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Stereocontrolled synthesis of (5+5), (5+6) and (6+6) 3-spiropseudonucleosides

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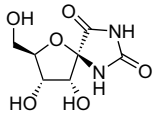
ABSTRACT

3-Spiropseudonucleosides, in which the heterocyclic base is a five-membered (oxazolidine, imidazolidine, thiohydantoin) or six-membered (perhydrooxazine) heterocycle, have been prepared starting from a hexofuranos-3-ulose. The method leads to good yields and is completely stereoselective. The key intermediate is a sugar iso(thio)cyanate.

1. Introduction

The term spironucleoside (**1**) is used to designate a type of sugar derivative in which the anomeric carbon belongs simultaneously to a pyranoid or furanoid sugar ring and to a nitrogenated heterocyclic moiety.[1] The term spiropseudonucleoside (**2**) is used when the spiranic carbon atom is different from anomeric carbon, and the numbers $n+m$ (5+5, as example) are indicative of the size of the sugar and nitrogenated heterocyclic rings. The first natural spironucleoside known was (+)-hydantocidin (**1**), isolated in 1991 from culture broths of *Streptomices hygroscopicus*. The hydantocidin and related synthetic compounds show important biological activities, such as inhibition of adenylsuccinate shyntase,[2] glycogen phosphorilase[3] and glycosidases.[4] Syntheses of (+)-hydantocidin have been reported[5] and starting from 1993 many syntheses of hydantocidin 1-spiroanalogues, other spironucleosides, and related carbocyclic derivatives have been described.[1b,6] In the case of 3-spiropseudonucleosides, the preparation of spiroglycooxazolidines,[7] 3-spiroglycohydantoins,[8] 3-glycopiperazinediones[9] and thiazolidines[10] has recently been reported. Also syntheses of spirosugar derivatives with a heterocyclic moiety on the anomeric position have been described.[11,12] At the same time, chiral oxazolidine-2-ones[13] and oxazolidine-2-thiones[14] are important chiral inducers in asymmetric syntheses and a D-galacto-3-spirothiazolidine has activity in inflammatory and metastasis processes.[10]



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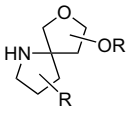

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In this paper, we described a general procedure[15] to prepare 3-spiropseudonucleosides with oxazolidine-2-thione, imidazolidine-2-thione, oxazine-2-thione, thiohydantoin and oxazin-2-one as heterocyclic moieties starting from a D-*ribo*-hexofuranos-3-ulose (**3**) being the key intermediate a sugar isothiocyanate or a sugar isocyanate (**5**).[16]

2. Results and discussion

The starting material to prepare the different 3-spiropseudonucleosides is 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**3**),[17] and the method is based on the formation, through the amine **4**, of an isothiocyanate derivative **5**, which cyclizes to the spiroheterocycle **6** (Scheme 1). As the isothiocyanato group and the nucleophile (HX) in **5** are very close, the cyclization takes place spontaneously. However, in the cases of strong steric hindrance, the isolation of the isothiocyanates **5** is possible (see below).

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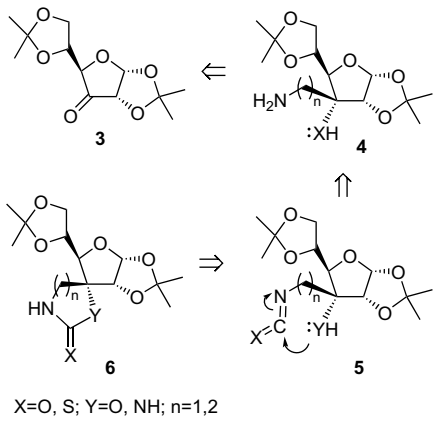
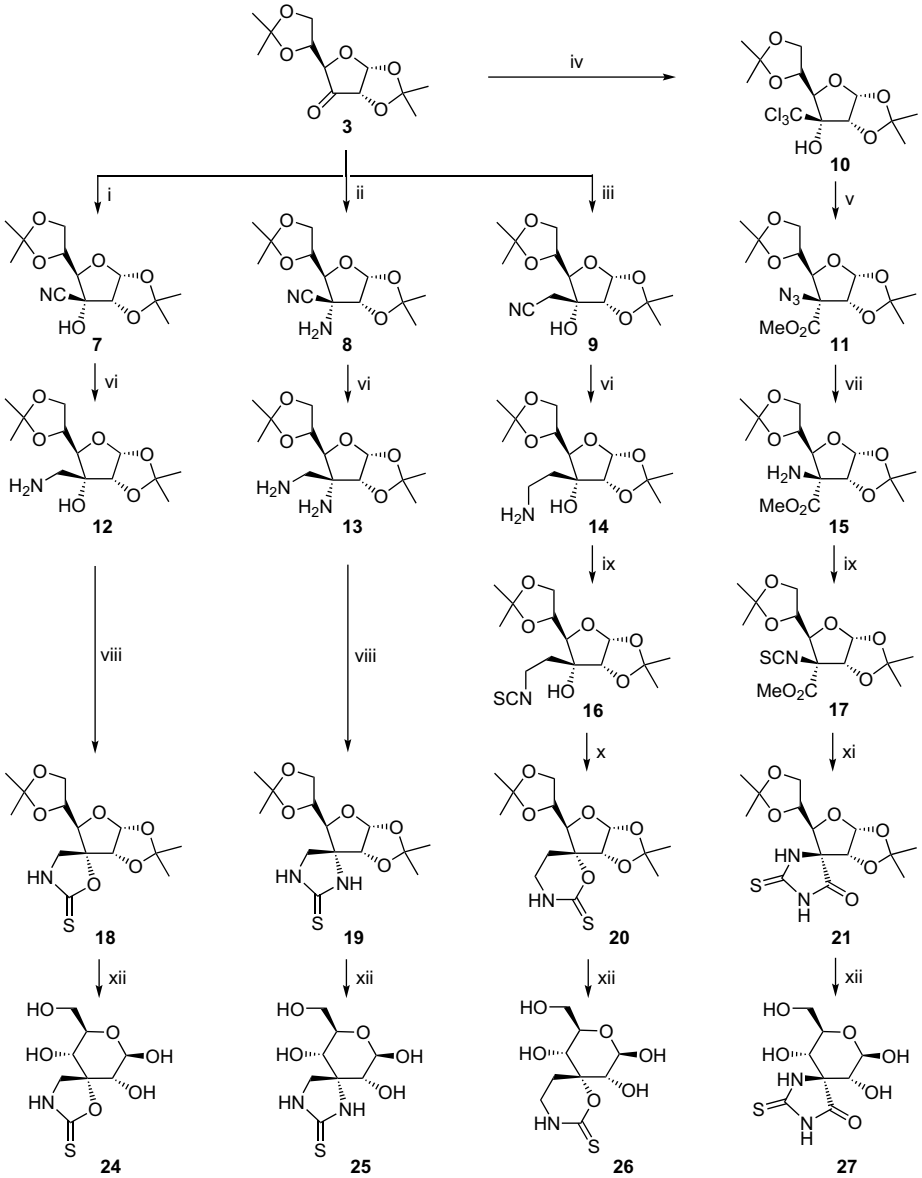


Scheme 1. General method for the synthesis of 3-spiropseudonucleosides.

