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Stereoselective synthesis of imidazolidine, imidazoline and imidazole *C*- and *N*-pseudonucleosides

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Abstract

Methyl 2-deoxy-2-isothiocyanato-α-D-glucopyranoside **2**, which exists in equilibrium with the corresponding 2,3-cyclic carbamate **1**, reacts with D-glucosamine producing the pseudo-*C* and *N*-nucleoside of chiral imidazolidine-2-thione **3**, in good yield and high stereoselectivity. Starting from **3**, different pseudo-*C*- and *N*-nucleosides of imidazoline-2-thione **6**–**11**, and of imidazole **12** and **13** are obtained. Conformational aspects of some of the prepared compounds are discussed.

1. Introduction

Nucleosides are well known compounds having important pharmacological properties; for example they are used in AIDS treatment[1,2] and as antibiotics,[3] and much effort is being given to the syntheses and transformations of this type of molecule.[4] In addition, 2-oxo- and 2-thioxo-1,3-*N*-heterocycles are interesting compounds from a pharmaceutical point of view; in particular the antibiotics SF-1993[5] and CV-1[6] have the structure of 2-oxo-imidazolidines. The isolation of hydantocidin, a natural hydantoin spironucleoside, with potent herbicidal activity,[7] has stimulated the preparation of hydantocidin mimics and surrogates having a 2-oxo- or 2-thioxoimidazolidine ring.[8,9]

The reaction of 2-amino-2-deoxy-aldoses with alkyl and aryl isothiocyanates has been widely studied and constitutes a route to imidazolidine and imidazole *C*-nucleosides.[10] The mechanism of this reaction was established in 1991 when a chiral 5-hydroxyimidazolidine-2-thione was isolated as first reaction product[11] and this mechanism was subsequently confirmed.[12] Imidazole *N*-nucleosides have been prepared from glycosyl isothiocyanates and aminoacetone,[13] and the reaction of *O*-protected glycosyl isothiocyanates with D-glucosamine to obtain chiral imidazolidine-2-thione *N*-nucleosides has also been reported.[14]

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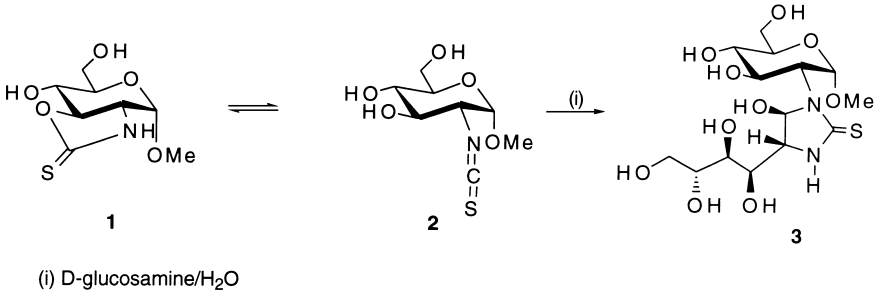
Recently, we have described[15] the preparation of an *O*-unprotected glucoside bicyclic thiocarbamate **1** which acts as latent 2-deoxy-2-isothiocyanato-glucoside **2** and is useful for the synthesis of 2-thioureido sugars. In this paper we report on the use of the thiocarbamate **1** in the stereocontrolled syntheses of imidazolidines **3**–**5**, imidazolines **8**–**11**, and thioimidazoles **12**,**13** *N*-pseudonucleosides (position 2 of the sugar ring). The structures of the prepared compounds are, simultaneously, *N*-pseudonucleosides and acyclic **3**,**6**,**7** or cyclic **8**–**13** *C*-nucleosides.

2. Results and discussion

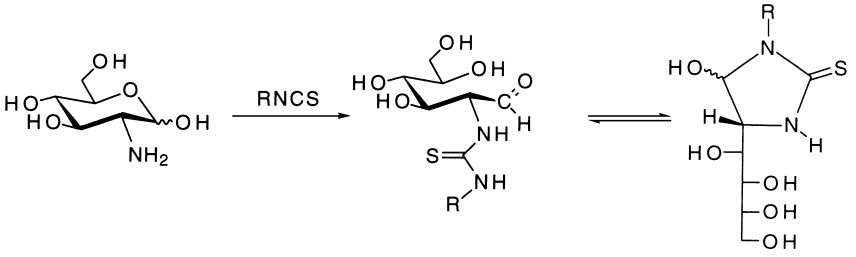
The equilibrium mixture of the thiocarbamate **1** and the isothiocyanate **2** was prepared[15] from methyl 2-benzamido-2-deoxy-α-D-glucopyranoside[16] and thiophosgene, and was used, without purification, in the reaction with 2-amino-2-deoxy-D-glucopyranose. After 20 h of reaction the (4*R*,5*R*)-5-hydroxy-4-(tetritol-1-yl)imidazolidine-2-thione pseudo *N*-nucleoside **3** was obtained in high yield after column chromatography (Scheme 1). The minor 5*S* stereoisomer could not be isolated.



Scheme 1.

The assignment of the 5*R* configuration was based on the close resemblance of the ^{1}H and ^{13}C NMR data of **3** and reported data for related 5-hydroxyimidizolidines.[11,14] The NMR spectra of described (5*R*)- and (5*S*)-5-hydroxy-4-polyhydroxyalkylimidazolidines show significant differences in the values δ H-4 (~3.7 ppm for *R* isomers and ~4.25 ppm for *S* isomers), δ C-4 (~66.0 ppm for *R* isomers and ~60.0 ppm for *S* isomers), and in the value of $J_{4,5}$ (1.3–2.3 Hz for *R* isomers and 6.2–6.8 Hz for the *S* isomers). The δ H-4, δ C-4 and $J_{4,5}$ values for **3** were 3.79 ppm, 66.0 ppm, and 1.4 Hz respectively, confirming the 5*R* configuration. No measurable mutarotation was observed when a solution of **3** in pyridine was left at rt for 24 h. However, small amounts of the 5*S* isomer ($J_{4,5}$=6.4 Hz, in D_2O) were detected by ^{1}H NMR in a solution of recrystallized **3** (5 min after solution, 5*R*:5*S* ratio of 98:2 in DMSO-d_6 and 95:5 in D_2O; 7 days after, 93:7 in D_2O). These results indicate an equilibrium between the 5*R* and 5*S* stereoisomers, shifted towards the 5*R* form due to the *trans* relationship between the hydroxyl group and the tetritolyl chain. Formation of **3** was monitored in deuterium oxide by ^{1}H NMR spectroscopy, and the reaction mixture showed no change in the **1**:**2** ratio (2.5:1) and in the 5*R*:5*S* ratio (94:6) during the reaction time. The reaction of the aminosugar and the sugar isothiocyanate takes place through a 2-deoxy-2-(3-substituted thioureido)-D-aldose (Scheme 2) which cyclizes spontaneously to the chiral 5-hydroxyimidazolidine-2-thione,[11] following the 5-*exo-trig* cyclization mode according to Baldwin rules.[17]

