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Isothiocyanato derivatives of sugars in the stereoselective synthesis of spironucleosides and spiro-*C*-glycosides†

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Abstract—A stereocontrolled synthesis of pyranoid and furanoid spironucleosides and spiro-*C*-glycosides (D-*ribo* and D-*arabino* configurations) of oxazolidines, oxazolines and perhydrooxazines via isothiocyanato sugar derivatives is reported. The intermediate isothiocyanates are prepared from sugar spiroketals by stereoselective opening of the acetal ring with trimethylsilyl *N*- and *C*-nucleophiles, and later formation of the isothiocyanato group.

1. Introduction

The term spironucleoside was introduced in 1990 to designate a class of spiranic sugar derivatives in which the anomeric carbon belongs to both the sugar ring and to a heterocyclic base.[1] Data on this type of compound were reported before 1990 but, as far as we are aware, without using the term spironucleoside. Of the different classes of nucleosides, the spironucleosides are probably the least well known. However, the isolation from *Streptomyces hygroscopicus*, in 1991, of (+)-hydantocidin,[2] the first natural spironucleoside, and later[3] the discovery of its potent herbicidal and regulatory plant growth activities and its low mammalian toxicity, have resulted in great interest in the chemistry of spironucleosides. The structure of (+)-hydantocidin, a furanoid spironucleoside of hydantoin, was completely established through its synthesis.[4,5] In the last eight years, other syntheses of hydantocidin,[6] spirofuranoid derivatives of different heterocycles,[7] pyranoid analogues of hydantocidin,[8] and carbocyclic derivatives[9] have been reported.

Sugar isothiocyanates are versatile synthetic intermediates, which have been widely used in the preparation of heteroaryl derivatives of carbohydrates including *N*- and *C*-nucleosides.[10,11] However, their use in the preparation of spironucleosides is very scarce and, to the best of our knowledge, limited to oxazolidine[1,12] and imidazolidine derivatives.[11] The most suitable starting materials to prepare deoxy-isothiocyanato sugars (sugar isothiocyanates with the NCS group situated on a non-glycosidic position) are amino sugars. These are obtained by degradation of a natural polysaccharide, as in the case of D-glucosamine, by reaction of a monosaccharide with ammonia or an ammonium salt, as in the case of glycosylamines, or by introducing the amino group through an azido derivative which is frequently obtained from reaction of a sulfonyloxysugar with sodium azide.[13] Glycosyl isothiocyanates can also be obtained by reaction of a protected glycosyl halide with an inorganic thiocyanate.[10]

Silylated nucleophiles are well-known reactants which have been used for carbon–carbon and carbon–heteroatom bond formation by reactions with aldehydes, ketones and acetals,[14] although there are only a few examples of reactions with sugar spiroacetals.[15] Herein, we report the preparation of different spironucleosides and spiro-*C*-glycosides of five- and six-membered heterocycles, through transient or stable isothiocyanato (and in one case isocyanato) sugar derivatives. These isothiocyanato sugars were obtained by opening of the spiranic dioxolane ring of the monosaccacharide spiroketals **1** and **2**, using nitrogen-containing trimethylsilyl derivatives as nucleophiles.

2. Results and discussion

Reaction of the β-D-ribohexulofuranose (psicofuranose) spiroketal[16] **1** with trimethylsilyl isothiocyanate in the

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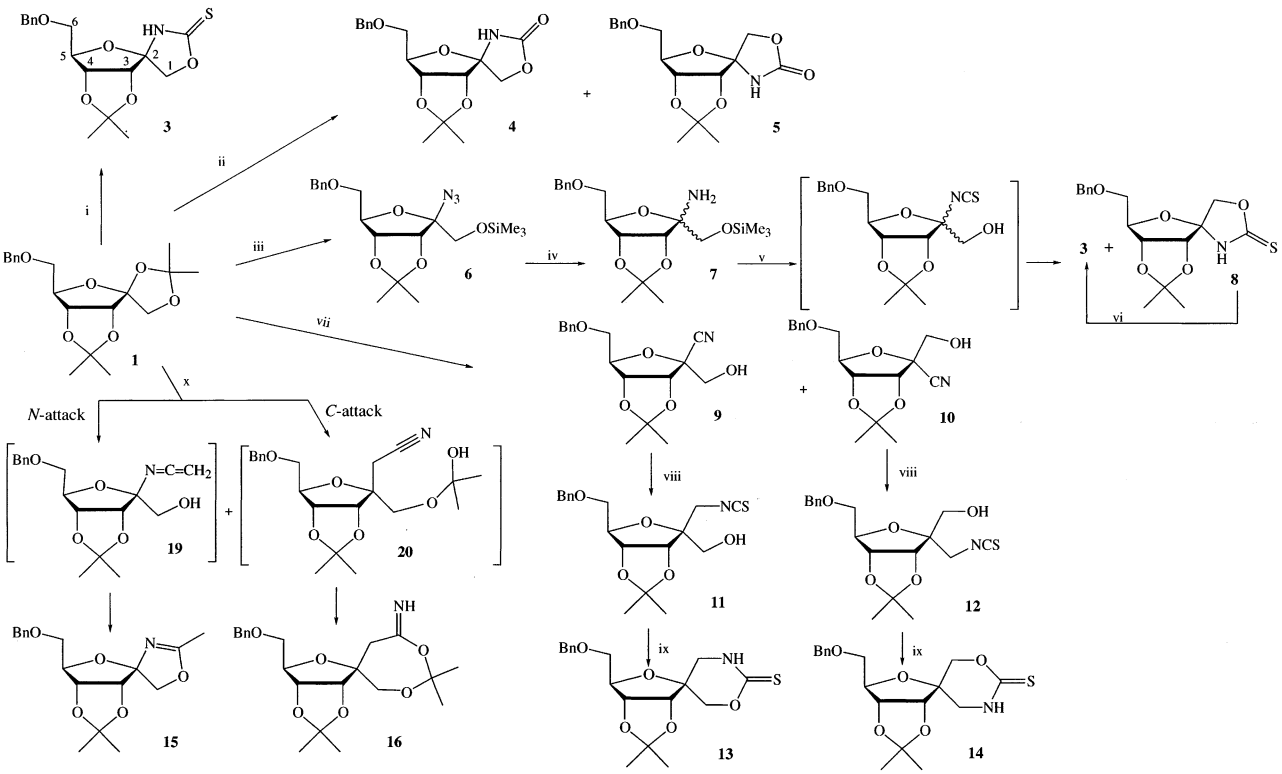
presence of trimethylsilyl triflate gave the *O*-protected thioxo-oxazolidine spironucleoside **3** in unexpectedly low yield (Scheme 1). This was formed from the corresponding transient β-D-ribohexulofuranosyl isothiocyanate. Similarly, attempts at *N*-glycosylation of **1** with trimethylsilyl isocyanate in the presence of a Lewis acid gave mixtures of the β-(**4**) and α-(**5**) oxospironucleosides which could be separated. The best results, a 22% yield of **4** and a 5% yield of **5**, were obtained when trimethylsilyl triflate was used as the Lewis acid in dichloromethane as solvent with equimolar amounts of the Lewis acid and the nucleophilic reagent. These results are parallel to that described[5] for a related glycosidation.

As the yield for the glycosidation of **1** with TMSNCS was low, to obtain **3** we followed the sequence indicated in Scheme 1. The reaction of **1** with trimethylsilyl azide in acetonitrile to obtain 2-azido-6-*O*-benzyl-2-deoxy-3,4-*O*-isopropylidene α- and β-D-psicofuranoses has been reported previously.[5] We observed that when the reaction was carried out at 0°C under stringently anhydrous conditions (see Section 4), the corresponding trimethylsilyl ether **6** was obtained in high yield, and only as the β-anomer. Data for related trimethylsilyl ethers have been reported.[17] Hydrogenation of **6** at room temperature for 2 h gave **7** as a pair of anomers quantitatively (α:β ratio 3:2). Partial silyl deprotection was observed during attempts at chromatographic resolution of these anomers, so **7** was directly used in the next step of the synthesis. Thus, desilylation of **7** with tetrabutylammonium fluoride, and reaction with thiocarbonyl diimidazole, produced the corresponding α- and β-psicofuranosyl isothiocyanate, which spontaneously cyclized to the α-(**8**) and β-(**3**) spirooxazolidines. These nucleosides were isolated in ca. 5:1 ratio. Treatment of **8** with triethylamine in dichloromethane produced an equilibrium mixture of both anomers (α:β ratio 1:5), from which **8** (15%) and **3** (80%) were isolated.

