z,E*). EIMS: *m/z* 303 (20, M^+), 288 (20, M^+-Me$^·$), 229 (20, M^+-$CH_2NHCHS^·$), 171 (10, 229-Me_2CO), 113 (100, 2,2-dimethyl-*m*-dioxenium cation), 100 (25, 2,2-dimethyl-*m*-dioxolene cation), 85 (30, 2-methyl-*m*-dioxolenium). *Anal.* Calcd for $C_{13}H_{21}NO_5S$: C, 51.48; H, 6.98; N, 4.62; S, 10.55. Found: C, 51.38 ; H, 7.00 ; N, 4.54; S, 10.59.

1-Deoxy-2,3:4,5-di-O-isopropylidene-1-thioformamido-β-D-fructopyranose (**3d**). Yield 0.25 g (62%), syrup, $[\alpha]_D$ -41.0 (*c* 1, CH_2Cl_2), λ_{max} 264 nm (ε_{mM} 16.6); ν_{max} 3305, 1539, and 1069 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): Table 1 and δ 1.53, 1.51, 1.39, 1.36 (4 s, 12 H, 4 Me). ^{13}C NMR: Table 2 and δ 109.0, 108.8 (2 *C*Me$_2$ *Z,E*), 101.8 (C-2 *Z*), 100.6 (C-2 *E*), 72.4 (C-3 *Z*), 71.1 (C-3 *E*), 70.4 (C-5 *Z,E*), 69.9 (C-4 *Z*), 69.8 (C-4 *E*), 63.3 (C-6 *Z,E*), 25.9, 25.7, 24.7, and 23.8 (4 Me *Z,E*). EIMS: *m/z* 303 (70%, M^+), 288 (30, M^+-Me$^·$), 229 (45, M^+-$CH_2NHCHS^·$), 171 (75, 229-Me_2CO), 113 (35, 4-methylidene-2,2-dimethyl-*m*-dioxolene cation), 100 (10, 2,2-dimethyl-*m*-dioxolene cation), 85 (55, 2-methyl-*m*-dioxolenium cation). *Anal.* Calcd for $C_{13}H_{21}NO_5S$: C, 51.48; H, 6.98; N, 4.62; S, 10.55. Found: C, 51.41; H, 6.95; N, 4.70; S, 10.38.

6-Deoxy-1,2:3,4-di-O-isopropylidene-6-thioacetamido-α-D-galactopyranose (**1e**). Yield 0.62 g (82%), syrup, $[\alpha]_D$ +11.3 (*c* 1, CH_2Cl_2), λ_{max} 265 nm (ε_{mM} 33.4); ν_{max} 3320, 1537, and 1078 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): Table 4 and δ 1.49, 1.44, 1.34, 1.31 (4 s, 12 H, 4 Me). ^{13}C NMR: Table 2 and δ 108.9, 108.5 (2 *C*Me$_2$), 97.7 (C-1), 74.2 (C-4), 70.2 (C-3), 70.0 (C-2), 64.6 (C-5), 33.4 (*Me*CS), 25.8, 25.0, 24.5, and 23.6 (4 Me). EIMS: *m/z* 317 (50%, M^+), 302 (50, M^+-Me$^·$), 227 (10, 302-NH_2CSMe), 169 (100, 227-Me_2CO), 113 (20, 4-methylidene-2,2-dimethyl-*m*-dioxolene cation), 100 (25, 2,2-dimethyl-*m*-dioxolene cation), 85 (20, 2-methyl-*m*-dioxolenium cation). *Anal.* Calcd for $C_{14}H_{23}NO_5S$: C, 52.97; H, 7.30; N, 4.41; S, 10.10. Found: C, 52.68; H, 7.36; N, 4.49; S, 10.24.

6-Deoxy-1,2:3,5-di-O-isopropylidene-6-thioacetamido-α-D-glucofuranose (**2e**). Yield 0.65 g (85%), syrup, $[\alpha]_D$ +46.5 (*c* 1, CH_2Cl_2), λ_{max} 266 nm (ε_{mM} 21.5); ν_{max} 3325, 1539, and 1075 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): Table 4 and δ 1.48, 1.37, 1.35, 1.33 (4 s, 12 H, 4 Me). ^{13}C NMR: Table 2 and δ 119 (*C*Me$_2$ dioxolane), 106.2 (C-1), 106.0 (*C*Me$_2$ dioxane), 83.4 (C-2), 80.5 (C-4), 74.6 (C-3), 69.3 (C-5), 33.7 (*Me*CS), 26.6, 26.3, 23.5, and 23.1 (4 Me). EIMS: *m/z* 317 (15%, M^+), 302 (40, M^+-Me$^·$), 229 (10, M^+-$CH_2NHCSMe^·$), 171 (10, 229-Me_2CO), 113 (50, 2,2-dimethyl-*m*-dioxenium cation), 100 (20, 2,2-dimethyl-*m*-dioxolene cation), 85 (20, 2-methyl-*m*-dioxolenium cation). *Anal.* Calcd for $C_{14}H_{23}NO_5S$: C, 52.97; H, 7.30; N, 4.41; S, 10.10. Found: C, 52.85; H, 7.24; N, 4.41; S, 9.96.

1-Deoxy-2,3:4,5-di-O-isopropylidene-1-thioacetamido-β-D-fructopyranose (**3e**). Yield 0.58 g (75%), mp 124-125°C (ethyl acetate-hexane), $[\alpha]_D$ -51.0 (*c* 1, CH_2Cl_2), λ_{max} 265 nm (ε_{mM} 13.4); ν_{max} 3305, 1539, and 1077 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): Table 4 and δ 1.43, 1.42, 1.28, 1.26 (4 s, 12 H, 4 Me). ^{13}C NMR: Table 2 and δ 108.7, 108.6 (2 *C*Me$_2$), 101.7 (C-2), 71.8 (C-3), 70.3 (C-5), 69.7 (C-4), 61.2 (C-6), 33.4 (*Me*CS), 25.9, 25.6, 24.4, and 23.6 (4 Me). EIMS: *m/z* 317 (100%, M^+), 302 (40, M^+-Me$^·$), 229 (18, M^+-$CH_2NHCSMe^·$), 171 (60, 229-Me_2CO), 113 (40, 4-methylidene-2,2-dimethyl-*m*-dioxolene cation), 100 (10, 2,2-dimethyl-*m*-dioxolene cation), 85 (55, 2-methyl-*m*-dioxolenium cation). *Anal.* Calcd for $C_{14}H_{23}NO_5S$: C, 52.97; H, 7.30; N, 4.41; S, 10.10. Found: C, 52.71; H, 7.28; N, 4.30; S, 9.90.

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