The high degree of stereoselection observed for the reaction of *O*-protected glycosyl isothiocyanates and D-glucosamine has been explained assuming that the Cram's rule of steric control of the asymmetric induction is fulfilled.[14] We now suggest the transition state indicated in Fig. 1 for the cyclization of the intermediate thiourea, in which the thiureido group takes up a perpendicular relationship to the plane of the carbonyl group.[18] The nucleophilic attack of the NH (following the Burgi–Dunitz trajectory)[19] on



Scheme 2.

the *si* face of the carbonyl group to give the 5*R* stereoisomer of **3** implies lower steric hindrance than the attack on the *re* face due to the interaction between the carbonyl oxygen and C-3 of glucosamine. The high stereoselectivity found in the formation of **3** compared with that found for aryl isothiocyanates indicates a second asymmetric induction due to the stereochemistry of the sugar ring (α-D-glucopyranoside).

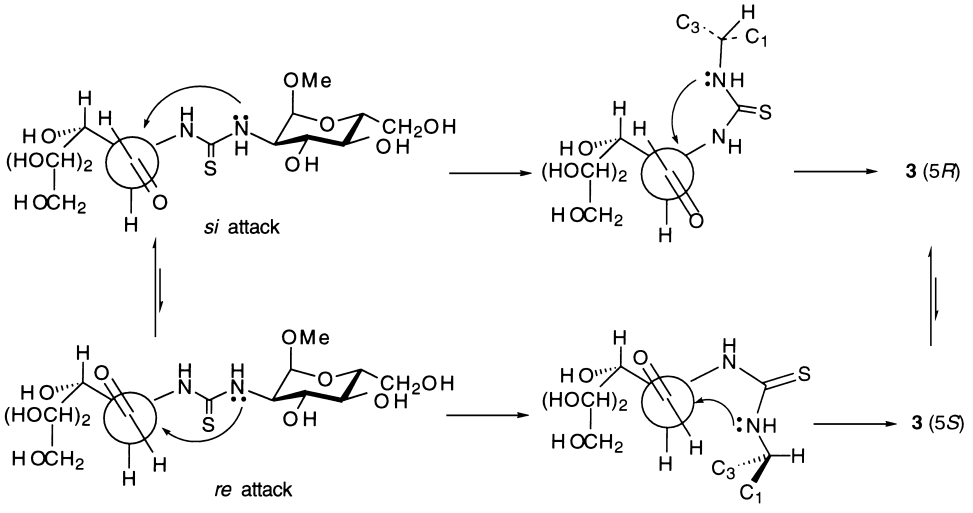
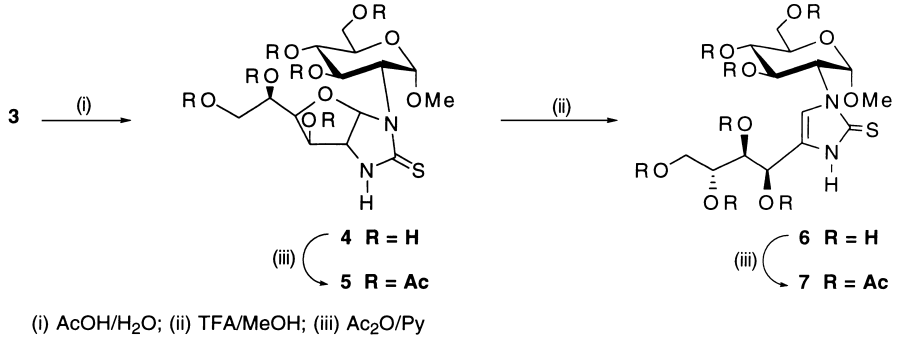


Figure 1. Diastereoselective induction on C-5 configuration of **3**

The cyclodehydration of **3** with acetic acid gave in high yield the glucofuranoimidazolidine-2-thione **4** (Scheme 3), which was conventionally acetylated to produce **5**. The ^{1}H NMR spectra of **4** and **5** showed $J_{2'',3''} \sim 0.0$ Hz as is characteristic of 2,3-*trans*-related protons in bicyclic tetrahydrofuranoimidazolidines.[10b,14] The furanoid structure is also supported by the value of the chemical shift for the resonance of H-4″ in **5** (4.15 ppm) which appears at higher field than the resonances for H-3″ and H-5″ (*H*COAc groups). According to reported data[10b,11] for glucofuranoimidazolidine-2-thiones, the *J* values for the furan ring of **4** and **5** indicate the E_4 conformation; the protons H-4″ and H-5″ are in *anti* relationship; and the exocyclic dihydroxyethyl chain presents the usual chain end flexibility (Fig. 2). The glucopyranoid ring shows undistorted $^4C_1$ conformation.

The pseudo-*N*-nucleoside of imidazoline-2-thione **6** was prepared by treatment of **4** with trifluoroacetic acid in methanol at rt and also by treatment of **3** with aqueous acetic acid followed by trifluoroacetic acid, the yields being similar in both cases. Conventional acetylation of **6** gave the tetra-*O*-acetyl derivative **7**. The δ values for the resonances of H-5 (Table 1), C-2, C-4 and C-5 (Table 2) of **6** and **7** supported the dehydration with formation of the imidazolidine-2-thione ring. The vicinal coupling constant values corresponding to the protons of the D-*arabino*-tetraacetoxybutyl chain showed that this chain was, in aqueous **6** or chloroformic solutions **7**, an equilibrium of the planar *P* conformation and the



Scheme 3.

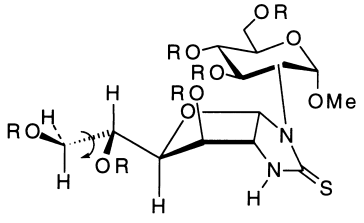


Figure 2. Conformational analysis of **4** and **5**

$_3G^+$ conformation (Fig. 3a), associated with the chain-end flexibility described for the other D-*arabino* compounds.[20] NOE difference experiments were performed on **6**. Irradiation of H-5 showed an increase in the area of the signals corresponding to H-3′ (4%), H-1′′ (0.8%) and H-2′′ (0.6%), and irradiation of H-3′ also produced a 4% increase in the signal of H-5, according to the conformation depicted in Fig. 3b.