The structures of compounds **3**, **4**, **6**, **7** and **8** were confirmed by IR, ^{1}H and ^{13}C NMR spectroscopic data (see Table 1 and Section 4). For **5**, only IR and HRMS data could be obtained. Compounds **3** and **8** showed the ^{13}C resonance for the C=S group at roughly 189 ppm in accord with that described for five-membered cyclic thiocarbamates.[18,19] The IR band for C=O of **4** and **5** appeared[20] at 1755 cm^{-1} and that for the azido group of **6** at 2118 cm^{-1} (see Ref. 5). The amino groups of the mixture of anomers **7** presented the IR absorption at 3311 cm^{-1} and the ^{1}H resonance at 2.24 ppm. The Me_3Si-group of the same compounds was evident from the NMR signals at 0.08 and 0.14 ppm (^{1}H), and −0.7 and −0.5 ppm (^{13}C). The anomeric configuration of **6** was shown to be β because treatment with tetrabutylammonium fluoride gave the corresponding desilylated β-psicofuranosyl azide.[5] Moreover, the chemical



Scheme 1. *Reagents and conditions*: (i) TMSNCS, TMSOTf, −20°C, 1 h, 10%; (ii) TMSNCO, TMSOTf, −20°C, 2 h, 22% for **4** and 5% for **5**; (iii) 1. $TMSN_3$, 0°C, 5 min; 2. TMSOTf, 0°C, 5 min, 90%; (iv) H_2/Pd–C, rt, 2 h, 80%; (v) 1. $Bu_4NF{\cdot}3H_2O$, rt, 1 h; 2. Im_2CS, rt, 3 h, 63% for **8**, 16% for **3**; (vi) Et_3N, CH_2Cl_2, rt, 3 h, 80%; (vii) TMSCN, TMSOTf, −20°C, 2 h[7b] (viii) 1. $LiAlH_4$, Et_2O, 0°C, 30 min and then rt, 2 h; 2. Cl_2CS, rt, 6 h, 39% for **11**, 36% for **12**; (ix) Et_3N, 80°C, 40 min, 85% for **13**, 96% for **14**; (x) $TMSCH_2CN$, TMSOTf, −20°C, 1 h, 23% for **15**, 5% for **16**.

Table 1. Relevant NMR data for compounds **3**, **4**, **6**, **8**, **11**–**16**, **21**–**28**, and **29** in $CDCl_3$[a,b]

	δ (ppm)							$J_{H,H}$ (Hz)	
	C(1)H	C(1′)H	C(3)H	C(1)	C(2)	C(3)	C=X	1,1′	3,4
3	4.88	4.46	4.61	75.8	100.1	84.8	189.1	11.1	5.8
4	4.66	4.23	4.80	71.3	97.5	82.4	157.5	10.5	5.8
6	3.95		4.38	65.2	100.6	85.2	–	–	5.9
8	4.58	4.33	4.55	81.2	99.5	83.7	188.9	10.8	5.9
11	3.84	3.77	4.57	48.7	83.3	85.7	132.7	14.3	6.6
12	3.75	3.69	4.75	46.5	86.5	83.1	132.7	14.6	6.1
13	4.31	4.26	4.51	71.1	76.7	84.0	186.5	11.5	6.3
14	4.33	4.19	4.48	72.1	77.3	82.4	186.7	11.2	6.3
15	4.50	4.18	4.54	72.0	110.1	85.5	167.7	10.7	5.9
16	4.47	4.19	4.56	71.3	68.7	85.4	169.3	10.8	5.9
21	3.90	3.78	3.60	65.2	92.4	75.7	–	10.8	7.1
29[c]	3.85	3.76	3.68	63.0	92.3	75.6	–	10.8	6.0
22	3.54		3.46	67.7	85.8	77.0	–	–	6.8
24	4.47		3.76	80.4	90.9	75.8	189.7	–	5.3
25	3.94	3.79	3.64	65.3	79.2	76.1	–	11.9	7.2
27	4.24		3.52	72.5	68.8	74.6	186.0	–	5.3
28	4.08	3.94	3.51	72.3	100.9	77.5	169.1	5.3	7.3

[a] For comparison of the NMR data the compounds are numbered as D-psicose or D-fructose derivatives (see **3** in Scheme 1 and **24** in Scheme 3). The nomenclature as spiranic heterocycles is included in Section 4.
[b] For the NMR frequency see Section 4.
[c] **29** is the α-anomer of **21**, its NMR data were obtained from a mixture **21**+**29** (see Section 4).

shifts and the coupling constants for the ^1H resonances of **6** and those for the non-silylated CH_2OH derivative[5] are practically identical. There are no antecedents for ^{13}C resonances. In all the described nucleophilic ring openings of sugar spiroketals with trimethylsilyl nucleophiles,[15] the β-anomer was the major product. The anomeric configurations of **3**, **4**, **5**, **7** and **8** are supported by NOE experiments performed on **3** and **8**, and on the major (β) and minor (α) components of the mixture **7** (Fig. 1).

The *trans*-fused bicyclic sugar thiocarbamates can act as sugar isothiocyanates. A thiocarbamate–isothiocyanate equilibrium has been studied[18] for solutions of such compounds in various solvents. In the reaction of **8** with triethylamine, formation of neither the isothiocyanate **18** nor the isothiocyanate decomposition products was observed. Taking this fact into account, we propose, as a route for the transformation **8** to **3**, the direct anomerization through the partially *O*-protected open chain form **17**, shown in Scheme 2. Attack of the hydroxyl group on the *Re* face of the imino group, to give the β-anomer **3**, is more favorable than attack on the *Si* face which leads to the α-anomer **8**, because in the latter the associated dipoles to the C=N and C(3)O bonds are roughly parallel. Open chain structures, similar to **17**, have been proposed for anomeric equilibria of *N*-substituted glycosylamines.[21]

With the aim of preparing spiro-*C*-glycosides of five- and six-membered rings, we synthesized the isothiocyanatomethyl derivatives **11** and **12**, which were prepared from the described[7b] psicofuranosyl cyanides **9** and **10**.[22] Reduction[7b] with lithium aluminum hydride, followed by treatment of the resulting syrup with thiophosgene, gave the corresponding isothiocyanates **11** and **12**. Treatment of **11** and **12** with triethylamine produced the intramolecular cycloaddition, giving the spiro-*C*-glycosides **13** and **14**, respectively, in high yields. Chromatographic and MS analysis showed a small amount (less than 3%) of the intermolecular addition product.

The structures **11**–**14** were based on analytical and spectroscopic data (Table 1 and Section 4). Thus, the IR spectra of the isothiocyanates **11** and **12** showed the absorption for the NCS group at 2201 and 2106 cm^{-1}, respectively, and the carbon atom of the same group resonated at 132.7 ppm, in agreement with reported[10] data for related isothiocyanates. The C=S group of the spirothiocarbamates **13** and **14** resonated at roughly

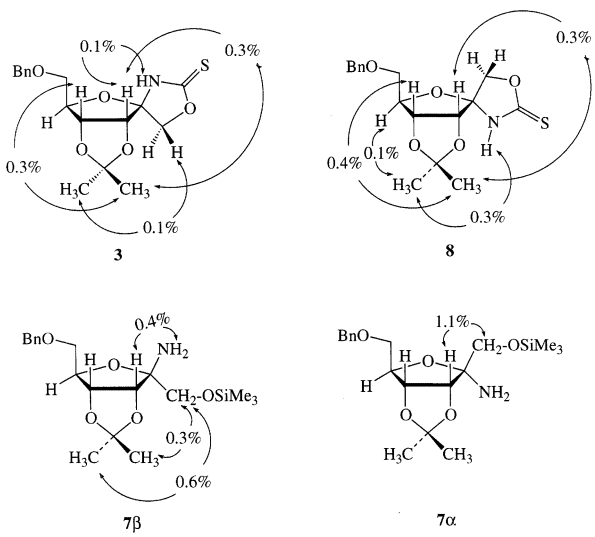
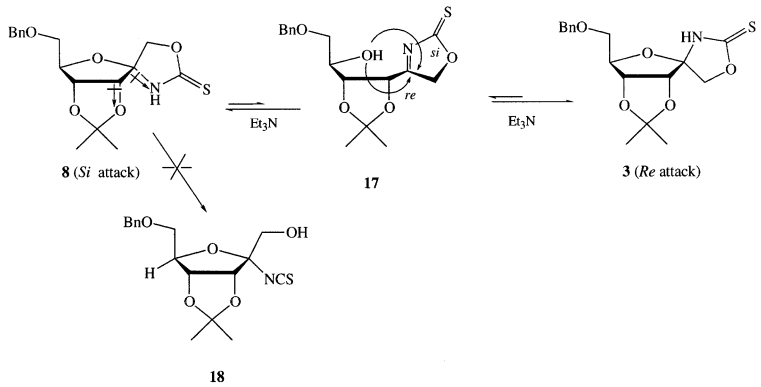


Figure 1. NOE effects of **3**, **7α**, **7β**, and **8**.