The 3-cyano derivatives **7**[17] and **8**[18] (Scheme 2) were prepared as is described in literature. Reaction of **3** with trimethylsilyl acetonitrile in the presence of tetrabutyl ammonium fluoride (TBAF), as transfer phase catalyst, produced **9** in high yield. The group CH_2CN of **9** was evident from the IR absorption at 2250 cm^{-1} (C≡N), from the signals in the ^1H NMR spectrum (Table 1 and Experimental) at 2.95, 2.61 (CH_2) and 3.14 ppm (HO), and from the resonances in the ^{13}C NMR spectrum (Table 1 and Experimental) at 22.7 (CH_2) and 116.3 ppm (C≡N). No signals for other stereoisomer were observed. The configuration of C-3 is supported on 2D-NOESY experiments performed on the isothiocyanate **16** (see below) and is in agreement with the configuration of C-3 reported[17,18] for **7** and **8**.

The nucleophilic addition of chloroform on the carbonyl group of **3** in the presence of lithium hexamethyldisilylazide (LiHMDS) gave **10**, which by treatment with sodium azide and DBU[19] yielded the azidoester **11**. The molecular peak in the MS of **10** showed the pattern for three chloro atoms, the chemical shift for the resonance of the Cl_3C group appeared at 100.9 ppm, and NMR signals for only



Scheme 2. Preparation of thioxo-pseudospironucleosides. Reagents and conditions. (i) See Ref. 17; (ii) see Ref. 18; (iii) $TMSCH_2CN$, TBAF, THF, rt; (iv) $CHCl_3$/LiHMDS, THF, −78 °C; (v) NaN_3/DBU, 18-crown-6, MeOH, 50 °C; (vi) $LiAlH_4$, Et_2O, 0 °C, → rt; (vii) H_2/Pd, MeOH, rt; (viii) Im_2CS, CH_2Cl_2, rt; (ix) $CSCl_2$, $CaCO_3$, Cl_2CH_2/H_2O, rt; (x) Et_3N, CH_2Cl_2, rt; (xi) NH_3, CH_2Cl_2, rt; (xii) HCl/MeOH, 60 °C.

Table 1
Selected NMR chemical shifts (ppm) for compounds **9**–**27**

Comp.	H-2	H-4	C-2	C-3	C-4	CH_2	C=S[d]
9[a]	4.51	3.79	82.0	77.9	80.9	22.7	—
10[a]	4.80	4.15	82.1	87.6	85.1	—	—
11[a]	4.64	4.63	85.3	74.5	81.4	—	—
12[b]	4.53	3.90	82.1	80.7	82.7	43.5	—
13[b]	4.52	3.87	83.5	80.3	84.7	43.7	—
14[a]	4.38	3.84	80.5	83.3	83.1	33.5, 37.3	—
15[a]	4.26	4.67	88.7	68.2	82.0	—	—
16[a]	4.39	3.76	81.0	78.3	82.1	40.3	131.2
17[a]	4.72	4.60	82.0	75.0	87.7	—	142.5
18[a,c]	4.55	4.21	83.9	91.3	77.2	47.8	188.6
19[a,c]	4.43	3.86	84.5	71.1	78.4	48.5	183.9
20[a,c]	4.36	4.27	82.5	84.7	81.1	37.4, 21.6	186.1
21[a,c]	4.71	4.36	85.7	60.5	81.9	—	181.7
22[a,c]	4.46	4.11	83.9	85.5	77.3	44.3	158.4
23[a,c]	4.37	4.07	81.7	83.2	80.7	36.1, 22.1	153.3
24[c,e]	3.52	3.74	72.7	93.0	68.3	47.9	188.1
25[c,e]	3.52	3.73	75.2	95.4	70.8	50.4	190.6
26[c,e]	3.48	3.72	74.5	86.0	70.0	38.2, 23.6	185.7
27[c,e]	3.63	3.90	72.9	72.2	68.1	—	184.2

[a] In $CDCl_3$.
[b] In MeOD.
[c] Using the numbering of the sugar ring.
[d] C=O for **21** and **22**.
[e] In D_2O.

one stereoisomer were observed. The configuration of C-3 was demonstrated by 2D-NOESY experiments performed on **21** (see below). The azido group of **11** was evident from the IR absorption at 2120 cm^{-1} and for the shielding of the resonances for C-3, H-2 and H-4 (see Table 1). Reduction of **7**–**9** with lithium aluminium hydride and of **11** with H_2/Pd gave the amino derivatives **12**–**15**, respectively, in moderate to high yields. The spectroscopic data of **12**–**15** (Table 1) supported the proposed structures.

The treatment of amino compounds **12** and **13** with thiocarbonyldiimidazole, or with thiophosgene directly gives the spiropseudonucleosides **18**[20] and **19**, respectively, without isolation of a transient isothiocyanate (see Scheme 1). However, in the cases of **14** and **15** the isothiocyanato derivatives **16** and **17**, respectively, were isolated by reaction with thiophosgene in the presence of calcium carbonate and in a heterogeneous medium. Intramolecular cyclization of **16**, promoted by triethylamine, afforded the spirooxazine-2-thione **20** in high yield. In the case of **17** the cyclization to **21** was promoted by treatment with ammonia in dichloromethane. The IR spectra of the isothiocyanates **16** and **17** had the absorption at 2107 and 2255 cm^{-1}, respectively, characteristic of the NCS group. The ^{13}C resonance for the NCS group of **16** appeared at 131.2 ppm as it is described[21] for isothiocyanato sugar derivatives; in the case of **17** that resonance appeared at 142.5 ppm, very close to the value reported[6a] for isothiocyanatoulosonates. Moreover, the described[22] deshielding for the resonance of the carbon atom adjacent to the NCS group (CH_2 in **16** and C-3 in **17**) was also observed. The structures of the spiropseudonucleosides **18**–**21** were based on NMR data (Table 1 and Experimental). Thus, the chemical shift for the resonance of the C=S group of **18**, **19**, **20** and **21** was in agreement with reported data for oxazolidine-2-thiones,[7a,13a] for imidazolidine-2-thione[13a,23] for six-membered cyclic thiocarbamates,[24] and for thiohydantoins,[6a] respectively.