Treatment of **6** with aqueous trifluoroacetic acid at 80°C produced cyclodehydration of the polyhydroxyalkyl chain with formation of the erythrofuranosyl *C*-nucleosides **8** and **9** (Scheme 4), which were isolated in a 1:4 ratio after chromatography. In spite of the strongly acidic medium, no hydrolysis of the methyl glycoside was detected. There were no strong changes in the NMR data (Tables 1 and 2) of the glucopyranosyl and imidazoline rings of **8** and **9** when they were compared with the corresponding data for **6**. The formation of the erythrofuranose ring produced shielding in the resonance of H-1′′ (0.15, 0.43 ppm) and deshielding in the resonances of H-2′′ (0.50, 0.36 ppm), H-3′′ (0.55, 0.43 ppm), C-1′′ (~10.0 ppm), and C-4′′ (~10.0 ppm); the ^{1}H NMR being in agreement with reported data for erythrofuranosides,[21] although we have not found ^{13}C NMR data for erythrofuranosides. The anomeric configuration, α for **8** and β for **9**, was assigned from polarimetric and NMR data. The α anomer **8** was dextrorotatory and the β-anomer **9** levorotatory; the value of $J_{1'',2''}$ was smaller for the α-anomer (5.4 Hz) than for the β-anomer (8.1 Hz), and the resonance for the anomeric proton appeared at lower field in the α-anomer (4.83 ppm) than in the β-anomer (4.55 ppm), in agreement with reported data for other pairs of erythrofuranosyl *C*-nucleosides,[22] 4-thio-*C*-nucleosides,[23] and for *N*- and *C*-ribofuranosyl nucleosides[24] which have close structural features with erythrofuranosides.

NOE experiments performed on compound **9** showed that the proton H-5 is close to H-3′ and H-1′′, according to the main conformation presented in Fig. 4. The plane of the imidazoline ring is roughly perpendicular to both, the mean plane of the D-glucopyranosyl ring and of the erythrofuranosyl ring. The vicinal coupling constants showed that the glucopyranosyl ring is in the normal $^4C_1$ conformation, and the tetrahydrofuran ring is, as is frequent,[23] in the zone ^2E–$^2T_5$ of the pseudorotational itinerary with a value of $J_{1'',2''}$ (8.1 Hz) corresponding to protons in *anti* relationship. The mechanism of the cyclodehydration of **6** to give **8** and **9** involves, as in pentahydroxypentyl[10c] and 4-thiotetrahydroxybutyl[23] imidazoles, a

Table 1
Selected ^{1}H NMR data (δ in ppm, *J* in hertz)

Compound	H-5	H-1'[a]	H-2'	H-3'	H-1"[b]	H-2"	H-3"	H-4"a	H-4"b
6[c]	7.24	4.94	4.87	4.21	4.98	3.76	3.81	3.84	3.67
7[d]	6.82	4.88	5.25	5.64	5.91	5.34	5.16	4.21	4.13
8[e]	7.04	4.86	4.84	4.03	4.83	4.26	4.36	3.92	3.84
9[e]	7.05	4.85	4.87	4.05	4.55	4.12	4.24	4.21	3.78
10[d]	6.82	4.93	5.28	5.61	5.01	5.47	5.47	4.10	4.04
11[d]	6.82	4.94	5.25	5.65	4.78	5.20	5.43	4.37	3.94
12[c]	7.51	4.94	4.50	4.22	5.05	4.46	4.56	4.14	3.93
13[c]	7.73	4.86	4.57	4.16	4.71	4.30	4.34	4.24	3.86

	$J_{1',2'}$	$J_{2',3'}$	$J_{3',34'}$	$J_{1",2"}$	$J_{2",3"}$	$J_{3",4"a}$	$J_{3",4"b}$	$J_{4"a,4"b}$
6[c]	3.5	11.1	8.8	2.7	7.9	2.8	5.8	11.6
7[d]	3.4	11.5	9.0	3.6	8.3	2.8	5.1	12.5
8[e]	3.4	-	8.7	5.4	-	5.6	4.6	9.1
9[e]	3.4	10.3	8.6	8.1	4.7	4.4	1.9	9.5
10[d]	3.4	11.4	9.0	5.4	-	-	-	-
11[d]	3.4	11.5	9.0	7.4	3.2	5.0	3.2	10.5
12[c]	3.4	10.7	8.8	5.2	4.8	6.1	5.1	9.4
13[c]	3.3	10.7	8.9	7.7	4.6	3.9	-	10.2

[a] (') refers to the glucopyranoside ring.
[b] (") refers to the tetritol chain or to the erythrofuranoside ring.
[c] In D_2O.
[d] In $CDCl_3$.
[e] In CD_3OD.

carbocation in C-1′′ (Fig. 5), stabilized by the imidazoline ring, which undergoes nucleophilic attack of the hydroxy group on C-4′′ to give **8** (retention of the configuration of C-1′′) or **9** (inversion of the configuration of C-1′′).

Acetylation of **8** and **9** with acetic anhydride and pyridine gave the di-*O*-acetyl derivatives **10** and **11**, respectively. The α-anomer **10** was dextrorotatory, presenting the resonance of H-1′′ at 5.01 ppm with $J_{1'',2''}$ as 5.4 Hz, whereas **11** was levorotatory and the values of the chemical shift of H-1′′ and $J_{1'',2''}$ were 4.55 ppm and 7.4 Hz, respectively. These facts confirmed the assigned anomeric configuration to **10** and **11** and, congruently, to **8** and **9**.

Table 2
Selected ^{13}C NMR data (δ in ppm)

Compound	C-2	C-4	C-5	C-1'[a]	C-2'	C-3'	C-1"[b]	C-2"	C-3"	C-4"
6[c]	160.0	130.9	116.6	98.5	60.9	71.5	65.9	74,1	72.2	64.0
7[d]	163.7	122.9	115.3	96.9	57.2	68.6	64.3	70.4	68.3	61.4
8[e]	162.8	126.8	118.0	98.9	61.4	71.9	75.7	73.9	72.9	73.1
9[e]	163.6	128.2	117.3	98.8	61.3	71.7	76.0	76.7	72.2	74.4
10[d]	164.0	122.7	116.2	97.0	57.3	69.1	72.3	72.0/	71.6	69.6
11[d]	163.5	125.1	114.8	97.0	57.2	69.0	73.4	69.0	71.0	71.0
12[c]	145.7	138.4	121.2	99.3	61.5	72.1	78.2	73.1	72.9	72.7
13[c]	145.2	136.5	120.5	97.8	60.9	70.8	75.4	75.4	71.0	73.0

[a] (') refers to the glucopyranoside ring.
[b] (") refers to the tetritol chain or to the erythrofuranoside ring.
[c] In D_2O.
[d] In $CDCl_3$.
[e] In CD_3OD.