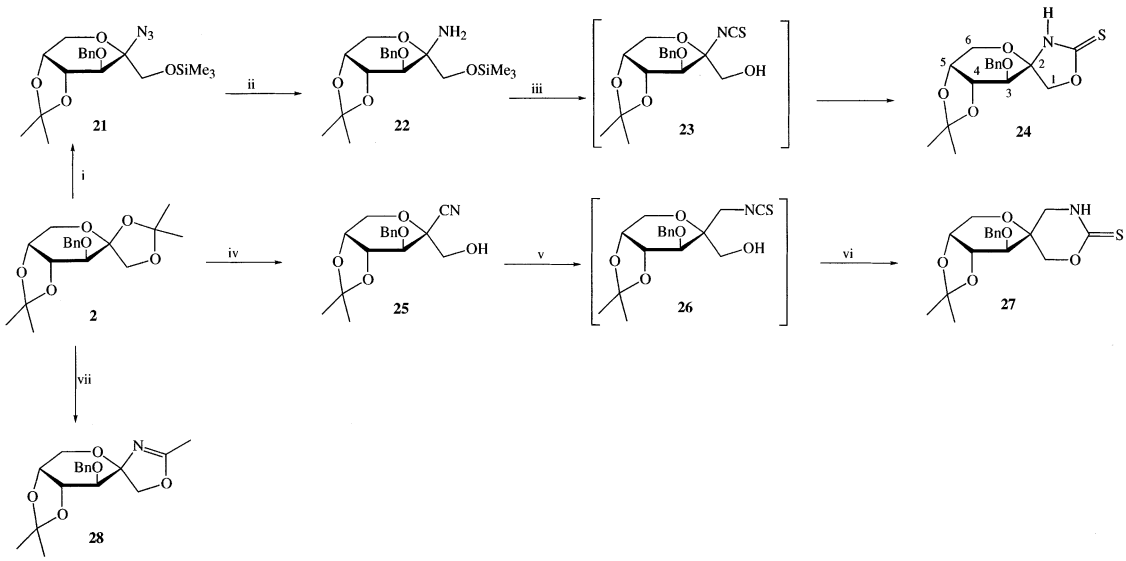


Scheme 2. Mechanism of the anomerization of **8**.

186.6 ppm, a value very close to that reported[19] for oxazine-2-thiones with non-spiranic structure. Compounds **13** and **14** showed ^{1}H NMR resonances for the NH group. Table 1 shows that the spiranic carbon (C(2) using the numbering indicated in Table 1) resonates at lower field in the spironucleosides **3**, **4**, and **8** than in the spiro-*C*-glycosides **13** and **14**.

In the reaction of **1** with (trimethylsilyl)acetonitrile, using the conditions mentioned above for the other silyl derivatives, the spironucleosides **15**, and the spiro-*C*-glycoside **16** (minor product), were isolated. Compound **15** has been described previously[7b] although its ^{13}C NMR data were not reported. The molecular formula and the spectroscopic data (ν C≡N 1649 cm^{-1} and δ C≡N 169.3 ppm) of the minor product suggest that the probable structure is **16**. Nucleophilic attack of (trimethylsilyl)acetonitrile on the anomeric carbon (Scheme 1) can take place from the nitrogen atom (*N*-attack) or the methylenic carbon (*C*-attack). In the first case, the heterocumulene intermediate **19** is formed, which by internal cycloaddition gives the major product **15**. In the second case, the key intermediate is the nitrile **20**, without loss of the isopropylidene group. Compound **20** by internal cyclization can produce the minor product **16**.

To prepare 6+5 and 6+6 spironucleosides and spiro-*C*-glycosides, we started from the fructopyranose spiroketal derivative **2**[16] (Scheme 3). The *N*-glycosylation of **2** with trimethylsilyl azide, in the same conditions described above for the preparation of **6**, gave with high stereoselectivity the expected fructopyranosyl azides **21** (β) and **29** (α) as a 9:1 β:α anomeric mixture. From this mixture, **21** could be isolated after chromatography. (The NMR data for **29** were measured from the spectra of the mixture; see Section 4.) Hydrogenation of **21** for 2 h at room temperature produced, in almost quantitative yield, the β-fructopyranosylamine **22**. On treatment with tetrabutylammonium fluoride followed by thiocarbonyldiimidazole, **22** was converted to the pyranosyl isothiocyanate **23**, which spontaneously cyclized to give the spironucleoside **24**, in 75% overall yield from **21**.



Scheme 3. *Reagents and conditions*: (i) 1. $TMSN_3$, 0°C, 5 min; 2. TMSOTf, 0°C, 5 min, 85%; (ii) H_2/Pd–C, rt, 2 h, 90%; (iii) 1. $Bu_4NF{\cdot}3H_2O$, rt, 1 h; 2. Im_2CS, rt, 3 h, 83%; (iv) 1. TMSCN, –20°C, 5 min; 2. TMSOTf, 0°C, 5 min; 3. $Bu_4NF{\cdot}3H_2O$, rt, 8 h, 55%; (v) 1. $LiAlH_4$, 0°C, 30 min; 2. Im_2CS; (vi) Et_3N, rt, 10 h, 60% from **25**; (vii) $TMSCH_2CN$, TMSOTf, –20°C, 1 h, 75%.

The IR spectrum of compound **21** contained the band for the azido group at 2114 cm^{-1}, close to that for **6**, whereas in the spectrum of **22**, the NH group was seen at 3286 cm^{-1}. The trimethylsilyl groups of **21** and **22** were evident from the corresponding ^1H (0.13 and 0.11 ppm, respectively) and ^{13}C (−0.5 and −0.4 ppm, respectively) NMR resonances. The chemical shift for the resonance of the C=S group of **24** was 189.7 ppm, confirming[19] the oxazolidine-2-thione structure. The β anomeric configuration of **24** was supported by the observed NOE effects between C(3)H and C(1a)H (numbering as sugar derivative, Fig. 2), C(4)H and the NH proton. The vicinal coupling constants for the protons of the sugar ring of **24** and the NOE for C(3)H–NH supported the slightly distorted chair conformation depicted in Fig. 2. The distortion in the C(3)–C(4) region (numbering of the sugar structure), probably due to condensation with the dioxolane ring, is evident from the values of $J_{3,4}$ and $J_{4,5}$ (5.3 and 6.9 Hz, respectively). The β configuration of **24** supports the same configuration for **21** and **22**.

C-Glycosylation of **2** with trimethylsilyl cyanide in the presence of trimethylsilyl triflate, followed by desilylation with tetrabutylammonium fluoride, gave the β-fructopyranosyl cyanide **25**. Lithium aluminum hydride reduction of **25**, followed by reaction with thiocarbonyl diimidazole, produced the transient isothiocyanate **26**, which cyclized to the spiro-*C*-fructopyranoside **27** upon treatment with triethylamine.

The IR spectrum of **25** had absorptions for the OH group at 3298 cm^{-1} and contained no band for the C≡N group in accord with that described for other glycosyl cyanides.[23] The presence of the C≡N group was confirmed by the ^{13}C resonance at 116.8 ppm, and the glycosyl cyanide structure was supported by this and also by the chemical shift of the anomeric carbon (65.3 ppm); both signals are in agreement with reported data[23] for glycopyranosyl cyanides. In the case of **27**, there was an IR band at 3269 cm^{-1} (NH), a ^1H broad resonance at 8.18 ppm (NH), and a ^{13}C resonance at 186.0 ppm (C=S). The latter value is very close to that for the six-membered cyclic thiocarbamates **13** and **14**, and to that described[19] for other perhydrooxazine-2-thiones. The anomeric configuration of **25** and **27** is supported by the fact that **25** is the only product obtained in the glycosylation of **2** and by the NOE experiment for **27** shown in Fig. 2. As in the case of **24**, the pyranose ring presented a slightly distorted chair conformation.

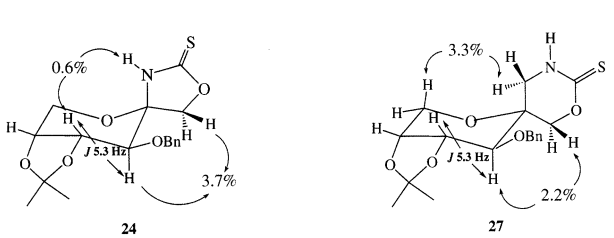


Figure 2. NOE effects of **24** and **27**.

The reaction of **2** with (trimethylsilyl)acetonitrile under the same conditions yielded the β-spironucleoside **28** (75%). The C=N band of **28** in the IR spectrum was seen at 1663 cm^{-1} as in the case of **15**. The C=N group resonated at 169.1 ppm and there were ^1H (2.05, 1.56 and 1.40 ppm) and ^{13}C (28.2, 26.2, and 14.4 ppm) NMR resonances for three methyl groups (Me_2C and CH_3-C=). The mechanism that we propose for the formation of **28** is the same as that proposed for the formation of **15** (Scheme 3, *N*-attack). In this case no side product resulting from *C*-attack was isolated.