The configuration of C-3 in **12**, **18**[20] and in **13**, **19** is the same of that described for **7**[17] and **8**,[18] respectively. The 2D-NOESY spectrum of the isothiocyanato derivative **16** supported the indicated configuration for C-3 (sugar ring). Both ^1H signals of the CH_2 group (diasterotopic protons) bonded to C-3 showed NOEs with the protons H-1, H-2, H-5 and H-6, indicating that all these protons are situated on the same face of the sugar ring (Fig. 1). Additionally, the HO group on C-3 showed NOE with H-4. These results support the

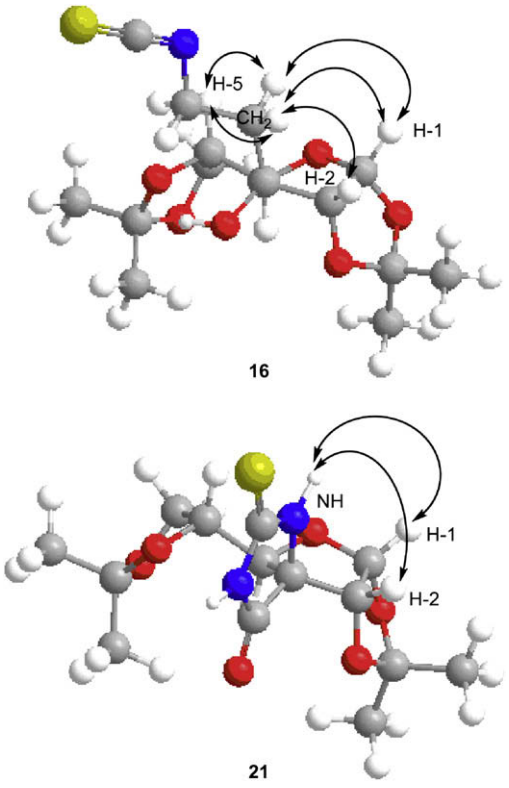
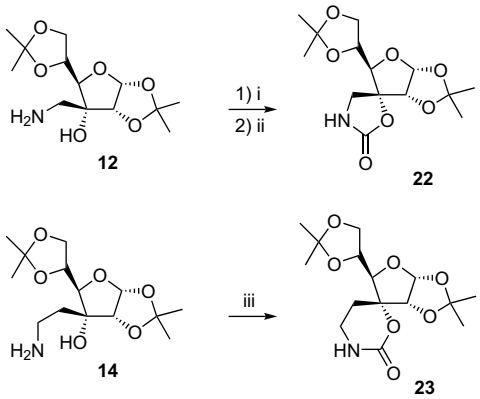


Figure 1. Representative NOEs in compounds **16** and **21**.

configuration *R* for C-3 in **16**, and, consequently, the same configuration for C-3 in **9**, **14** and **20**. A similar study performed on **21** demonstrated *S* configuration for C-3 of **21**, **11**, **15** and **17**. In these cases was crucial the NOE observed between the N–H bonded to the spiranic carbon and the protons H-1 and H-2 (numbering of sugar derivative) of the sugar ring (Fig. 1).

With the aim of preparing oxo-analogues of **18** and **20** we have carried out the reactions of **12** and **14** with triphosgene[25] (Scheme 3). In this way, the oxo-spironucleosides **22** and **23**, respectively, were obtained without isolation of the intermediate isocyanato derivative. The chemical shifts for the resonance of C-3 (sugar ring numbering) of **22** and **23** (Table 1) were very close to that for the thioxo analogues **18** and **20**. The C=O group resonated at 158.4 and 153.3 ppm as it is reported[26] for related compounds.

O-Deprotection of compounds **18**–**21** with HCl in methanol afforded **24**–**27**, respectively, in 77–85% yield, and only as pyranoid β-anomers. The pyranoid structure was evident from the values of



Scheme 3. Preparation of oxo-pseudonucleosides. Reagents and conditions. (i) Triphosgene, DMF, DIEA, rt; (ii) Et_3N, 80 °C; (iii) triphosgene, CH_2Cl_2, $NaHCO_3$, 0 °C.

$J_{4,5}$ (ring sugar numbering), and from the chemical shifts for the resonances of the sugar ring carbons. The $J_{4,5}$ values were in the range 10.0–10.2 Hz (see Experimental), indicating trans-relationship between the corresponding protons. The ^{13}C resonance for the non-anomeric, non-spiranic carbon atoms of the sugar ring (C-2, C-4 and C-5 using the sugar numbering) was in the range (see Experimental) for pyranoid sugar derivatives, 5–12 ppm shielded with respect to the same signals for furanoid derivatives.[27]

3. Conclusions

We have developed a high yielding and stereoselective method for the synthesis of 2-thioxo and 2-oxo-spiro-glyco-1-*O*(*N*)-3-*N*-five- and six-membered heterocycles from a 3-oxo-D-glucofuranose (**3**) being the key chiral intermediate a sugar isothiocyanato (isocyanato) derivative. The method has been applied to the preparation of glycospiro-thioxooxazolidine (**18**), -oxooxazolidine (**22**) and -thioxoperhydrooxazine (**20**), -oxoperhydrooxazine (**23**) and thiohydantoin (**21**). The *O*-protected derivatives have furanoid structure, whereas the unprotected compounds have pyranoid structure.

4. Experimental

4.1. General methods

Unless otherwise noted, starting materials were obtained for commercial suppliers and used without purification. All manipulations of air-sensitive compounds were carried out in an inert atmosphere under recirculation of nitrogen or argon. The following reaction solvents were distilled under nitrogen immediately before use: THF and Et_2O from Na/benzophenone; CH_2Cl_2 from CaH_2; toluene from Na; and MeOH from Mg. Et_2O and petroleum ether for column chromatography were also distilled under nitrogen from Na/benzophenone before use. TLC were performed on silica gel HF_{254}, with visualization by UV light or charring with 10% H_2SO_4 (EtOH) or 1% $Ce(SO_4)_2\cdot 4H_2O$–5% ammonium molybdate–6% H_2SO_4. Silica gel 60 (Merck, 70–230 or 230–400 mesh) was used for preparative chromatography. A Perkin–Elmer model 141 MC polarimeter, tubes of 1 cm, and solutions in CH_2Cl_2, unless other stated, at 589 nm, were used for measurements of specific rotations. IR were recorded for KBr discs or films on a Bomen Michelson MB 120 FTIR spectrophotometer. Mass spectra (EI, CI and FAB) were recorded with a Kratos MS-80RFA or a Micromass AutoSpecQ instrument with a resolution of 1000 or 60,000 (10% valley resolution). For the FAB spectra; ions were produced by a beam of xenon atoms (6–7 KeV), using 3-nitrobenzyl alcohol or thioglycerol as matrix and NaI as salt. A Waters 2690 instrument, with a PDA 996 detector, and a μBondpack C18 column (7.8×300 mm) was used for HPLC. NMR experiments were recorded on a Bruker AMX 500 (500.13 MHz for ^1H and 125.75 MHz for ^{13}C) or on a Bruker AMX300 (300.5 MHz for ^1H and 75.50 MHz for ^{13}C). Sample concentrations were typically in the range 10–15 mg per 0.5 mL of solvent. Chemical shifts are given in parts per million, and tetramethylsilane was the internal standard. 2D COSY, HMQC, TCOSY, HMBC and 1D NOESY experiments were carried out to assist in NMR signal assignments.

Compounds **3**,[17] **7**[17] and **8**[18] were prepared according to the described literature procedures.