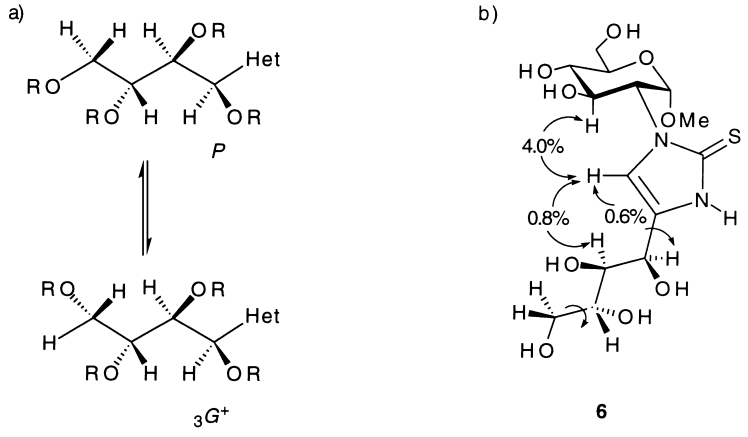
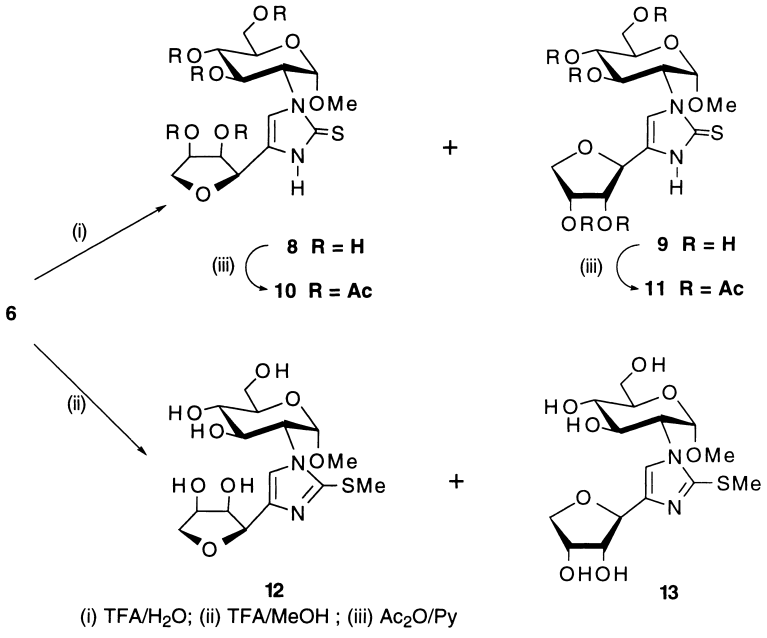


Figure 3. (a) Conformational equilibrium of the polyhydroxyalkyl chain of **6** (R=H) and **7** (R=Ac). (b) Major conformation of **6**

When trifluoroacetic acid treatment of **6** was carried out by refluxing in methanol, *S*-methylation, in addition to cyclodehydration, took place and the *S*-methylimidazoles **12** and **13** were isolated in a 1:7 ratio, after chromatography. To avoid the presence of **8** and **9** in the reaction mixture the reflux was left for 6 days. In spite of the prolonged heating in an acidic medium no epimerization on C-1′ was detected. The partial positive charge on the imidazole N-1 could explain this stability. The structures **12** and **13** were based on NMR data (Tables 1 and 2 and experimental) and the anomeric configurations (α for **12** and β for **13**) were assigned by the above-discussed polarimetric and spectroscopic data. Thus **12** was strongly dextrorotatory (+106°), whereas **13** had a specific rotation of +42, the H-1′′ proton of **12** resonated at lower field than the same proton for **13**, and the $J_{1'',2''}$ value for **12** was smaller than for **13**.



Scheme 4.

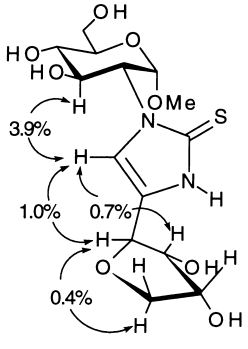


Figure 4. Major conformation of **9**

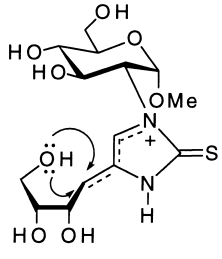


Figure 5. Cyclodehydration of **6**

3. Conclusion

The reaction of D-glucosamine with a 2-deoxy-2-isothiocyanato sugar, is a convenient way to prepare, with high control of the stereochemistry, a variety of pseudo-*C*- and *N*-nucleosides of imidazolidine-2-thiones **3** and **4**, imidazoline-2-thiones **6**, **8** and **9**, and 2-methylthioimidazoles **12** and **13**.

4. Experimental

4.1. General methods

Melting points were determined with an Electrothermal apparatus and were uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. IR spectra (KBr discs) were recorded with an FT-IR Bomem MB-120 spectrophotometer. ^{1}H (500 MHz) and ^{13}C NMR spectra (125.7 MHz) were recorded with a Bruker AMX-500 for solutions in D_2O (internal DOH 4.75 ppm and external 1,4-dioxane at 67.4 ppm), in $CDCl_3$, and MeOH-d_4 (Me_4Si as internal standard). The assignments of ^{1}H signals were confirmed by COSY experiments and heteronuclear 2D correlated spectra were used for ^{13}C signal assignments. FAB-MS were taken with a Kratos MS-80 RFA instrument with a resolution of 1000 (10% valley definition). Ions were produced by a beam of Xe atoms (6–7 kV) using a matrix consisting of thioglycerol or 3-nitrobenzyl alcohol and NaI as salt. HRCIMS (150 eV) and HRFAB/LSIMS experiments were performed with a Micromass AutoSpecQ instrument with a resolution of 10 000 (5% valley definition). All reactions were monitored by TLC on aluminum sheets coated with silica gel 60 F_{254} (E. Merck) with visualization by UV light and by charring with 10% H_2SO_4 in EtOH. Column chromatography and preparative TLC were carried out using silica gel 60 HF_{254} (E. Merck). Microanalyses were performed at the 'Instituto Químico de Sarriá', Barcelona and the 'Instituto de Investigaciones Químicas', Seville, Spain.