3. Conclusion

The reaction of sugar spiroketals with trimethylsilyl *N*- and *C*-nucleophiles, followed by suitable methods to introduce the N=C=S group, is a convenient stereoselective route to prepare spironucleosides and spiro-*C*-glycosides of 1,3-*O*,*N*-heterocycles.

4. Experimental

4.1. General methods

Melting points are uncorrected. Optical rotations were measured for solutions in CH_2Cl_2. FTIR spectra were recorded as KBr discs or thin films. ^1H NMR (500 or 300 MHz) and ^{13}C NMR (125.7 or 75.4 MHz) spectra were obtained for solutions in $CDCl_3$. Chemical shifts are given in ppm, and the spectra were calibrated on $CDCl_3$ signals. When this was not possible, TMS was used as an internal reference. Assignments were confirmed by homonuclear 2D COSY and heteronuclear 2D correlated experiments. Mass spectra (EI and FAB) were recorded with a Kratos MS-80RFA or a Micromass AutoSpecQ instrument with a resolution of 1000 or 10,000 (10% valley definition). For the FAB spectra, ions were produced by a beam of xenon atoms (6–7 keV), using 3-nitrobenzyl alcohol and thioglycerol as matrix and NaI as salt. TLC was performed on silica-gel HF254, with detection by UV light or charring with H_2SO_4. Silica-gel 60 (Merck, 70–230 and 230–400 mesh) was used for preparative chromatography.

4.2. Preparation of compounds 3, 4, 5 and 16

To a solution of **1** (100 mg, 0.29 mmol) in freshly distilled CH_2Cl_2 (2 mL) under argon and at temperature *T*, TMSNCS (121 μL, 0.86 mmol) for **3**, TMSNCO (86 μL, 0.86 mmol) for **4** and **5**, or $TMSCH_2CN$ (156 μL, 1.14 mmol) for **15** and **16**, and then TMSOTf (82 μL, 0.43 mmol) were added. The resulting solution was kept at temperature *T* for *t* h (monitoring the reaction by TLC; ether/petroleum ether 2:1), then poured into a saturated aqueous solution of ammonium chloride, extracted with CH_2Cl_2, washed with water, dried ($MgSO_4$), and concentrated. Purification of the resulting products was performed by column chromatography as indicated in each case.

4.2.1. (2*R*,3*R*,4*R*,5*R*)-6-Aza-2-benzyloxymethyl-3,4-dimethylmethylenedioxy-1,8-dioxaspiro[4.4]nonan-7-thione 3. $T=-20$°C, $t=1$ h. Column chromatography (ether/petroleum ether 1:2) of the residue gave **3** as a colorless syrup. Yield 10%; $[\alpha]_D^{26}=-119$ (c 0.9); IR ν_{max} 3370, 3028, 2930, 1462, 1375, 1262, 1211, 1082, and 1026 cm^{-1}; ^1H NMR (500 MHz): δ 8.20 (s, 1H, H-6), 7.46–7.26 (m, 5H, Ph), 4.88 (d, 1H, $J_{9a,9b}=11.1$, H-9a), 4.80 (d, 1H, $J_{2,3}=0.0$, $J_{3,4}=5.8$, H-3), 4.63 (d, 1H, $^2J_{H,H}=11.2$, C*H*HPh), 4.61 (d, 1H, H-4), 4.57 (d, 1H, CH*H*Ph), 4.46 (d, 1H, H-9b), 4.31 (sa, 1H, H-2), 3.75, 3.56 (each dd, each 1H, $^2J_{H,H}=10.6$, $J_{2,H}=1.3$, $J_{2,H}=1.8$, respectively, CH_2OBn), 1.42, and 1.31 (each s, each 3H, $2CH_3$) ppm; ^{13}C NMR (125.7 MHz): δ 189.1 (C-7), 135.3–128.3 (6C, Ph), 112.4 (CCH_3), 100.1 (C-5), 84.8 (C-4), 83.7 (C-2), 82.0 (C-3), 74.2 (CH_2 from Bn), 75.8 (C-9), 70.9 (CH_2OBn), 25.7 and 24.2 ($2CH_3$) ppm; FABMS m/z 374 (100, $[M+Na]^{+\bullet}$); HREIMS m/z obsd. 351.1137, calcd for $C_{17}H_{21}NO_5S$ 351.1140.

4.2.2. (2*R*,3*R*,4*R*,5*R*)-6-Aza-2-benzyloxymethyl-3,4-dimethylmethylenedioxy-1,8-dioxaspiro[4.4]nonan-7-one 4 and (2*R*,3*R*,4*R*,5*S*)-6-aza-2-benzyloxymethyl-3,4-dimethylmethylenedioxy-1,8-dioxaspiro[4.4]nonan-7-one 5. $T=-20$°C, $t=2$ h. Column chromatography (ether/petroleum ether 1:2) of the residue gave **4** (22%) and **5** (5%) as colorless syrups.

Compound **4**: $[\alpha]_D^{27}=-79$ (c 0.8); IR ν_{max} 3389, 3060, 2982, 1755, 1458, 1377, 1263, 1078, and 1028 cm^{-1}; ^1H NMR (500 MHz): δ 7.41–7.26 (m, 5H, Ph), 6.57 (s, 1H, H-6), 4.80 (d, 1H, $J_{3,4}=5.8$, H-4), 4.66 (d, 1H, $J_{9a,9b}=10.5$, H-9a), 4.65 (d, 1H, $^2J_{H,H}=11.5$, C*H*HPh), 4.62 (d, 1H, $J_{2,3}=0.0$, H-3), 4.51 (d, 1H, CH*H*Ph), 4.28 (s, 1H, H-2), 4.23 (d, 1H, H-9b), 3.71, 3.55 (each d, each 1H, $^2J_{H,H}=10.6$, CH_2OBn), 1.43 and 1.31 (each s, each 3H, $2CH_3$) ppm; ^{13}C NMR (125.7 MHz): δ 157.5 (C-7), 135.9–128.2 (6C, Ph), 112.4 (CCH_3), 97.5 (C-5), 85.7 (C-3), 83.7 (C-2), 82.4 (C-4), 74.2 (CH_2 of Bn), 71.3 (C-9), 71.1 (CH_2OBn), 26.1 and 24.5 ($2CH_3$) ppm; FABMS m/z 358 (100, $[M+Na]^{+\bullet}$); HREIMS m/z obsd. 335.1363, calcd for $C_{17}H_{21}NO_6$ 335.1369.

Compound **5**: IR ν_{max} 3389, 3060, 2982, 1755, 1458, 1377, 1263, 1078, and 1028 cm^{-1}; FABMS m/z 358 (100, $[M+Na]^{+\bullet}$); HREIMS m/z obsd. 335.1349, calcd *para* $C_{17}H_{21}NO_6$ 335.1369.

4.2.3. (2*R*,3*R*,4*R*,5*R*)-6-Aza-2-benzyloxymethyl-3,4-dimethylmethylenedioxy-7-methyl-1,8-dioxa-spiro[4.4]non-6-ene 15 and (2*R*,3*R*,4*R*,5*R*)-2-benzyloxymethyl-8,8-dimethyl-3,4-dimethylmethylenedioxy-10-imino-1,7,9-trioxaspiro[4.6]undecane 16. $T=-20$°C, $t=1$ h. Column chromatography (ether/petroleum ether 1:2) of the residue gave **15** (23%) and **16** (5%) as colorless syrups.

The IR and ^1H NMR data of **15** were consistent with reported data.[7a] ^{13}C NMR (125.7 MHz): δ 167.7 (C-7), 136.8–127.5 (6C, Ph), 112.6, 110.1 (CCH_3, C-5), 85.5 (C-4), 83.9 (C-2), 83.4 (C-3), 73.7 (CH_2 from Bn), 72.0 (C-9), 70.9 (CH_2OBn), 26.4, 25.1 ($2CH_3$), and 14.2 (=C-CH_3) ppm; FABMS m/z 356 (100, $[M+Na]^{+\bullet}$); HREIMS m/z obsd. 333.1576, calcd for $C_{18}H_{23}NO_5$ 333.1576.