4.2. 3-*C*-Cyanomethyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (9)

A solution of TBAF in dry THF (1 M, 0.5 mL) was added, at 0 °C under argon, to another solution of compound **3** (150 mg, 0.58 mmol) and $TMSCH_2CN$ (157 μL, 1.16 mmol) in dry THF (1 mL). The reaction mixture was stirred for 24 h at room temperature and then diluted with AcOEt (2 mL). The mixture was washed with water at 0 °C and brine. The organic layer was dried with $MgSO_4$ and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography (CH_2Cl_2/MeOH=30:1) to afford compound **9** (141 mg; 81%) as an amorphous solid. $[\alpha]_D^{22}$ +18 (*c* 1.0, CH_2Cl_2); IR: ν_{max} 3434, 2987, 2939, 2250, 1380, 1215, 1075, 1006, 851 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 5.83 (d, 1H, $J_{1,2}$=3.9, H-1), 4.51 (d, 1H, H-2), 4.14 (dd, 1H, $J_{5,6a}$=5.9, $J_{6a,6b}$=8.3, H-6a), 4.03 (ddd, 1H, $J_{4,5}$=8.7, $J_{5,6b}$=4.7, H-5), 3.94 (dd, 1H, H-6b), 3.79 (d, 1H, H-4), 3.14 (d, 1H, $J_{OH,CH2}$=0.6, OH), 2.95 (d, 1H, $J_{H,H}$=16.8, C*H*H), 2.61 (dd, 1H, CH*H*), 1.60, 1.46, 1.39, 1.36 (each s, each 3H, 2 (CH_3)$_2$C); ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 116.3 (CN), 113.3, 110.2 [2*C*(CH_3)$_2$], 103.5 (C-1), 82.0 (C-2), 80.9 (C-4), 77.9 (C-3), 73.4 (C-5), 67.9 (C-6), 26.6, 26.4, 26.4, 25.0 [2C(CH_3)$_2$], 22.7 (CH_2); HRCIMS: Calcd for $C_4H_2NO_6$: 300.1447. Found: 300.1444.

4.3. General procedure for the preparation of amines 12–14

To a solution at 0 °C of the corresponding nitrile **7**–**9** (*x* mg) in dry ether (*y* mL), $LiAlH_4$ (*z* mg) was added. The mixture was stirred at 0 °C for 30 min and then for 2.5 h at room temperature. The reaction mixture was treated with 1 M K_2CO_3 solution and the precipitate was filtered off over Celite. The solution was washed with brine and water, dried with $MgSO_4$, and evaporated to dryness under reduced pressure. The residue was purified by column chromatography as indicated below.

*4.3.1. 3-C-Aminomethyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (**12**)*

x=100 mg (0.35 mmol); *y*=3 mL; *z*=27.2 mg (0.70 mmol). Syrup (59.9 mg; 59%). $[\alpha]_D^{22}$ +44 (*c* 1.0, CH_2Cl_2); IR: ν_{max} 3459, 2988, 2930, 1577, 1458, 1216, 1160, 1072, 853 cm^{-1}; ^1H NMR: (500 MHz, MeOD) δ 5.71 (d, 1H, $J_{1,2}$=3.8, H-1), 4.53 (d, 1H, H-2), 4.12 (ddd, 1H, $J_{4,5}$=7.4, $J_{5,6a}$=6.3, $J_{5,6b}$=5.7, H-5), 4.06 (dd, 1H, $J_{6a,6b}$=8.2, H-6a), 3.90 (d, 1H, H-4), 3.83 (dd, 1H, H-6b), 2.94 (d, 1H, $J_{H,H}$=13.5, C*H*HNH$_2$), 2.59 (d, 1H, CH*H*NH$_2$), 1.53, 1.40, 1.35, 1.32 [each s, each 3H, 2C(CH_3)$_2$]; ^{13}C NMR: (125.7 MHz, MeOD) δ 113.6, 110.7 [2*C*(CH_3)$_2$], 104.9 (C-1), 82.7 (C-4), 82.1 (C-2), 80.7 (C-3), 74.6 (C-5), 68.4 (C-6), 43.5 (CH_2NH_2), 26.9, 26.8, 26.6, 25.5 [2C(CH_3)$_2$]; HRFABMS: calcd for $C_{13}H_{23}NO_6Na$: 312.1525; found: 312.1524.

*4.3.2. 3-Amino-3-C-aminomethyl-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (**13**)*

x=172 mg (0.61 mmol); *y*=6 mL; *z*=47 mg (1.21 mmol). Syrup (90.8 mg; 52%). IR: ν_{max} 3510, 3308, 2990, 2929, 1579, 1466, 1214, 1160, 1079, 1002, 865 cm^{-1}; ^1H NMR: (500 MHz, MeOD) δ 5.74 (d, 1H, $J_{1,2}$=3.7, H-1), 4.52 (d, 1H, H-2), 4.19 (m, 1H, H-5), 4.11 (dd, 1H, $J_{5,6a}$=7.0, $J_{6a,6b}$=4.7, H-6a), 3.87 (d, 1H, $J_{4,5}$=8.9, H-4), 3.73 (dd, 1H, $J_{5,6b}$=8.7, H-6b), 2.82 (d, 1H, $J_{H,H}$=13.0, C*H*HNH$_2$), 2.61 (d, 1H, CH*H*NH$_2$), 1.53, 1.42, 1.34, 1.34 [each s, each 3H, 2C(CH_3)$_2$]; ^{13}C NMR: (125.7 MHz, MeOD) δ 113.3, 110.9 [2*C*(CH_3)$_2$], 105.3 (C-1), 84.7 (C-4), 83.5 (C-2), 80.3 (C-3), 74.7 (C-5), 69.3 (C-6), 43.7 (CH_2NH_2), 26.9, 26.9, 26.4, 25.4 [2C(CH_3)$_2$]; HRFABMS: calcd for $C_{13}H_{25}N_2O_5Na$: 311.1583; found: 311.1589.

*4.3.3. 3-C-Aminoethyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (**14**)*

x=374 mg (1.25 mmol); *y*=12 mL; *z*=97 mg (2.50 mmol). Syrup (240 mg; 56%). $[\alpha]_D^{22}$ +23 (*c* 1.0, MeOH); IR: ν_{max} 3502, 3461, 2986, 2935, 1581, 1459, 1377, 1216, 1163, 1074, 1008, 872, 849 cm^{-1}; ^1H NMR: (500 MHz, $CDCl_3$) δ 5.68 (d, 1H, $J_{1,2}$=3.7, H-1), 4.38 (d, 1H, H-2), 4.15 (ddd, 1H, $J_{4,5}$=6.9, $J_{5,6a}$=6.3, $J_{5,6b}$=6.0, H-5), 4.07 (dd, 1H, $J_{6a,6b}$=8.1, H-6a), 3.85 (dd, 1H, H-6b), 3.84 (d, 1H, H-4), 2.97 (m, 2H, $CH_2CH_2NH_2$), 1.92, 1.55 (each m, each 1H, $CH_2CH_2NH_2$), 1.54, 1.39, 1.33, 1.33 [each s, each 3H, 2C(CH_3)$_2$]; ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 113.7, 110.5 [2*C*(CH_3)$_2$], 104.8 (C-1), 83.3 (C-3), 83.1 (C-4), 80.5

(C-2), 74.7 (C-5), 68.3 (C-6), 37.3 ($CH_2CH_2NH_2$), 33.5 ($CH_2CH_2NH_2$), 26.9, 26.8, 26.6, 25.5 [2C(CH_3)$_2$]. Anal. Calcd for $C_{14}H_{25}NO_6$: C, 55.43; H, 8.31; N, 4.62. Found: C, 55.64; H, 8.34; N, 4.69%.