4.2. (4R,5R)-5-Hydroxy-1-(methyl 2-deoxy-α-D-glucopyranosid-2-yl)-4-(D-arabino-tetritol-1-yl) imidazolidine-2-thione **3**

A solution of methyl 2-benzamido-2-deoxy-α-D-glucopyranoside[16] (2 g, 6.72 mmol) in aqueous sodium hydroxide 3 M (10 mL) was refluxed for 14 h. After cooling to room temperature the solution was brought to pH 8 by bubbling CO_2, diluted with dioxane (20 mL) and cooled to −10°C. Thiophosgene (0.568 mL, 7.41 mmol) was added and the mixture was stirred for 10 min and extracted with ether (2×10 mL) and ethyl acetate (5×30 mL). The organic fractions were dried ($MgSO_4$) and concentrated to give a mixture of **1** and **2**. To a solution of **1** and **2** (0.608 g, 2.58 mmol) in water (14 mL) 2-amino-2-deoxy-D-glucopyranose (0.509 g, 2.847 mmol) was added and stirred at 40°C for 20 h. The crude reaction product was concentrated to dryness and the residue was purified by column chromatography (CH_2Cl_2→CH_2Cl_2:methanol 3:1). Crystallization from methanol gave **3** (0.766 g, 72%); mp 158–160°C; $[\alpha]_D^{30}$ +116 (c 1.0, DMSO), $[\alpha]_D^{25}$ +104 (c 1.0, pyridine); IR ν_{max} 3434, 3275, 2934, 2907, 1626, 1507, 1458, 1235, 1096 and 1042 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): δ 5.64 (d, 1H, $J_{4,5}$=1.4 Hz, H-5), 4.78 (d, 1H, $J_{1',2'}$=3.4 Hz, H-1′), 4.57 (dd, 1H, $J_{2',3'}$=11.2 Hz, H-2′), 4.09 (dd, 1H, $J_{3',4'}$=8.7 Hz, H-3′), 3.84 (dd, 1H, $J_{6'a,6'b}$=11.9 Hz, H-6′a), 3.82 (m, 1H, H-4′′a), 3.79 (d, 1H, H-4), 3.72 (dd, 1H, H-6′b), 3.70 (m, 1H, H-1′′), 3.69 (m, 1H, H-3′′), 3.64 (m, 1H, H-4′′b), 3.60 (ddd, 1H, $J_{5',6'a}$=2.4 Hz, $J_{5',6'b}$=5.6 Hz, H-5′), 3.51 (m, 1H, $J_{2'',3''}$=8.6 Hz, H-2′′), 3.49 (t, 1H, $J_{4',5'}$=9.9 Hz, H-4′) and 3.45 ppm (s, 3H, OMe); ^{13}C NMR (125.7 MHz, CD_3OD): δ 184.0 (C=S), 100.4 (C-1′), 85.5 (C-5), 74.1 (C-5′), 72.5 (C-3′′), 72.2 (C-2′′), 71.9 (C-4′), 71.7 (C-3′), 71.0 (C-1′′), 66.0 (C-4), 65.0 (C-4′′), 62.7 (C-6′), 61.0 (C-2′) and 55.6 ppm (OMe); HRFABMS *m/z* calcd for $[M+H]^+$ 415.1386; found: 415.1388. Anal. calcd for $C_{14}H_{26}O_{10}N_2S$: C, 40.57; H, 6,32; N, 6.76; S, 7.74; found: C, 40.81; H, 6.36; N, 6.73; S, 7.34.

4.3. 1-(Methyl 2-deoxy-α-D-glucopyranosid-2-yl)-(1,2-dideoxy-α-D-glucofurano)[2,1-d] imidazolidine-2-thione **4**

To a solution of **3** (100 mg, 0.241 mmol) in water (3 mL), acetic acid was added (0.33 mL). The resulting solution was stirred at 60°C for 1.5 h. Then it was co-concentrated with ethanol to dryness. The residue was purified by column chromatography ($CH_2Cl_2 \rightarrow CH_2Cl_2$:methanol 3:1). This gave **4** (68 mg, 90%) as an amorphous solid; [α] +94 (c 1.0, pyridine); IR ν_{max} 3378, 2930, 1595, 1491, 1454, 1238 and 1028 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 6.07 (d, 1H, $J_{1'',2''}$=6.6 Hz, H-1″), 5.08 (dd, 1H, $J_{1',2'}$=3.2 Hz, H-1′), 4.43 (dd, 1H, $J_{2',3'}$=11.2 Hz, H-2′), 4.22 (d, 1H, $J_{3'',4''}$=2.5 Hz, H-3″), 4.14 (d, $J_{2'',3''}$=0 Hz, H-2″), 3.99 (dd, 1H, $J_{3',4'}$=8.5 Hz, H-3′), 3.93 (ddd, 1H $J_{5'',6''a}$=3.3 Hz, $J_{5'',6''b}$=6.8 Hz, H-5″), 3.83 (dd, 1H, $J_{6'a,6'b}$=11.9 Hz, H-6′a), 3.81 (dd, 1H, $J_{6'',6''b}$=11.4 Hz, H-6″a), 3.71 (dd, 1H, H-6′b), 3.62 (dd, 1H, $J_{4'',5''}$=8.6 Hz, H-4″), 3.59 (ddd, 1H, $J_{5',6'a}$=2.3 Hz, $J_{5',6'b}$=5.5 Hz, H-5″), 3.58 (dd, 1H, H-6″b), 3.42 (t, 1H, $J_{4',5'}$=9.9 Hz, H-4′) and 3.37 ppm (s, 3H, OMe); ^{13}C NMR (125.7 MHz, CD_3OD) δ 178.0 (C=S), 99.4 (C-1′), 92.6 (C-1″), 81.0 (C-4″), 76.2 (C-3″), 73.5 (C-5′), 73.3 (C-4′), 70.5 (2C, C-3′, C-5″), 67.1 (C-2″), 66.0 (C-6″), 62.8 (C-6′), 61.1 (C-2′) and 55.8 ppm (OMe); HRFABMS *m/z* calcd for $[M+H]^+$ $C_{14}H_{24}O_9N_2S$: 397.1281; found: 397.1281.