Compound **16**: $[\alpha]_D^{26}=-77$ (c 0.9); IR ν_{max} 3445, 3060, 2976, 1649, 1460, 1373, 1250, 1209, and 1063 cm^{-1}; ^1H NMR (300 MHz): δ 7.40–7.26 (m, 5H, Ph), 4.81 (dd, 1H, $J_{2,3}=1.2$, $J_{3,4}=5.9$, H-3), 4.60 (d, 1H, $^2J_{H,H}=12.0$, C*H*HPh), 4.56 (d, 1H, H-4), 4.51 (d, 1H, CH*H*Ph), 4.47 (d, 1H, $J_{6a,6b}=10.8$, H-6a), 4.33 (dt, 1H, $J_{2,CHHOBn}=J_{2,CHHOBn}=7.2$, H-2), 4.19 (d, 1H, H-6b), 3.60 (m, 2H, CH_2OBn), 2.44 (s, 2H, H-11a, 11b), 1.46, 1.33, 1.29, and 1.28 (each s, each 3H, $4CH_3$) ppm; ^{13}C NMR (75.4 MHz): δ 169.3 (C-10), 138.8–127.6 (6C, Ph), 112.6, 109.6 ($2CCH_3$), 85.4 (C-4), 83.8 (C-2), 83.4 (C-3), 73.3 (CH_2 of Bn), 71.3 (C-6), 70.6 (CH_2OBn), 68.7 (C-5), 40.3 (C-11), 29.2, 29.8, 26.3, and 25.0 ($4CH_3$) ppm; FABMS m/z 414 (100, $[M+Na]^{+\bullet}$); HREIMS m/z obsd. 391.1993, calcd for $C_{21}H_{29}NO_6$ 391.1995.

4.3. 2-Azido-6-*O*-benzyl-2-deoxy-3,4-*O*-isopropylidene-1-*O*-trimethylsilyl-β-D-psicofuranose 6

To a solution of **1** (100 mg, 0.29 mmol) in freshly distilled acetonitrile (3 mL) at 0°C, under argon in the presence of activated 4 Å molecular sieves, $TMSN_3$ (75 μL, 0.57 mmol) was added. The solution was stirred for 5 min, then TMSOTf (25 μL, 0.15 mmol) was added dropwise, and the stirring was continued at 0°C for a further 5 min. The mixture was neutralized with Et_3N, diluted with Et_2O, filtered through Celite and concentrated. Column chromatography (ether/petroleum ether 1:12) gave **6** as colorless syrup; yield 90%; $[\alpha]_D^{30}=-87$ (c 1.0); IR ν_{max} 3053, 2986, 2118 (N_3), 1454, 1375, 1249, 1070 and 1022 cm^{-1}; ^1H NMR (500 MHz): δ 7.36–7.28 (m, 5H, Ph), 4.79 (dd, 1H, $J_{3,4}=5.9$, $J_{4,5}=1.7$, H-4), 4.59 (s, 2H, CH_2Ph), 4.42 (ddd, 1H, $J_{5,6a}=5.9$, $J_{5,6b}=7.4$, H-5), 4.38 (d, 1H, H-3), 3.95 (m, 2H, H-1a, H-1b), 3.63 (m, 2H, H-6a, H-6b), 1.49, 1.31 (each s, each 3H, $2CH_3$), 0.17 (s, 9H, $Si(CH_3)_3$) ppm; ^{13}C NMR (125.7 MHz): δ 137.8–127.6 (6C, Ph), 113.2 (CCH_3), 100.6 (C-2), 85.7 (C-5), 85.2 (C-3), 82.8 (C-4), 73.5 (CH_2Ph), 70.2 (C-6), 65.2 (C-1), 26.4, 25.1 ($2CH_3$), –0.7 ($Si(CH_3)_3$) ppm; FABMS m/z 430 (100, $[M+Na]^{+\bullet}$); HRFABMS m/z obsd. 430.17769, calcd for $C_{19}H_{29}NaN_3O_5Si$ 430.17742.

4.4. 2-Amino-6-*O*-benzyl-2-deoxy-3,4-*O*-isopropylidene-1-*O*-trimethylsilyl-D-psicofuranose 7 (α+β)

A mixture of the azide **6** (100 mg, 0.25 mmol) and 10% Pd–C in MeOH (7 mL) was hydrogenated under a slightly positive pressure of hydrogen (balloon) at rt for 2 h, then diluted with MeOH, filtered through Celite and concentrated to give the corresponding amine **7**. The crude product thus obtained was used without purification for the next step. To obtain samples for NMR characterization flash column chromatography (ether/petroleum ether 1:2 as eluent) was used. Yield 80%; the NMR data were obtained from the mixture of **7β** and **7α** (2:3 ratio).

Compound **7β**: ^{1}H NMR (500 MHz): δ 7.33–7.25 (m, 5H, Ph), 4.60–4.54 (m, 3H, H-4, CH_2Ph), 4.46 (d, 1H, $J_{3,4}=6.4$, H-3), 4.21 (m, 1H, H-5), 3.57 (d, 1H, $J_{1a,1b}=10.2$, H-1a), 3.54 (d, 2H, $J_{5,6}=5.1$, 2H-6), 3.50 (d, 1H, H-1b), 2.24 (bs, 2H, NH_2), 1.57, 1.36 (each s, each 3H, $2CH_3$), 0.08 (s, 9H, $Si(CH_3)_3$) ppm; ^{13}C NMR (125.7 MHz): δ 138.0–127.6 (6C, Ph), 113.6 (CCH_3), 94.4 (C-2), 82.4 (C-4), 81.9 (C-3), 81.4 (C-5), 73.6 (CH_2Ph), 71.2 (C-6), 67.4 (C-1), 27.0, 25.3 ($2CH_3$), −0.7 ($Si(CH_3)_3$) ppm.

Compound **7α**: ^{1}H NMR (500 MHz): δ 7.33–7.25 (m, 5H, Ph), 4.83 (dd, 1H, $J_{4,5}=2.0$, H-4), 4.60–4.54 (m, 2H, CH_2Ph), 4.50 (d, 1H, $J_{3,4}=6.3$, H-3), 4.23 (m, 1H, H-5), 3.79 (d, 1H, $J_{1a,1b}=10.4$, H-1a), 3.69 (d, 1H, H-1b), 3.67 (dd, 1H, $J_{5,6a}=3.3$, $J_{6a,6b}=10.2$, H-6a), 3.59 (dd, 1H, $J_{5,6b}=3.5$, H-6a), 2.24 (bs, 2H, NH_2), 1.48, 1.30 (each s, each 3H, $2CH_3$), 0.14 (s, 9H, $Si(CH_3)_3$) ppm; ^{13}C NMR (125.7 MHz): δ 137.4–127.6 (6C, Ph), 112.4 (CCH_3), 95.7 (C-2), 86.9 (C-3), 83.5 (C-5), 82.8 (C-4), 73.4 (CH_2Ph), 71.8 (C-6), 65.7 (C-1), 26.3, 24.9 ($2CH_3$), −0.5 ($Si(CH_3)_3$) ppm; FABMS for **7** (**α**+**β**) m/z 382 (100, $[M+H]^{+\bullet}$); HRCIMS m/z obsd. 382.20492, calcd for $C_{19}H_{32}NO_5Si$ 382.20498.

4.5. (2*R*,3*R*,4*R*,5*S*)-6-Aza-2-benzyloxymethyl-3,4-dimethylmethylenedioxy-1,8-dioxaspiro[4.4]nonan-7-thione 8 and (2*R*,3*R*,4*R*,5*R*)-6-aza-2-benzyloxymethyl-3,4-dimethylmethylenedioxy-1,8-dioxaspiro[4.4]nonan-7-thione 3

To a solution of crude **7** (100 mg, 0.26 mmol) in CH_2Cl_2 (3 mL), a catalytic amount of $TBAF{\cdot}3H_2O$ was added. The mixture was stirred at rt for 1 h, then washed with brine, water and further brine, dried ($MgSO_4$), and concentrated to dryness. The resulting residue was taken up into CH_2Cl_2 (3 mL) and 1,1′-thiocarbonyldiimidazole (160 mg, 0.89 mmol) was added. After 3 h at rt the solvent was evaporated. Column chromatography (ether/petroleum ether 3:1) of the residue gave **8** (50% from **6**) as an amorphous solid and **3** (13% from **6**).