4.4. 1,2:5,6-Di-*O*-isopropylidene-3-*C*-trichloromethyl-α-D-allofuranosa (10)

To a solution of **3** (1.00 g, 3.88 mmol) in dry THF (16.4 mL) and dry $CHCl_3$ (1.7 mL) at −78 °C, another solution of 1 M LiHMDS in THF (14 mL, 14.0 mmol) was added dropwise. The mixture was stirred at −78 °C for 2 h and then was poured off over a saturated solution of $NaHCO_3$ at 0 °C. The mixture was extracted with CH_2Cl_2 (3×10 mL) and the combined CH_2Cl_2 layers were dried over $MgSO_4$. The solution was concentrated in vacuum to dryness and the residue was purified by column chromatography (ether/hexane=1:2) affording compound **10** as an amorphous solid (1.04 g; 71%). $[\alpha]_D^{22}$ +30 (*c* 1.0, CH_2Cl_2); IR: ν_{max} 3436, 2989, 2929, 1632, 1455, 1377, 1257, 1160, 1085, 740 cm^{-1}; ^1H NMR: (500 MHz, $CDCl_3$) δ 5.91 (d, 1H, $J_{1,2}$=4.5, H-1), 4.80 (d, 1H, H-2), 4.69 (m, 1H, H-5), 4.15 (d, 1H, $J_{4,5}$=7.5, H-4), 4.14 (dd, 1H, $J_{5,6a}$=5.8, $J_{6a,6b}$=8.5, H-6a), 3.91 (dd, 1H, $J_{5,6b}$=7.0, H-6b), 3.84 (s, 1H, OH), 1.63, 1.45, 1.43, 1.36 (each s, each 3H [2C(CH_3)$_2$]); ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 113.4, 109.9 [2*C*(CH_3)$_2$], 104.4 (C-1), 100.9 (CCl_3), 87.6 (C-3), 85.1 (C-4), 82.1 (C-2), 72.0 (C-5), 67.9 (C-6), 27.0, 26.7, 26.4, 25.6 [2C(*C*H_3)$_2$]. Anal. Calcd for $C_{13}H_{19}Cl_3O_6$: C, 41.35; H, 5.07. Found: C, 41.44; H, 5.11%.

4.5. 3-Azido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-methoxycarbonyl-α-D-glucofuranose (11)

To a solution of **10** (2.27 g, 6.02 mmol) in dry MeOH (28 mL), NaN_3 (1.18 g, 18.15 mmol) and 18-crown-6 (17 mg, 0.07 mmol) was added. Then DBU (4.54 mL, 30.33 mmol) was added dropwise and the reaction mixture was heated at 50 °C for 1 h. The mixture was poured off over a saturated solution of NH_4Cl and extracted with ether. The organic layer was dried with $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (AcOEt/Hexane=1:4) to afford compound **11** as a syrup (1.674 g; 81%). $[\alpha]_D^{22}$ +73 (*c* 1.0, CH_2Cl_2); IR: ν_{max} 3442, 2989, 2926, 2120, 1746, 1630, 1455, 1378, 1257, 846 cm^{-1}; ^1H NMR: (500 MHz, $CDCl_3$) δ 5.94 (d, 1H, $J_{1,2}$=4.0, H-1), 4.64 (d, 1H, H-2), 4.63 (d, 1H, $J_{4,5}$=8.0, H-4), 4.21 (m, 1H, H-5), 4.11 (dd, 1H, $J_{5,6a}$=6.5, $J_{6a,6b}$=9.0, H-6a), 4.03 (dd, 1H, $J_{5,6b}$=4.5, H-6b), 3.85 (s, 3H, CO_2CH_3), 1.53, 1.39, 1.32, 1.32 [each s, each 3H, 2C(*C*H_3)$_2$]; ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 166.7 (C=O), 113.5, 109.7 [2*C*(CH_3)$_2$], 105.1 (C-1), 85.3 (C-2), 81.4 (C-4), 74.5 (C-3), 73.2 (C-5), 67.0 (C-6), 52.9 (CO_2CH_3), 26.8, 26.5, 26.1, 25.0 [2C(*C*H_3)$_2$]. Anal. Calcd for $C_{14}H_{21}N_3O_7$: C, 48.98; H, 6.17; N, 12.24. Found: C, 49.21; H, 6.22; N, 12.19%.

4.6. 3-Amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-methoxycarbonyl-α-D-glucofuranose (15)

A solution of compound **11** (300 mg, 0.875 mmol) in MeOH (30 mL) was hydrogenated, at 1 atm and room temperature, in the presence of 10% Pd/C (60 mg) for 3 h. The catalyst was filtered off over Celite and the resulting solution was concentrated to dryness in vacuum. The crude product was purified by column chromatography (AcOEt/Hexane=2:1) affording compound **15** as a syrup (245 mg; 89%). $[\alpha]_D^{22}$ +92 (*c* 1.0, CH_2Cl_2); IR: ν_{max} 3385, 3324, 2987, 2942, 1735, 1605, 1455, 1378, 1258, 846 cm^{-1}; ^1H NMR: (500 MHz, $CDCl_3$) δ 5.95 (d, 1H, $J_{1,2}$=3.5, H-1), 4.67 (d, 1H, $J_{4,5}$=8.0, H-4), 4.26 (d, 1H, H-2), 4.14 (m, 2H, H-5, H-6a), 4.01 (dd, 1H, $J_{5,6b}$=3.2, $J_{6a,6b}$=7.4, H-6b), 3.76 (s, 3H, CO_2CH_3), 1.75 (s, 2H, NH_2), 1.52, 1.35, 1.29, 1.28 [each s, each 3H, [2C(*C*H_3)$_2$]]; ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 172.0 (C=O), 112.8, 109.6 [2*C*(CH_3)$_2$], 105.6 (C-1), 88.7 (C-2), 82.0 (C-4), 73.4 (C-5), 68.2 (C-3), 68.0 (C-6), 52.2 (CO_2CH_3), 26.8, 26.7, 26.0, 25.0 [2C(*C*H_3)$_2$]. Anal. Calcd for $C_{14}H_{23}NO_7$: C, 52.99; H, 7.31; N, 4.41. Found: C, 53.23; H, 7.25; N, 4.42%.

4.7. General procedure for the synthesis of isothiocyanates 16 and 17

To a mixture of the corresponding amine **14** or **15** (*x* mg), in dry CH_2Cl_2 (*y* mL) and $CaCO_3$ (*a* mg) in H_2O (*b* mL), $CSCl_2$ (*z* μL) was added. The mixture was vigorously stirred at room temperature for *t* h, then diluted with CH_2Cl_2, and washed with water and brine. The organic layer was dried over $MgSO_4$ and the solvent was evaporated in vacuum. The crude product was purified by column chromatography as indicated below.