4.4. 1-(Methyl 3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosid-2-yl)-(3,5,6-tri-O-acetyl-1,2-dideoxy-α-D-glucofurano)[2,1-d]imidazolidine-2-thione **5**

Conventional treatment of **4** (94 mg, 0.24 mmol) with acetic anhydride (0.5 mL) in pyridine (0.5 mL) at 0°C for 12 h gave a residue which was purified by preparative TLC (ether:petroleum ether 6:1). This gave **5** (99 mg, 64%) as an amorphous solid, $[\alpha]_D^{28}$ +110 (c 1.0, CH_2Cl_2); IR ν_{max} 3324, 2940, 2845, 1746, 1481, 1373, 1233 and 1042 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.36 (s, 1H, NH), 6.06 (d, 1H, $J_{1'',2''}$=6.0 Hz, H-1″), 5.38 (dd, 1H, $J_{3',4'}$=9.2 Hz, H-3′), 5.26 (t, 1H, $J_{4',5'}$=10.1 Hz, H-4′), 5.23 (m, 2H, $J_{3'',4''}$=2.9 Hz, $J_{5'',6''a}$=2.2 Hz, $J_{5'',6''b}$=5.2 Hz, H-3″, H-5″), 5.00 (d, 1H, $J_{2',3'}$=10.8 Hz, H-2′), 4.79 (d, 1H, $J_{1',2'}$=2.7 Hz, H-1′), 4.53 (dd, 1H, $J_{6''a,6''b}$=12.4 Hz, H-6″a), 4.24 (dd, 1H, $J_{6'a,6'b}$=12.4 Hz, H-6′a), 4.15 (dd, 1H, $J_{4'',5''}$=9.1 Hz, H-4″), 4.13 (dd, 1H, H-6′b), 4.10 (dd, 1H, H-6″b), 4.09 (d, 1H, $J_{2'',3''}$=0 Hz, H-2″), 4.01 (ddd, 1H, $J_{5',6'a}$=4.7 Hz, $J_{5',6'b}$=4.6 Hz, H-5′), 3.43 (s, 3H, OMe), 2.12 (s, 3H, Ac), 2.06 (s, 3H, Ac), 2.04 (s, 3H, Ac), 2.01 (s, 3H, Ac) and 1.97 ppm (s, 3H, Ac); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 184.6 (C=S), 171.4 ($COCH_3$), 170.7 ($COCH_3$), 170.5 ($COCH_3$), 169.8 ($COCH_3$), 169.5 ($COCH_3$), 169.1 ($COCH_3$), 98.3 (C-1′), 91.7 (C-1″), 75.8 (C-4″), 74.5 (C-3′), 69.8 (C-3′), 68.3 (C-4′), 67.6 (2 C, C-5′, C-5″), 63.1 (C-2″), 62.9 (C-6″), 62.1 (C-6′), 57.4 (C-2′), 55.8 (OMe), 20.8 ($COCH_3$), 20.7 ($COCH_3$), 20.6 (3C, 3$COCH_3$) and 20.5 ppm ($COCH_3$); HRCIMS *m/z* calcd for $[M+H]^+$ 649.1915; found: 649.1901. Anal. calcd for $C_{26}H_{36}O_{15}N_2S$: C, 48.15; H, 5.59; N, 4.32, S, 4.94; found: C, 48.29; H, 5.23; N, 4.35 S, 4.90.

4.5. 1-(Methyl 2-deoxy-α-D-glucopyranosid-2-yl)-4-(D-arabino-tetritol-1-yl)-4-imidazoline-2-thione **6**

(a) From **4**: to a solution of **4** (0.208 g, 0.52 mmol) in methanol (8 mL), trifluoroacetic acid was added (0.08 mL). After 4 h stirring at rt, **6** crystallized, and was filtered (142 mg). The mother liquor was kept in the reaction mixture for a further 20 h and then co-concentrated with ethanol to dryness. The residue was crystallized from methanol to give a further 18 mg. Total yield 160 mg (77%). (b) From **3**: to a solution of **3** (189 mg, 0.456 mmol) in water (5 mL) acetic acid was added (0.56 mL). After 1.5 h at 60°C the crude reaction mixture was concentrated to dryness by coevaporating with ethanol. To a solution of this residue in methanol (7 mL), trifluoroacetic acid was added (0.07 mL). The mixture was stirred at rt for

24 h, concentrated to dryness by coevaporating with ethanol and crystallized from methanol. This gave **6** (132 mg, 73%); m.p. 152–154°C; $[\alpha]_D^{28}$ +60 (c 1.0, pyridine); IR ν_{max} 3327, 3250, 2936, 2918, 1638, 1481, 1416, 1279, 1150, 1099 and 1034 cm^{-1}; ^1H NMR (500 MHz, D_2O) Table 1 and δ 3.95 (m, 1H, H-6′a), 3.82–3.88 (m, 2H, H-5′, H-6′b), 3.66 (dd, 1H, H-4′) and 3.38 ppm (s, 3H, OMe); ^{13}C NMR (125.7 MHz, D_2O) Table 2 and δ 73.2 (C-5′), 71.7 (C-4′), 61.9 (C-6′) and 56.4 ppm (OMe); HRFABMS *m/z* calcd for $[M+H]^+$ 397.1281; found: 397.1282. Anal. calcd for $C_{14}H_{24}O_9N_2S$: C, 42.42; H, 6.10; N, 7.07; S, 8.09; found: C, 42.20; H, 6.26; N, 6.74; S, 8.34.

*4.6. 1-(Methyl 3,4,6-tri-*O*-acetyl-2-deoxy-α-*D*-glucopyranosid-2-yl)-4-(1,2,3,4-tetra-*O*-acetyl-*D*-arabino-tetritol-1-yl)-4-imidazolidine-2-thione* ***7***