Compound **8**: $[\alpha]_D^{27}=-128$ (c 0.9); IR ν_{max} 3283, 3030, 2926, 1464, 1375, 1267, 1219, 1070, and 1041 cm^{-1}; ^{1}H NMR (500 MHz): δ 7.43–7.02 (m, 5H, Ph), 7.20 (s, 1H, H-6), 4.78 (dd, 1H, $J_{2,3}=0.9$, $J_{3,4}=5.9$, H-3), 4.58 (d, 1H, $J_{9a,9b}=10.8$, H-9a), 4.55 (d, 1H, H-4), 4.47 (m, 2H, CH_2Ph), 4.33 (d, 1H, H-9b), 4.31 (sa, 1H, H-2), 3.61 (dd, 1H, $^2J_{H,H}=10.3$, $J_{2,H}=2.0$, C*H*HOBn), 3.52 (dd, 1H, 10.3, $J_{2,H}=2.0$, CH*H*OBn), 1.53, and 1.37 (each s, each 3H, $2CH_3$) ppm; ^{13}C NMR (125.7 MHz): δ 188.9 (C-7), 136.7–128.7 (6C, Ph), 113.3 (CCH_3), 99.5 (C-5), 83.7 (C-4), 82.1 (C-3), 81.7 (C-2), 81.2 (C-9), 74.0 (CH_2Ph), 71.5 (CH_2OBn), 26.3 and 24.2 ($2CH_3$) ppm; CIMS m/z 352 (100, $[M+H]^{+\bullet}$); HRCIMS m/z obsd. 352.12200, calcd for $C_{17}H_{22}NO_5S$ 352.12187. Anal. calcd for $C_{17}H_{21}NO_5S$: C, 58.10; H, 6.02; N, 3.98. Found: C, 58.26; H, 6.20; N, 3.91%.

Treatment of **8** (100 mg, 28 mmol) with Et_3N (1 mL) in CH_2Cl_2 (4 mL) at rt for 3 h gave **3** (80%) and **8** (15%).

4.6. Preparation of the isothiocyanates 11 and 12

A solution of the starting nitrile[22] (160 mg, 0.50 mmol) **9** for **11** or **10** for **12** in Et_2O (5.4 mL) was cooled to 0°C, then $LiAlH_4$ (38 mg, 1.00 mmol) was added and the resulting mixture was stirred at 0°C for 30 min and then at rt for 2 h (the process was monitored by TLC, ether/petroleum ether 2:1). The mixture was treated with K_2CO_3 (1 M, 0.26 mL) which effected the formation of a grey precipitate that was removed by filtration through Celite. The organic layer was washed with brine and dried on $MgSO_4$. Evaporation of the solvent gave the expected product as a colorless syrup which was dissolved in CH_2Cl_2 (9 mL) and treated with $CaCO_3$ (126 mg, 1.26 mmol), water (9 mL) and thiophosgene (62 μL, 0.63 mmol). The heterogeneous mixture was stirred vigorously for 6 h (the process was monitored by TLC, ether/petroleum ether 2:1). The mixture was filtered and the organic layer of the filtrate was separated, washed with water and dried ($MgSO_4$). The solvent was then evaporated. The residue was purified by column chromatography (ether/petroleum ether 1:2).

4.6.1. 6-*O*-Benzyl-2-deoxy-3,4-*O*-isopropylidene-2-isothiocyanatomethyl-β-D-psicofuranose 11

Yield 39% from **9**; $[\alpha]_D^{25}=-43$ (c 1.0); IR ν_{max} 3680–3450, 3063, 2976, 2201 (NCS), 2083 (NCS), 1454, 1387, 1262, 1078, and 1030 cm^{-1}; ^{1}H NMR (300 MHz): δ 7.35–7.26 (m, 5H, Ph), 4.76 (dd, 1H, $J_{3',4'}=6.6$, $J_{4',5'}=3.7$, H-4), 4.59 (s, 2H, CH_2Ph), 4.27 (m, 1H, H-5), 3.84 (d, 1H, $J_{1a,1b}=14.3$, H-1a), 3.83–3.74 (m, 1H, C*H*HNCS), 3.77 (d, 1H, H-1b), 3.67–3.61 (m, 1H, CH*H*NCS), 3.66–3.54 (m, 2H, H-6a, 6b), 3.58 (d, 1H, H-3), 1.56 and 1.35 (each s, each 3H, $2CH_3$) ppm; ^{13}C NMR (75.4 MHz): δ 137.7–127.7 (6C, Ph), 132.7 (NCS), 114.4 (CCH_3), 85.7 (C-3), 83.4, 83.3 (C-2, 5), 82.9 (C-4), 73.6 (CH_2 from Bn), 70.8 (C-6), 62.6 (CH_2NCS), 48.7 (C-1), 26.1 and 24.6 ($2CH_3$) ppm; FABMS m/z 388 (100, $[M+Na]^{+\bullet}$); HREIMS m/z obsd. 365.1286, calcd for $C_{18}H_{23}O_5NS$ 365.1297. Anal. calcd for $C_{18}H_{23}NO_5S$: C, 59.16; H, 6.34; N, 3.83. Found: C, 59.08; H, 6.43; N, 3.65%.

4.6.2. 6-*O*-Benzyl-2-deoxy-3,4-*O*-isopropylidene-2-isothiocyanatomethyl-α-D-psicofuranose 12

Yield 36% from **10**; $[\alpha]_D^{25}=+5$ (c 0.8); IR ν_{max} 3451, 3030, 2987, 2199 (NCS), 2106 (NCS), 1449, 1375, 1256, 1211, and 1078 cm^{-1}; ^{1}H NMR (500 MHz): δ 7.37–7.30 (m, 5H, Ph), 4.93 (dd, 1H, $J_{3',4'}=6.1$, $J_{4',5'}=5.0$, H-4), 4.75 (d, 1H, H-3), 4.61, 4.54 (each d, each 1H, $^2J_{H,H}=11.8$, CH_2Ph), 4.19 (m, 1H, H-5), 3.77 (dd, 1H, $J_{5,6a}=2.7$, $J_{6a,6b}=10.5$, H-6a), 3.75 (d, 1H, $J_{1a,1b}=14.6$, H-1a), 3.71 (d, 1H, $^2J_{H,H}=11.6$, C*H*HNCS), 3.69 (d, 1H, H-1b), 3.63 (dd, 1H, $J_{5,6b}=2.1$, H-6b), 3.60 (d, 1H, CH*H*NCS), 1.54 and 1.34 (each s, each 3H, $2CH_3$) ppm; ^{13}C NMR (125.7 MHz): δ 136.8–127.9 (6C, Ph), 132.7 (NCS), 113.7 (CCH_3), 86.5 (C-2), 84.6 (C-5), 83.1 (C-3), 81.6 (C-4), 73.8 (CH_2 of Bn), 69.9 (C-6), 65.9 (CH_2NCS), 46.5 (C-1), 27.0 and 25.1 ($2CH_3$) ppm; FABMS m/z 388 (100, $[M+Na]^{+\bullet}$); HREIMS m/z obsd. 365.1274, calcd for $C_{18}H_{23}NO_5S$ 365.1297.

4.7. Cyclization of the isothiocyanates 11 and 12

To a solution of the corresponding isothiocyanate (65 mg, 0.18 mmol), **11** for **13** and **12** for **14**, in DMF (1 mL), triethylamine (20 μL, 0.14 mmol) was added. The reaction mixture was heated to 80°C for 40 min and then evaporated to dryness to give the product indicated in each case. The reaction was monitored by TLC (ether/petroleum ether 2:1).

4.7.1. (2*R*,3*R*,4*R*,5*R*)-9-Aza-2-benzyloxymethyl-3,4-dimethylmethylenedioxy-1,7-dioxaspiro[4.5]decane-8-thione 13. Column chromatography (ether/petroleum ether 1:2) of the residue gave **13** as a white solid. Yield 85%; $[\alpha]_D^{25}=-22$ (*c* 1.1); IR ν_{max} 3266, 3063, 2988, 1580, 1458, 1377, 1265, 1204, 1159, and 1078 cm^{-1}; ^1H NMR (500 MHz): δ 7.88 (bs, 1H, H-9), 7.39–7.26 (m, 5H, Ph), 4.88 (dd, 1H, $J_{2,3}=2.2$, $J_{3,4}=6.3$, H-3), 4.56 (d, 1H, $^2J_{H,H}=$ 11.8, C*H*HPh), 4.51 (d, 1H, H-4), 4.50 (d, CH*H*Ph), 4.36 (m, 1H, H-2), 4.31 (d, 1H, $J_{6a,6b}=11.5$, H-6a), 4.26 (dd, 1H, $^4J_{6b,10a}=2.2$, H-6b), 3.62 (dd, 1H, $^2J_{H,H}=10.4$, $J_{2,H}=2.8$, C*H*HOBn), 3.57 (dd, 1H, $J_{2,H}=2.8$, CH*H*OBn), 3.44 (m, 1H, $J_{10a,10b}=12.8$, H-10a), 3.35 (d, 1H, H-10b), 1.51 and 1.33 (each s, each 3H, $2CH_3$) ppm; ^{13}C NMR (125.7 MHz): δ 186.5 (C-8), 137.2–127.8 (6C, Ph), 114.0 (CCH_3), 84.0 (C-4), 83.2 (C-2), 82.9 (C-3), 73.7 (CH_2 from Bn), 71.1 (C-6), 70.8 (CH_2OBn), 65.8 (C-5), 49.2 (C-10), 25.9, and 25.4 ($2CH_3$) ppm; FABMS *m*/*z* 388 (100, $[M+Na]^{+\bullet}$). Anal. calcd for $C_{18}H_{23}NO_5S$: C, 59.16; H, 6.34; N, 3.83. Found: C, 58.95; H, 6.36; N, 4.12%.