*4.7.1. 1,2:5,6-Di-O-isopropylidene-3-C-isothiocyanatoethyl-α-D-allofuranose (**16**)*

x=250 mg (0.83 mmol); *y*=5.8 mL; *a*=577 mg (5.78 mmol); *b*=1.4 mL; *z*=288 μL (2.89 mmol), *t*=3. Column chromatography: AcOEt/Hexane=1:2. Amorphous solid (225 mg; 79%). $[\alpha]_D^{22}$ +13 (*c* 1.0, CH_2Cl_2); IR: ν_{max} 3464, 2989, 2925, 2179, 2107, 1379, 1262, 1213, 1158, 1078, 1015, 875, 753 cm^{-1}; ^1H NMR: (500 MHz, $CDCl_3$) δ 5.77 (d, 1H, $J_{1,2}$=3.8, H-1), 4.39 (d, 1H, H-2), 4.15 (dd, 1H, $J_{6a,6b}$=8.5, $J_{5,6a}$=6.1, H-6a), 4.09 (ddd, 1H, $J_{4,5}$=8.7, $J_{5,6b}$=5.2, H-5), 3.94 (dd, 1H, H-6b), 3.89 (ddd, 1H, $^2J_{H,H}$=14.7, $^3J_{H,H}$=8.5, $^3J_{H,H}$=5.6, C*H*HNCS), 3.80 (ddd, 1H, $^2J_{H,H}$=14.7, $^3J_{H,H}$=8.5, $^3J_{H,H}$=6.5, CH*H*NCS), 3.76 (d, 1H, H-4), 2.77 (br s, 1H, OH), 2.33 (ddd, 1H, $^2J_{H,H}$=14.2, $^3J_{H,H}$=8.7, $^3J_{H,H}$=5.6, C*H*HCH$_2$NCS), 1.83 (dddd, 1H, $^2J_{H,H}$=14.3, $^3J_{H,H}$=8.5, $^3J_{H,H}$=6.5, $^4J_{H,OH}$=1.2, CH*H*CH$_2$NCS), 1.61, 1.47, 1.39, 1.39 (each s, each 3H [2C(CH_3)$_2$]); ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 131.2 (C=S), 113.0, 110.0 [*C*(CH_3)$_2$], 103.5 (C-1), 82.1 (C-4), 81.0 (C-2), 78.3 (C-3), 73.2 (C-5), 68.2 (C-6), 40.3 (*C*H$_2$NCS), 31.9 (*C*H$_2$CH$_2$NCS), 26.7, 26.6, 26.4, 25.2 [2C(*C*H_3)$_2$]; HRFABMS: calcd for $C_{15}H_{23}NO_6SNa$: 368.1143; found: 368.1150.

*4.7.2. 3-Deoxy-1,2:5,6-di-O-isopropylidene-3-isothiocyanato-3-C-methoxycarbonyl-α-D-glucofuranose (**17**)*

x=293 mg (0.93 mmol); *y*=6.5 mL; *a*=649 mg (6.49 mmol); *b*=1.6 mL; *z*=260 μL (3.25 mmol), *t*=15. Column chromatography: AcOEt/Hexane=2:1. Amorphous solid (287 mg; 87%). $[\alpha]_D^{22}$ +41 (*c* 1.0, CH_2Cl_2); IR: ν_{max} 2988, 2938, 2255, 1755, 1438, 1378, 1261, 844 cm^{-1}; ^1H NMR: (500 MHz, $CDCl_3$) δ 5.97 (d, 1H, $J_{1,2}$=3.7, H-1), 4.72 (d, 1H, H-2), 4.60 (d, 1H, $J_{4,5}$=8.0, H-4), 4.20 (ddd, 1H, $J_{5,6a}$=6.3, $J_{5,6b}$=4.0, H-5), 4.14 (dd, 1H, $J_{6a,6b}$=8.8, H-6a), 4.05 (dd, 1H, H-6b), 3.84 (s, 3H, OMe), 1.54, 1.38, 1.32, 1.31 [each s, each 3H, [2C(*C*H_3)$_2$]; ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 164.7 (C=O), 142.5 (C=S), 114.0, 110.0 [*C*(CH_3)$_2$], 105.1 (C-1), 87.7 (C-4), 82.0 (C-2), 75.0 (C-3), 73.6 (C-5), 67.1 (C-6), 53.3 (OMe), 27.0, 26.4, 26.1, 25.0 [2C(*C*H_3)$_2$]; HRFABMS: calcd for $C_{15}H_{21}NO_7SNa$: 382.1039; found: 382.1040.

4.8. General procedure for the synthesis of compounds 18 and 19

To a solution of the corresponding amine **12** or **13** (*x* mg) in dry CH_2Cl_2 (*y* mL), 1,1′-thiocarbonyldiimidazole (*z* mg) was added. The mixture was stirred at room temperature for *t* h. The solvent was evaporated in vacuum and the residue was purified by column chromatography as indicated below.

*4.8.1. (5R,6R,8R,9R,4′R)-6-(2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)-8,9-dimethylmethylenedioxy-1,7-dioxa-3-azaspiro[4.4]nonane-2-thione (**18**)*

x=462 mg (1.60 mmol), *y*=14 mL, *z*=323 mg (1.80 mmol), *t*=5. Column chromatography: AcOEt/Hexane=1:2. Amorphous solid (423.4 mg; 80%). The data for this compound have been recently described.[7a]

*4.8.2. (5R,6S,8R,9R,4′R)-6-(2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)-8,9-dimethylmethylenodioxy-7-oxa-1,3-diazaspiro[4.4]nonane-2-thione (**19**)*

x=88 mg (0.31 mmol); y=3 mL; z=160 mg (0.89 mmol); t=3. Column chromatography: AcOEt/Hexane=1:2. Amorphous solid (71%). $[\alpha]_D^{22}$ +43 (c 1.0, MeOH); IR: ν_{max} 3358, 2986, 2936, 2885, 1638, 1523, 1491, 1375, 1211, 1116, 1075, 1014, 750 cm^{-1}; ^1H NMR: (500 MHz, $CDCl_3$) δ 6.42 (br s, 1H, NH), 6.32 (br s, 1H, NH), 5.71 (d, 1H, $J_{8,9}$=3.5, H-8), 4.43 (d, 1H, H-9), 4.14 (m, 2H, H-4′, H-5′a), 3.97 (dd, 1H, $J_{4',5'b}$=3.5, $J_{5'a,5'b}$=3.5, H-5′b), 3.95 (d, 1H, $J_{4a,4b}$=10.0, H-4a), 3.86 (d, 1H, $J_{4',6}$=7.5, H-6), 3.41 (d, 1H,H-4b), 1.55, 1.45, 1.33, 1.33 (each s, each 3H [2C(CH_3)$_2$]); ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 183.9 (C=S), 113.3, 110.1 [2C(CH_3)$_2$], 102.9 (C-8), 84.5 (C-9), 78.4 (C-6), 73.6 (C-4′), 71.1 (C-5), 67.9 (C-5′), 48.5 (C-4), 26.7, 26.6, 26.3, 25.1 [2C(CH_3)$_2$]. Anal. Calcd for $C_{14}H_{22}N_2O_5S$: C, 50.89; H, 6.71; N, 8.48; S, 9.70. Found: C, 50.63; H, 6.80; N, 8.38; S, 9.53%.