Conventional treatment of **6** (100 mg, 0.252 mmol) with acetic anhydride (0.5 mL) in pyridine (0.5 mL) at 0°C for 20 h gave a residue that showed by TLC (60:1, CH_2Cl_2:methanol) **7** (R_F 0.19) and its *N*-acetyl derivative (R_F 0.22). Ethanol was added and the resulting solution was heated at 50°C for 4 h until TLC showed disappearance of the product with a higher R_F value. Then it was concentrated to dryness and purified by preparative TLC (ether). This gave **7** (141 mg, 81%) as an amorphous solid; $[\alpha]_D^{28}$ +20 (c 1.0, CH_2Cl_2); IR ν_{max} 3298, 3021, 2934, 1748, 1474, 1371, 1235 and 1044 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) Table 1 and δ 11.24 (d, 1H, $J_{NH,H5}$=2.0 Hz, NH), 5.18 (t, 1H, $J_{4',5'}$=10.2 Hz, H-4′), 4.30 (dd, 1H, $J_{6'a,6'b}$=12.5 Hz, H-6′a), 4.13 (dd, 1H, H-6′b), 4.04 (ddd, 1H, $J_{5',6'a}$=4.6 Hz, $J_{5',6'b}$=2.4 Hz, H-5′), 3.34 (s, 3H, OMe), 2.11 (9H, 3Ac), 2.08 (s, 3H, Ac), 2.03 (s, 6H, 2Ac), 2.02 (s, 3H, Ac) and 1.90 ppm (s, 3H, Ac); ^{13}C NMR (125.7 MHz, $CDCl_3$) Table 2 and δ 170.6 ($COCH_3$), 170.4 ($COCH_3$), 170.3 ($COCH_3$), 169.5 ($2COCH_3$), 169.1 ($COCH_3$), 169.0 ($COCH_3$), 69.0 (C-4′), 67.6 (C-5′), 61.8 (C-6′), 55.3 (OMe), 20.6 ($3COCH_3$), 20.5 ($2COCH_3$), 20.4 ($COCH_3$) and 20.2 ppm ($COCH_3$); HRFABMS *m/z* calcd for $[M+Na]^+$ 713.1840; found: 713.1834. Anal. calcd for $C_{28}H_{38}O_{16}N_2S$: C, 48.69; H, 5.54; N, 4.06; S, 4.64; found: C, 48.85; H, 5.70; N, 4.38; S, 4.91.

*4.7. 4-(α-*D*-Erythrofuranosyl-1-(methyl 2-deoxy-α-*D*-glucopyranosid-2-yl)-4-imidazoline-2-thione* ***8*** *and 4-(β-*D*-erythrofuranosyl-1-(methyl 2-deoxy-α-*D*-glucopyranosid-2-yl)-4-imidazoline-2-thione* ***9***

To a solution of **6** (150 mg, 0.378 mmol) in water (15 mL) trifluoroacetic acid was added (0.75 mL). The resulting solution was stirred at 80°C for 10 h, and then co-concentrated with ethanol to dryness. The residue was purified by column chromatography ($CH_2Cl_2 \rightarrow CH_2Cl_2$:methanol 9:1). Eluted first was **8** as a syrupy compound, 22 mg (11%); $[\alpha]_D^{33}$ +69 (c 0.6, pyridine); IR ν_{max} 3313, 3040, 2924, 1724, 1593, 1447, 1360, 1271, 1113 and 1038 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) Table 1 and δ 3.87 (dd, 1H, $J_{6'a,6'b}$=12.0 Hz, H-6′a), 3.74 (dd, 1H, H-6′b), 3.65 (ddd, 1H, $J_{5',6'a}$=2.3 Hz, $J_{5',6'b}$=5.6 Hz, H-5′), 3.30 (s, 3H, OMe) and 3.50 ppm (dd, 1H, $J_{4',5'}$=9.9 Hz, H-4′); ^{13}C NMR (125.7 MHz, CD_3OD) Table 2 and δ 74.0 (C-5′), 72.7 (C-4′), 62.7 (C-6′) and 55.5 ppm (OMe); HRCIMS *m/z* calcd for $[M+H]^+$ $C_{14}H_{23}O_8N_2S$: 379.1175; found: 379.1170. Eluted second was **9** which was further purified by preparative TLC (CH_2Cl_2:methanol 5:1) to give 92 mg (48%) as an amorphous solid; $[\alpha]_D^{33}$ −4 (c 1.0, pyridine); IR ν_{max} 3347, 3065, 2926, 1630, 1589, 1474, 1344, 1115, and 1042 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) Table 1 and δ 4.58 (NH), 3.86 (dd, 1H, $J_{6'a,6'b}$=12.0 Hz, H-6′a), 3.74 (dd, 1H, H-6′b), 3.65 (ddd, 1H, $J_{5',6'a}$=2.3 Hz, H-5′), 3.31 (s, 3H, OMe) and 3.50 ppm (t, 1H, $J_{4',5'}$=9.9 Hz, H-4′); ^{13}C NMR (125.7 MHz, CD_3OD) Table 2 and δ 74.0 (C-5′), 72.6 (C-4′), 62.6 (C-6′) and 55.4 ppm (OMe); HRFABMS *m/z* calcd for $[M+H]^+$ $C_{14}H_{22}O_8N_2S$: 379.1175; found: 379.1173.

4.8. 4-(2,3-Di-O-acetyl-α-D-erythrofuranosyl)-1-(methyl-3,4,6-tri-O-acetyl-2-deoxy-α-D-gluco-pyranosid-2-yl)-4-imidazoline-2-thione **10**

Conventional treatment of **8** (60 mg, 0.16 mmol) with acetic anhydride (0.5 mL) in pyridine (0.5 mL) at 0°C for 12 h gave a residue that showed by TLC (ether:petroleum ether 15:1) **10** (R_F 0.08) and its *N*-acetyl derivative (R_F 0.42). The residue was treated with ethanol as described for the preparation of **7**. The resulting solution, containing the product of lower R_F, was concentrated to dryness and purified by preparative TLC (ether:petroleum ether 15:1) to give **10** (76 mg, 81%) as a syrup; $[\alpha]_D^{26}$ +119 (c 1.0, CH_2Cl_2); IR ν_{max} 3298, 3030, 2934, 1750, 1468, 1371, 1238, 1109 and 1044 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) Table 1 and δ 10.14 (s, 1H, NH), 5.20 (t, 1H, $J_{4',5'}$=10.2 Hz, H-4′), 4.29 (dd, 1H, $J_{6'a,6'b}$=12.4 Hz, H-6′a), 4.13 (dd, 1H, H-6′b), 4.04 (ddd, 1H, $J_{5',6'a}$=4.6 Hz, $J_{5',6'b}$=2.3 Hz, H-5′) and 3.34 ppm (s, 3H, OMe); ^{13}C NMR (125.7 MHz, $CDCl_3$) Table 2 and δ 170.6 ($COCH_3$), 170.0 ($COCH_3$), 169.4 ($COCH_3$), 169.2 ($COCH_3$), 169.1 ($COCH_3$), 69.0 (C-4′), 67.5 (C-5′), 61.8 (C-6′), 55.3 (OMe), 20.6 (6H, 2Ac), 20.4 (s, 3H, Ac) and 20.3 ppm (6H, 2Ac); HRCIMS *m/z* calcd for $[M+H]^+$ 589.1703; found: 589.1685. Anal. calcd for $C_{24}H_{32}O_{13}N_2S$: C, 48.98; H, 5.48; N, 4.76; S, 5.45; found: C, 48.72; H, 5.06; N, 4.75; S, 5.72.