4.7.2. (2*R*,3*R*,4*R*,5*S*)-9-Aza-2-benzyloxymethyl-3,4-dimethylmethylenedioxy-1,7-dioxaspiro[4.5]decane-8-thione 14. Column chromatography (ether/petroleum ether 1:2) of the residue gave **14** as a white solid. Yield 96%; $[\alpha]_D^{22}$ −4 (*c* 0.7); IR ν_{max} 3306, 3063, 2986, 1543, 1458, 1377, 1260, 1173, 1080, and 1038 cm^{-1}; ^1H NMR (500 MHz): δ 7.56 (bs, 1H, H-9), 7.37–7.28 (m, 5H, Ph), 4.89 (dd, 1H, $J_{2,3}=2.1$, $J_{3,4}=6.3$, H-3), 4.57 (d, 1H, $^2J_{H,H}=$ 11.7, C*H*HPh), 4.48 (d, 1H, H-4), 4.48 (d, CH*H*Ph), 4.33 (m, 1H, H-2), 4.33 (dd, 1H, $J_{6a,6b}=11.2$, $^4J_{6a,10b}=$ 2.1, H-6a), 4.19 (dd, 1H, $^4J_{6b,10a}=1.0$, H-6b), 3.60 (dd, 1H, $^2J_{H,H}=10.6$, $J_{2,H}=2.7$, C*H*HOBn), 3.56–3.53 (m, 1H, H-10a), 3.55 (dd, 1H, $J_{2,H}=3.0$, CH*H*OBn), 3.23 (m, 1H, H-10b), 1.49 and 1.33 (each s, each 3H, $2CH_3$) ppm; ^{13}C NMR (125.7 MHz,): δ 186.7 (C-8), 137.1–127.8 (6C, Ph), 113.7 (CCH_3), 83.3 (C-2), 82.9 (C-3), 82.4 (C-4), 77.3 (C-5), 73.8 (CH_2 from Bn), 72.1 (C-6), 70.9 (CH_2OBn), 47.2 (C-10), 26.1 and 24.5 ($2CH_3$) ppm; FABMS *m*/*z* 388 (100, $[M+Na]^{+\bullet}$); HRFABMS *m*/*z* obsd. 388.1197, calcd for $C_{18}H_{23}NO_5NaS$ 388.1195.

4.8. 2-Azido-3-*O*-benzyl-2-deoxy-4,5-*O*-isopropylidene-1-*O*-trimethylsilyl-β-D-fructopyranose 21 and 2-azido-3-*O*-benzyl-2-deoxy-4,5-*O*-isopropylidene-1-*O*-trimethylsilyl-α-D-fructopyranose 29

Prepared following the procedure described for **6**. Ratio **21**:**29** (9:1). Column chromatography (ether/petroleum ether 1:15) gave **21** (85%) as a pure colorless syrup and a mixture of **21**+**29** (10%).

Compound **21**: $[\alpha]_D^{29}=-126$ (*c* 0.9); IR ν_{max} 3032, 2986, 2114 (N_3), 1458, 1384, 1253, 1093 and 1022 cm^{-1}; ^1H NMR (500 MHz): δ 7.35–7.26 (m, 5H, Ph), 4.89 (d, 1H, $^2J_{H,H}=11.9$, C*H*HPh), 4.66 (d, 1H, CH*H*Ph), 4.36 (t, 1H, $J_{3,4}=J_{4,5}=7.1$, H-4), 4.27 (ddd, 1H, $J_{5,6a}=1.3$, $J_{5,6b}=2.8$, H-5), 4.12 (dd, 1H, $J_{6a,6b}=13.6$, H-6a), 4.07 (dd, 1H, H-6b), 3.90 (d, 1H, $J_{1a,1b}=10.8$, H-1a), 3.78 (d, 1H, H-1b), 3.60 (d, 1H, H-3), 1.49, 1.37 (each s, each 3H, $2CH_3$), and 0.13 (s, 9H, $Si(CH_3)_3$) ppm; ^{13}C NMR (125.7 MHz): δ 137.9–127.6 (6C, Ph), 109.1 (CCH_3), 92.4 (C-2), 76.6 (C-4), 75.7 (C-3), 73.3 (CH_2Ph), 73.2 (C-5), 65.2 (C-1), 61.9 (C-6), 27.8, 26.0 ($2CH_3$), and −0.5 ($Si(CH_3)_3$) ppm; FABMS *m*/*z* 430 (60, $[M+Na]^{+\bullet}$); HRFABMS *m*/*z* obsd. 430.17771, calcd for $C_{19}H_{29}N_3O_5NaSi$ 430.17742.

NMR data for **29** (from the mixture): ^1H NMR (500 MHz): δ 7.35–7.26 (m, 5H, Ph), 4.75 (m, 2H, CH_2Ph), 4.37–4.35 (m, 2H, H-4, H-5), 4.10 (m, 2H, H-6a and H-6b), 3.85 (d, 1H, $J_{1a,1b}=10.6$, H-1a), 3.76 (d, 1H, H-1b), 3.678 (d, 1H, $J_{3,4}=6.0$, H-3), 1.49, 1.37 (each s, each 3H, $2CH_3$), and 0.13 (s, 9H, $Si(CH_3)_3$) ppm; ^{13}C NMR (125.7 MHz): δ 136.7–128.1 (6C, Ph), 109.8 (CCH_3), 92.3 (C-2), 78.6 (C-4), 75.6 (C-3), 73.7 (CH_2Ph), 71.4 (C-5), 63.0 (C-1), 64.2 (C-6), 27.2, 25.2 ($2CH_3$), and −0.7 ($Si(CH_3)_3$) ppm.

4.9. 2-Amino-3-*O*-benzyl-2-deoxy-4,5-*O*-isopropylidene-1-*O*-trimethylsilyl-β-D-fructopyranose 22

Compound **22** was prepared and purified following the procedure described for **7**. Yield 90%; d.e. 80%; IR ν_{max} 3286, 3034, 2978, 1449, 1370, 1248, 1069 and 1028 cm^{-1}; ^1H NMR (500 MHz): δ 7.34–7.27 (m, 5H, Ph), 4.90 (d, 1H, $^2J_{H,H}=11.6$, C*H*HPh), 4.62 (d, 1H, CH*H*Ph), 4.35 (t, 1H, $J_{3,4}=J_{4,5}=6.8$, H-4), 4.30 (dd, 1H, $J_{5,6a}=2.8$, $J_{6a,6b}=13.3$, H-6a), 4.21 (dd, 1H, H-5), 3.98 (d, 1H, H-6b), 3.54 (m, 2H, H-1a, H-1b), 3.46 (d, 1H, H-3), 1.53, 1.36 (each s, each 3H, $2CH_3$), and 0.11 (s, 9H, $Si(CH_3)_3$) ppm; ^{13}C NMR (125.7 MHz): δ 138.3–127.7 (6C, Ph), 108.5 (CCH_3), 85.8 (C-2), 77.0 (C-3), 74.0 (C-5), 73.3 (C-4), 73.0 (CH_2Ph), 67.7 (C-1), 59.0 (C-6), 27.9, 26.2 ($2CH_3$), and −0.4 ($Si(CH_3)_3$) ppm; EIMS *m*/*z* 382 (60, $[M+H]^{+\bullet}$); HREIMS *m*/*z* obsd. 382.20428, calcd for $C_{19}H_{32}NO_5Si$ 382.20498.

4.10. (5*R*,8*R*,9*R*,10*S*)-1-Aza-10-benzyloxy-8,9-dimethylmethylenedioxy-3,6-dioxaspiro[4.5]decan-2-thione 24

Prepared following the procedure described for **8**. Column chromatography (ether/petroleum ether 1:1) gave **24** as an amorphous solid. Yield 75% (from **21**); $[\alpha]_D^{24}=-78$ (*c* 1.0); IR ν_{max} 3160, 3034, 2982, 2932, 1462, 1381, 1231, 1021, 1088 and 1005 cm^{-1}; ^1H NMR (500 MHz): δ 7.39–7.26 (m, 5H, Ph), 4.77, 4.69 (each d, each 1H, $^2J_{H,H}=11.8$, CH_2Ph), 4.47 (s, 2H, H-4a, 4b), 4.44 (dd, 1H, $J_{8,9}=6.9$, $J_{9,10}=5.3$, H-9), 4.24 (ddd, 1H, $J_{7a,8}=2.1$, $J_{7b,8}=0.9$, H-8), 4.04 (dd, 1H, $J_{7a,7b}=13.3$, H-7a), 3.90 (bd, 1H, H-7b), 3.76 (d, 1H, H-10), 1.48 and 1.34 (each s, each 3H, $2CH_3$) ppm; ^{13}C NMR (125.7 MHz): δ 189.7 (C-2), 136.7–128.1 (6C, Ph), 110.0 (CCH_3), 90.9 (C-5), 80.4 (C-4), 75.8 (C-10), 73.7 (CH_2 from Bn), 72.7 (C-9), 72.1 (C-8), 63.3 (C-7), 26.6 and

24.9 ($2CH_3$) ppm; FABMS m/z 374 (100, $[M+Na]^{+\bullet}$); HREIMS m/z obsd. 351.1130, calcd for $C_{17}H_{21}NO_5S$ 351.1140. Anal. calcd for $C_{17}H_{21}NO_5S$: C, 58.10; H, 6.02; N, 3.98. Found: C, 58.10; H, 6.03; N, 3.94%.