4.9. (1*R*,3*R*,4*R*,5*R*,4′*R*)-1-(2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)-3,4-dimethylmethylenodioxy-2,6-dioxa-8-azaspiro[4.5]decane-7-thione (20)

A solution of the isothiocyanate **16** (180 mg, 0.52 mmol) and dry Et_3N (1 mL) in dry CH_2Cl_2 (10 mL) was stirred at room temperature for 3 h. The solvent was evaporated in vacuum and the residue was purified by column chromatography (CH_2Cl_2/MeOH=40:1) to afford compound **20** as an amorphous solid (166 mg; 93%). $[\alpha]_D^{22}$ +88 (c 1.0, CH_2Cl_2); IR: ν_{max} 3440, 2983, 2920, 1546, 1378, 1258, 1220, 1170, 1093, 842 cm^{-1}; ^1H NMR: (500 MHz, $CDCl_3$) δ 8.16 (s, 1H, NH), 5.78 (d, 1H, $J_{3,4}$=3.9, H-3), 4.36 (d, 1H, H-4), 4.27 (d, 1H, $J_{1,4'}$=8.8, H-1), 4.12 (dd, 1H, $J_{5'a,5'b}$=8.4, $J_{4',5'a}$=6.3, H-5′a), 4.06 (ddd, 1H, $J_{4',5'b}$=4.2, H-4′), 3.98 (dd, 1H, H-5′b), 3.52 (dddd, 1H, $^2J_{H,H}$=13.0, $^3J_{H,H}$=11.3, $^3J_{H,H}$=5.2, $^3J_{H,NH}$=3.0, H-9a), 3.46 (ddd, 1H, $^2J_{H,H}$=13.0, $^3J_{H,H}$=11.3, $^3J_{H,H}$=5.2, H-9b), 2.46 (ddd, 1H, $^2J_{H,H}$=14.1, $^3J_{H,H}$=11.2, $^3J_{H,H}$=6.3, H-10a), 1.82 (ddd, 1H, $^2J_{H,H}$=14.1, $^3J_{H,H}$=5.0, $^3J_{H,H}$=2.5, H-10b), 1.65, 1.48, 1.36, 1.33 [each s, each 3H, [2C(CH_3)$_2$]]; ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 186.1 (C=S), 114.3, 110.3 [2C(CH_3)$_2$], 103.8 (C-3), 84.7 (C-5), 82.5 (C-4), 81.1 (C-1), 73.3 (C-4′), 67.8 (C-5′), 37.4 (C-9), 27.1, 26.8, 26.7, 25.4 [2C(CH_3)$_2$], 21.6 (C-10); HRFABMS: calcd for $C_{15}H_{23}NO_6SNa$: 368.1143; found: 368.1153.

4.10. (5*S*,6*S*,8*R*,9*R*,4′*R*)-1-(2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)-8,9-dimethylmethylenedioxy-2-thioxo-7-oxa-1,3-diazaspiro[4.4]nonane-4-one (21)

To a solution of compound **17** (105 mg, 0.29 mmol) in THF (2 mL), ammonia was bubbled for 5 min. The reaction mixture was stirred at room temperature for 1 h. The solution was concentrated to dryness and the crude product was purified by column chromatography (AcOEt/Hexane=1:1) affording compound **21** as an amorphous solid (85 mg; 84%). $[\alpha]_D^{22}$ +36 (c 1.0, CH_2Cl_2); IR: ν_{max} 3442, 3249, 2989, 2924, 1766, 1515, 1379, 1257, 1076, 753 cm^{-1}; ^1H NMR: (500 MHz, $CDCl_3$) δ 8.91 (br s, 1H, NH), 8.59 (br s, 1H, NH), 5.99 (d, 1H, $J_{3,4}$=3.7, H-8), 4.71 (d, 1H, H-9), 4.36 (m, 1H, H-6), 4.12 (m, 2H, H-4′, H-5′a), 4.02 (m, 1H, H-5′b), 1.64, 1.35, 1.34, 1.27 (each s, each 3H, [2C(CH_3)$_2$]); ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 181.7 (C=S), 168.8 (C=O), 114.7, 110.5 [2C(CH_3)$_2$], 105.4 (C-8), 85.7 (C-9), 81.9 (C-6), 73.2 (C-4′), 67.2 (C-5′), 60.5 (C-5), 26.8, 26.5, 26.2, 25.0 [2C(CH_3)$_2$]; HRFABMS: calcd for $C_{14}H_{20}N_2O_6S$: 367.0940; found: 367.0950.

4.11. (5*R*,6*R*,8*R*,9*R*,4′*R*)-6-(2,2′-Dimethyl-1′,3′-dioxolan-4′-yl)-8,9-dimethylmethylenedioxy-1,7-dioxa-3-azaspiro-[4,4]nonane-2-one (22)

To a stirred solution of triphosgene (113 mg; 0.38 mmol) in dry DMF (4 mL) a solution of **12** (100 mg; 0.35 mmol) and diisopropylethylamine (2 mL) in dry DMF (2 mL) was added dropwise. The reaction mixture was stirred until the starting material disappeared (1 h) and then triethylamine (0.65 mL; 4.67 mmol) was added and the mixture was heated at 80 °C for 24 h. The solvent was removed in vacuum and the residue was purified by column chromatography (CH_2Cl_2/MeOH=80:1) to afford compound **22** as an amorphous solid (60 mg; 50%). $[\alpha]_D^{22}$ +52 (c 0.8, CH_2Cl_2); IR: ν_{max} 3335, 2988, 1768, 1375, 1219, 1168, 1076, 843, 737 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 6.39 (s, 1H, NH), 5.69 (d, 1H, $J_{8,9}$=3.5, H-8), 4.46 (d, 1H, H-9), 4.11 (m, 3H, H-1, H-4′, H-5′a), 4.02 (m, 1H, H-5′b), 3.84 (d, 1H, $J_{4a,4b}$=9.0, H-4a), 3.25 (d, 1H, H-4b), 1.58, 1.42, 1.34, 1.29 [each s, each 3H, 2C (CH_3)$_2$]; ^{13}C NMR: (75.5 MHz, $CDCl_3$) δ 158.4 (C-2), 114.4, 110.3 [2C(CH_3)$_2$], 103.0 (C-8), 85.5 (C-5), 83.9 (C-9), 77.3 (C-6), 73.8 (C-4′), 68.1 (C-5′), 44.3 (C-4), 26.8, 26.7, 26.5, 25.3 [2C(CH_3)$_2$]; HRCIMS: Calcd for $C_{14}H_{22}NO_7$: 316.1396. Found: 316.1376.

4.12. (1*R*,3*R*,4*R*,5*R*,4′*R*)-1-(2,2′-Dimethyl-1′,3′-dioxolan-4′-yl)-3,4-dimethylmethylenedioxy-2,6-dioxa-8-azaspiro-[4,5]nonane-7-one (23)