4.9. 4-(2,3-Di-O-acetyl-β-D-erythrofuranosyl)-1-(methyl-3,4,6-tri-O-acetyl-2-deoxy-α-D-gluco-pyranosid-2-yl)-4-imidazoline-2-thione **11**

Conventional treatment of **9** (98 mg, 0.26 mmol) with acetic anhydride (0.5 mL) in pyridine (0.5 mL) at 0°C for 12 h gave a residue that showed by TLC (ether:petroleum ether 15:1) **11** (R_F 0.19) and its *N*-acetyl derivative (R_F 0.58). The residue was treated with ethanol as described for the preparation of **7**. The resulting solution, containing the product of lower R_F, was concentrated to dryness and purified by preparative TLC (ether:petroleum ether 15:1) to give **11** (112 mg, 73%) as a syrup; $[\alpha]_D^{26}$ −19 (c 1.0, CH_2Cl_2); IR ν_{max} 3302, 3036, 2959, 1748, 1462, 1370, 1229, 1107 and 1040 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) Table 1 and δ 11.58 (s, 1H, NH), 5.20 (t, 1H, $J_{4',5'}$=10.2 Hz, H-4′), 4.30 (dd, 1H, $J_{6'a,6'b}$=12.4 Hz, H-6′a), 4.12 (dd, 1H, H-6′b), 4.04 (ddd, 1H, $J_{5',6'a}$=4.6 Hz, $J_{5',6'b}$=2.3 Hz, H-5′), 3.34 (s, 3H, OMe), 2.11 (s, 3H, Ac), 2.10 (s, 3H, Ac), 2.06 (s, 3H, Ac), 2.01 (s, 3H, Ac) and 1.88 ppm (s, 3H, Ac); ^{13}C NMR (125.7 MHz, $CDCl_3$) Table 2 and δ 170.6 ($COCH_3$), 170.1 ($COCH_3$), 169.7 ($COCH_3$), 169.5 ($COCH_3$), 169.2 ($COCH_3$), 74.5 (C-4′), 67.5 (C-5′), 61.8 (C-6′), 55.2 (OMe), 20.6 ($COCH_3$), 20.5 ($COCH_3$), 20.4 ($2COCH_3$) and 20.3 ppm ($COCH_3$); FABMS *m/z* 589 (32, $[M+H]^+$), 611 (100, $[M+Na]^+$). Anal. calcd for $C_{24}H_{32}O_{13}N_2S$: C, 48.98; H, 5.48; N, 4.76; S, 5.45; found: C, 48.74; H, 5.48; N, 4.61; S, 5.55.

4.10. 4-(α-D-Erythrofuranosyl)-1-(methyl 2-deoxy-α-D-glucopyranosid-2-yl)-2-methylthio-1H-imidazole **12** and 4-(β-D-erythrofuranosyl)-1-(methyl 2-deoxy-α-D-glucopyranosid-2-yl)-2-methylthio-1H-imidazole **13**

To a solution of **6** (300 mg, 0.757 mmol) in methanol (30 mL) trifluoroacetic acid was added (1.5 mL). The resulting solution was stirred under reflux for 6 days, and then co-concentrated with ethanol. The residue was purified by column chromatography (CH_2Cl_2→CH_2Cl_2:methanol 9:1). Eluted first was **12** (26 mg, 9%) as an amorphous solid; $[\alpha]_D^{30}$ +106 (c 1.0, pyridine); IR ν_{max} 3339, 2920, 1667, 1593, 1445, 1327, 1196, 1123 and 1040 cm^{-1}; ^1H NMR (500 MHz, D_2O) Table 1 and δ 3.97 (m, 1H, H-6′a), 3.87 (m, 2H, H-5′, H-6′b), 3.65 (t, 1H, $J_{4',5'}$=9.2 Hz, H-4′), 3.41 (s, 3H, OMe) and 2.55 ppm (s, 3H, SMe); ^{13}C NMR (125.7 MHz, D_2O) Table 2 and δ 73.1 (C-5′), 71.5 (C-4′), 61.9 (C-6′), 56.4 (OMe) and 18.0

ppm (SMe); HRCIMS *m/z* calcd for $[M+H]^+$ 393.1332; found: 393.1307. Anal. calcd for $C_{15}H_{24}N_2O_8S$: C, 45.91; H, 6.16; N, 7.14; found: C, 45.58; H, 6.09; N, 7.17.

Eluted second was **13** (180 mg, 61%) as an amorphous solid; $[\alpha]_D^{27}$ +42 (c 1.0, pyridine); IR ν_{max} 3331, 3044, 2936, 1680, 1595, 1449, 1358, 1202, 1142 and 1044 cm^{-1}; ^1H NMR (500 MHz, D_2O) Table 1 and δ 3.77 (m, 3H, H-5′, H-6′a, H-6′b), 3.58 (t, 1H, $J_{4',5'}$=8.9 Hz, H-4′), 3.40 (s, 3H, OMe) and 2.50 ppm (s, 3H, SMe); ^{13}C NMR (125.7 MHz, D_2O) Table 2 and δ 71.9 (C-5′), 70.2 (C-4′), 60.6 (C-6′), 55.1 (OMe) and 17.7 ppm (SMe); HRFABMS *m/z* calcd for $[M+H]^+$ $C_{15}H_{24}O_8N_2S$: 393.1332; found: 393.1321.

4.10.1. Glycosidase inhibition studies

Compound **6** was evaluated as an inhibitor towards 23 commercially avaible glycosidases: α-L-fucosidase (from bovine epididymis), α-galactosidases (from coffee beans, *Aspergillus niger* and *Escherichia coli*), β-galactosidases (from *Escherichia coli*, bovine liver, *Aspergillus niger, Aspergillus orizae* and Jack beans), α-glucosidases (maltase) (from yeast and rice), α-glucosidase (isomaltase) (from baker's yeasts), amyloglucosidases (from *Aspergillus niger* and *Rhizopus* mold), β-glucosidases (from almonds and *Caldocellum saccharolyticum*), α-mannosidases (Jack beans and almonds), β-mannosidase (from *Helix pomatia*), α-*N*-acetylgalactosaminidase (from chicken liver), β-*N*-acetylglucosaminidases (from Jack bean, bovine epididymis A and bovine epididymis B). It did not show activity at 1 mM concentration towards the selected enzymes, except a 50% of inhibition towards α-glucosidase (isomaltase) from baker's yeasts.[25]

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