4.11. 3-*O*-Benzyl-2-cyano-2-deoxy-4,5-*O*-isopropylidene-β-D-fructopyranose 25

A solution of **2** (100 mg, 0.29 mmol) and TMSCN (11 μL, 0.86 mmol) in CH_2Cl_2 (2.5 mL) was stirred at −20°C under argon in the presence of 4 Å molecular sieves. After stirring the mixture for 5 min, TMSTfO (52 μL, 0.29 mmol) was added and the stirring was maintained for 2 h. The mixture was neutralized with Et_3N, diluted with Et_2O, filtered through Celite and concentrated. The residue was dissolved in CH_2Cl_2 (3 mL), and a catalytic amount of $TBAF{\cdot}3H_2O$ was added. The mixture was kept at rt for 8 h, then washed with water and brine, dried ($MgSO_4$), and concentrated to dryness. The residue was purified by column chromatography (ether/petroleum ether 1:5). Yield (55%); $[\alpha]_D^{30}=-88$ (c 1.5); IR ν_{max} 3298, 3033, 2986, 2143, 1451, 1426, 1373, 1217, 1107, 1071, and 1020 cm^{-1}; ^1H NMR (500 MHz): δ 7.36–7.70 (m, 5H, Ph), 4.94 (d, 1H, $^2J_{H,H}=11.8$, C*H*HPh), 4.70 (d, 1H, CH*H*Ph), 4.42 (dd, 1H, $J_{3,4}=7.2$, $J_{4,5}=5.7$, H-4), 4.32 (d, 1H, $J_{6a,6b}=14.1$, H-6a), 4.30 (dd, 1H, $J_{5,6b}=2.6$, H-5), 4.12 (dd, 1H, H-6b), 3.94 (d, 1H, $J_{1a,1b}=11.9$, H-1a), 3.79 (d, 1H, H-1b), 3.64 (d, 1H, H-3), 1.61 (bs, 1H. HO), 1.48 and 1.39 (each s, each 3H, $2CH_3$) ppm; ^{13}C NMR (125.7 MHz): δ 137.2–128.0 (6C, Ph), 115.3 (CN), 109.8 (CCH_3), 76.9 (C-4), 74.4 (C-3), 72.9 (2C, C-5 and CH_2Ph), 64.8 (C-1), 64.2 (C-6), 27.8 and 26.0 ($2CH_3$) ppm; ^{13}C NMR (125.7 MHz, Me_2CO-d_6): δ 139.0–128.5 (6C, Ph), 116.8 (CN), 110.2 (CCH_3), 79.2 (C-2), 77.7 (C-4), 76.1 (C-3), 74.0 (CH_2Ph), 73.9 (C-5), 73.9 (C-5), 65.3 (C-1), 64.9 (C-6), 28.1 and 26.3 ($2CH_3$) ppm; IEMS m/z 342 (100, $[M+Na]^{+\bullet}$); HREIMS m/z obsd. 320.1500, calcd for $C_{17}H_{22}NO_5$ 320.1498.

4.12. (3*R*,4*R*,5*S*,6*R*)-10-Aza-5-benzyloxy-3,4-dimethylmethylenedioxy-1,8-dioxaspiro[5.5]undecan-9-thione 27

A solution of **25** (100 mg, 0.51 mmol) in diethyl ether (3 mL) was cooled to 0°C, then $LiAlH_4$ (24 mg, 0.62 mmol) was added and the resulting mixture was stirred for 30 min at 0°C, allowed to warm to rt and stirred for a further 2 h. Treatment with K_2CO_3 (1 M, 0.16 mL) gave a grey precipitate that was removed by filtration through Celite. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was dissolved in CH_2Cl_2 (3 mL), and 1,1′-thiocarbonyldiimidazole (160 mg, 0.89 mmol) and Et_3N (0.5 mL) were added. After stirring for 10 h at rt the solvent was evaporated and the residue was purified by column chromatography (ether/petroleum ether 3:1) to give **27** as an amorphous solid (60%); $[\alpha]_D^{29}=+29$ (c 1.4); IR ν_{max} 3269, 3034, 2980, 1460, 1373, 1287, 1244, 1070 and 1032 cm^{-1}; ^1H NMR (500 MHz): δ 8.18 (bs, 1H, NH), 7.39–7.25 (m, 5H, Ph), 4.81 (d, 1H, $^2J_{H,H}=11.7$, C*H*HPh), 4.52 (d, 1H, CH*H*Ph), 4.30 (dd, 1H, $J_{3,4}=6.5$, $J_{4,5}=5.3$, H-4), 4.27 (ddd, 1H, $J_{2a,3}=1.5$, $J_{2b,3}=2.6$, H-3), 4.24 (bs, H-7a and H-7b), 3.96 (dd, 1H, $J_{2a,2b}=13.8$, H-2a), 3.85 (dd, 1H, H-2b), 3.52 (d, 1H, H-5), 3.41 (m, 2H, H-11a and H-11b), 1.53 and 1.36 (each s, each 3H, $2CH_3$) ppm; ^{13}C NMR (125.7 MHz): δ 186.0 (C-9), 136.6–127.9 (6C, Ph), 109.6 (CCH_3), 74.6 (C-5), 73.7 (CH_2Ph), 73.4 (C-4), 72.7 (C-3), 72.5 (C-7), 68.8 (C-6), 61.5 (C-2), 41.6 (C-11), 27.1 and 25.3 ($2CH_3$) ppm; EIMS m/z 365 (10, $[M]^{+\bullet}$); HREIMS m/z obsd. 365.12972, calcd for $C_{18}H_{23}NO_5S$ 365.12969. Anal. calcd for $C_{18}H_{23}NO_5S$: C, 59.16; H, 6.34; N, 3.83. Found: C, 59.48; H, 6.26; N, 3.64%

4.13. (5*R*,8*R*,9*R*,10*S*)-1-Aza-10-benzyloxy-8,9-dimethylmethylenedioxy-2-methyl-3,6-dioxaspiro[4.5]dec-1-ene 28

Prepared following the procedure described for **15.** $T=-20$°C, $t=2$ h. Column chromatography (ether/petroleum ether 1:1). Yield 75%; $[\alpha]=-77$ (c 0.8); IR ν_{max} 3028, 2982, 1663, 1452, 1379, 1246, 1217, 1119, and 1082 cm^{-1}; ^1H NMR (500 MHz): δ 7.36–7.26 (m, 5H, Ph), 4.95 (d, 1H, $J_{4a,4b}=12.2$, C*H*HPh), 4.69 (d, 1H, CH*H*Ph), 4.53 (dd, 1H, $J_{8,9}=5.8$, $J_{9,10}=7.3$, H-9), 4.37 (dd, 1H, $J_{7a,7b}=13.3$, $J_{7a,\ 8}=2.8$, H-7a), 4.30 (dd, 1H, $J_{7b,8}=0$, H-8), 4.08 (d, 1H, $^2J_{H,H}=9.4$, H-4a), 3.99 (d, 1H, H-7b), 3.94 (d, 1H, H-4b), 3.51 (d, 1H, H-10), 2.05 (s, 3H, =C-CH_3), 1.56 and 1.40 (each s, each 3H, $2CH_3$) ppm; ^{13}C NMR (125.7 MHz): δ 169.1 (C-2), 137.9–127.6 (6C, Ph), 108.8 (CCH_3), 100.9 (C-5), 78.1 (C-9), 77.5 (C-10), 74.5 (CH_2 of Bn), 74.1 (C-8), 72.3 (C-4), 60.9 (C-7), 28.2, 26.2 ($2CH_3$) and 14.4 (=C-CH_3) ppm; FABMS m/z 356 (100, $[M+Na]^{+\bullet}$); HRFABMS m/z obsd. 334.1645, calcd for $C_{18}H_{24}N\ O_5$ 334.1654.

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