To a stirred solution of **14** (84 mg; 0.28 mmol) in CH_2Cl_2/$NaHCO_3$ saturated aqueous solution 1:1 at 0 °C triphosgene (30.5 mg; 0.10 mmol) was added. The reaction mixture was stirred for 35 min and then the organic layer was separated, washed with water and brine, and dried with $MgSO_4$. The solvent was removed in vacuum and the residue was purified by column chromatography (CH_2Cl_2/MeOH=80:1) to afford compound **23** as an amorphous solid (83 mg; 90%). $[\alpha]_D^{22}$ +73 (c 0.64, CH_2Cl_2); IR: ν_{max} 3271, 2987, 2936, 1715, 1451, 1374, 1218, 1116, 1032, 844, 735 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 6.94 (s, 1H, NH), 5.73 (d, 1H, $J_{3,4}$=3.9, H-3), 4.37 (d, 1H, H-4), 4.07 (m, 3H, H-1, H-4′, H-5′a), 3.94 (m, 1H, H-5′b), 3.48 (m, 2H, H-9a, H-9b), 2.31 (ddd, 1H, $J_{10a,10b}$=13.8, $J_{10a,9a}$=10.5, $J_{10a,9b}$=7.3, H-10a), 1.67 (dt, 1H, $J_{10b,9}$=2.81, H-10b), 1.58, 1.41, 1.32, 1.31 [each s, each 3H, 2C (CH_3)$_2$]; ^{13}C NMR: (75.5 MHz, $CDCl_3$) δ 153.3 (C-7), 113.7, 109.9 [2C(CH_3)$_2$], 103.6 (C-3), 83.2 (C-5), 81.7 (C-4), 80.7 (C-1), 73.2 (C-4′), 67.6 (C-5′), 36.1 (C-9), 26.8, 26.6, 26.5, 25.3 [2C(CH_3)$_2$]; HRFABMS: calcd for $C_{15}H_{23}NO_7Na$: 352.1372; found: 352.1378.

4.13. General procedure for the preparation of unprotected spirocompounds 24–27

To a solution of the protected spirocompounds **18**–**31** (x mg) in MeOH (y mL), concentrated HCl (z μL) was added at 0 °C. The solution was heated at 60 °C for 30 min. The solvent was removed in vacuum and the residue was purified by column chromatography as indicated below.

*4.13.1. (5S,6R,7S,9R,10R)-6,7,10-Trihydroxy-9-hydroxymethyl-1,8-dioxa-3-azaspiro[4.5]decane-2-thione (**24**)*

x=50.4 mg (0.15 mmol); y=4.2 mL; z=330 μL. Column chromatography: AcOEt–AcOEt/MeOH=3:1 gradient. Amorphous solid (32.4 mg; 85%). $[\alpha]_D^{22}$ +12 (c 0.7, D_2O); ^1H NMR: (500 MHz, D_2O) δ 5.02 (d, 1H, $J_{6,7}$=8.1, H-7), 3.97 (dd, 1H, $J_{9,1'a}$=2.2, $J_{1'a,1'b}$=12.3, H-1′a), 3.95 (m, 2H, H-4a, H-4b), 3.91 (ddd, 1H, $J_{9,10}$=10.1, $J_{9,1'b}$=5.4, H-9), 3.81 (dd, 1H, H-1′b), 3.74 (d, 1H, H-10), 3.52 (d, 1H, H-6); ^{13}C NMR: (125.7 MHz, D_2O) δ 188.1 (C=S), 94.2 (C-7), 93.0 (C-5), 74.6 (C-9), 72.7 (C-6), 68.3 (C-10), 60.8 (C-1′), 47.9 (C-4); HRFABMS: calcd for $C_8H_{13}NO_6SNa$: 274.0464; found: 274.0467.

*4.13.2. (5S,6R,7S,9R,10S)-6,7,10-Trihydroxy-9-hydroxymethyl-8-oxa-1,3-diazaspiro[4.5]decane-2-thione (**25**)*

x=83 mg (0.33 mmol); y=9.2 mL; z=721 μL. Column chromatography: AcOEt–AcOEt/MeOH=3:1 gradient. Amorphous solid (66.7 mg; 80%). $[\alpha]_D^{22}$ +17 (c 1.1, D_2O); ^1H NMR: (500 MHz, $CDCl_3$) δ 5.01 (d, 1H, $J_{6,7}$=8.1, H-7), 3.97 (dd, 1H, $J_{9,1'a}$=2.2, $J_{1'a,1'b}$=12.3, H-1′a), 3.95 (m, 2H, H-4a, H-4b), 3.91 (ddd, 1H, $J_{9,10}$=10.0, $J_{9,1'b}$=5.4, H-9), 3.80 (dd, 1H, H-1′b), 3.73 (d, 1H, H-10), 3.52 (d, 1H, H-6); ^{13}C

NMR: (125.7 MHz, $CDCl_3$) δ 190.6 (C=S), 96.3 (C-7), 95.4 (C-5), 77.1 (C-9), 75.2 (C-6), 70.8 (C-10), 63.3 (C-1′), 50.4 (C-4); HRCIMS: Calcd for $C_8H_{15}N_2O_5S$: 251.0623. Found: 251.0628.

4.13.3. (6R,7S,8R,10R,11R)-7,8,11-Trihydroxy-10-hydroxymethyl-1,9-dioxa-3-azaspiro[5.5]undecane-2-thione (**26**)

x=36.9 mg (0.11 mmol); y=3 mL; z=232 μL. Column chromatography: AcOEt–AcOEt/MeOH=3:1 gradient. Amorphous solid (21.8 mg; 77%). $[\alpha]_D^{22}$ +5 (c 0.9, D_2O); ^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.08 (d, 1H, $J_{7,8}$=8.1, H-8), 3.99 (m, 1H, H-10), 3.96 (dd, 1H, $J_{1'a,1'b}$=12.5, $J_{10,1'a}$=2.2, H-1′a), 3.78 (dd, 1H, $J_{10,1'b}$=5.5, H-1′b), 3.72 (d, 1H, $J_{10,11}$=10.1, H-11), 3.59 (m, 2H, H-4a, H-4b), 3.48 (d, 1H, H-7), 2.36 (t, 2H, $J_{H,H}$=6.5, H-5a, H-5b); ^{13}C NMR: (125.7 MHz, $CDCl_3$) δ 185.7 (C=S), 93.6 (C-8), 86.0 (C-6), 74.5 (C-7), 74.0 (C-10), 70.0 (C-11), 60.9 (C-1′), 38.2 (C-4), 23.6 (C-5); HRFABMS: calcd for $C_9H_{15}NO_6SNa$: 288.0518; found: 288.0516.

4.13.4. (5S,6R,7S,9R,10S)-6,7,10-Trihydroxy-9-hydroxymethyl-2-thioxo-8-oxa-1,3-diazaspiro[4.5]decane-4-one (**27**)

x=75 mg (0.22 mmol); y=6 mL; z=473 μL. Column chromatography: AcOEt–AcOEt/MeOH=3:1 gradient. Amorphous solid (47.8 mg; 83%). $[\alpha]_D^{22}$ +4 (c 1.1, D_2O); ^{1}H NMR: (500 MHz, D_2O) δ 5.41 (d, 1H, $J_{6,7}$=8.1, H-7), 4.28 (ddd, 1H, $J_{9,10}$=10.2, $J_{9,1'a}$=2.3, $J_{9,1'b}$=5.5, H-9), 3.95 (dd, 1H, $J_{1'a,1'b}$=12.4, H-1′a), 3.90 (d, 1H, H-10), 3.76 (dd, 1H, H-1′b), 3.63 (d, 1H, H-6); ^{13}C NMR: (125.7 MHz, D_2O) δ 184.2 (C=S), 175.7 (C=O), 92.8 (C-7), 75.4 (C-9), 72.9 (C-6), 72.2 (C-5), 68.1 (C-10), 60.7 (C-1′); HRFABMS: calcd for $C_8H_{12}N_2O_6SNa$: 287.0416; found: 287.0414.

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