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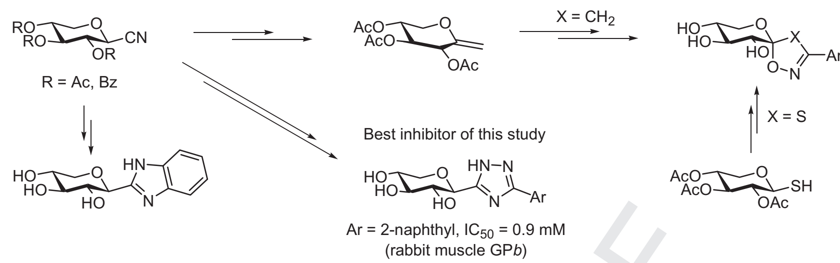
Graphical abstract

Synthesis of *C*-xylopyranosyl- and xylopyranosylidene-spiro-heterocycles as potential inhibitors of glycogen phosphorylase **pp xxx–xxx**

László Somsák *, Éva Bokor, Beáta Czibere, Katalin Czifrák, Csenge Koppány, László Kulcsár, Sándor Kun,
Enikő Szilágyi, Marietta Tóth, Tibor Docsa, Pál Gergely



Highlights

Q2 • Synthesis of *C*-xylopyranosyl benzimidazole and 1,2,4-triazoles. • Synthesis of xylopyranosylidene-spiro-isoxazolines and -1,4,2-oxathiazoles. • Weak inhibition of rabbit muscle glycogen phosphorylase *b* by a *C*-xylopyranosyl 1,2,4-triazole.

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Synthesis of *C*-xylopyranosyl- and xylopyranosylidene-spiro-heterocycles as potential inhibitors of glycogen phosphorylase

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Spiro-1,4,2-oxathiazole
Glycogen phosphorylase
Inhibitor

ABSTRACT

New derivatives of D-xylose with aglycons of the most efficient glucose derived inhibitors of glycogen phosphorylase were synthesized to explore the specificity of the enzyme towards the structure of the sugar part of the molecules. Thus, 2-(β-D-xylopyranosyl)benzimidazole and 3-substituted-5-(β-D-xylopyranosyl)-1,2,4-triazoles were obtained in multistep procedures from *O*-perbenzoylated β-D-xylopyranosyl cyanide. Cycloadditions of nitrile-oxides and *O*-peracetylated *exo*-xylal obtained from the corresponding β-D-xylopyranosyl cyanide furnished xylopyranosylidene-spiro-isoxazoline derivatives. Oxidative ring closure of *O*-peracetylated β-D-xylopyranosyl-thiohydroximates prepared from 1-thio-β-D-xylopyranose and nitrile-oxides gave xylopyranosylidene-spiro-oxathiazoles. The fully deprotected test compounds were assayed against rabbit muscle glycogen phosphorylase *b* to show moderate inhibition for 3-(2-naphthyl)-5-(β-D-xylopyranosyl)-1,2,4-triazole (IC_{50} = 0.9 mM) only.

1. Introduction

The quest for inhibitors of glycogen phosphorylases (GPs) has been based on and fuelled by the potential application of such compounds as medication in type II *diabetes mellitus*[1–3] and also as possible therapeutic means in other diseased states like myocardial[4,5] and cerebral[6,7] ischemias and tumors.[8–11]

A large variety of compounds targeting one of the six binding sites of GP (catalytic, inhibitor, new allosteric, storage and benzimidazole sites) have been developed to reach the nanomolar range in their inhibitory efficiency.[3,12] Catalytic site inhibitors are almost exclusively glucose derivatives[13] which have been designed and studied following the observation that both anomeric forms of D-glucose (**A** and **B** in Chart 1) are modest inhibitors of GP.[14] Early inhibitor design resulted in glucopyranosylidene-spiro-hydantoins **C** and **D** with low micromolar inhibition constants.[15,16] Most efficient representatives of *N*-glucopyranosyl-1,2,3-triazoles[17,18] **E** and *C*-glucopyranosyl-benzimidazoles[19–21] **F** proved similarly or somewhat less effective than the hydantoins. Among the recently designed and synthesized 5-β-D-glucopyranosyl-3-substituted-1,2,4-triazoles submicromolar inhibitors of GP (e.g., **G**) were found.[22,23] Best compounds in series of other types of anomeric spirocycles like isoxazolines[24] (e.g., **H**) and oxathiazoles[25,26] (e.g., **I**) showed inhibition approaching the low nanomolar range. To explain the strong binding of these compounds extensive interactions with the so-called β-channel[†] of the enzyme were invoked besides the ideal fit of the sugar moiety in the catalytic site.[12,13] Thus, the increasing binding strength must largely be attributed to the aglycon part of the molecules.

Investigations into the specificity of GP towards various monosaccharides revealed that changes in the sugar configuration or constitution resulted in a significant decrease of the inhibition: for example, D-xylose (**J**) proved a ~13–60-fold weaker inhibitor in comparison to the D-glucose anomers **A** and **B**.[27] Since the efficiency of the glucose derived inhibitors depended to a large extent on the fit of the aglycon in the β-channel, the D-*xylo* configured analogues of the best inhibitors were time to time synthesized

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† The β-channel of GPs is an empty space next to the active site in the direction of the β-substituent of the bound D-glucose surrounded by amino acid side chains of both polar and apolar character.

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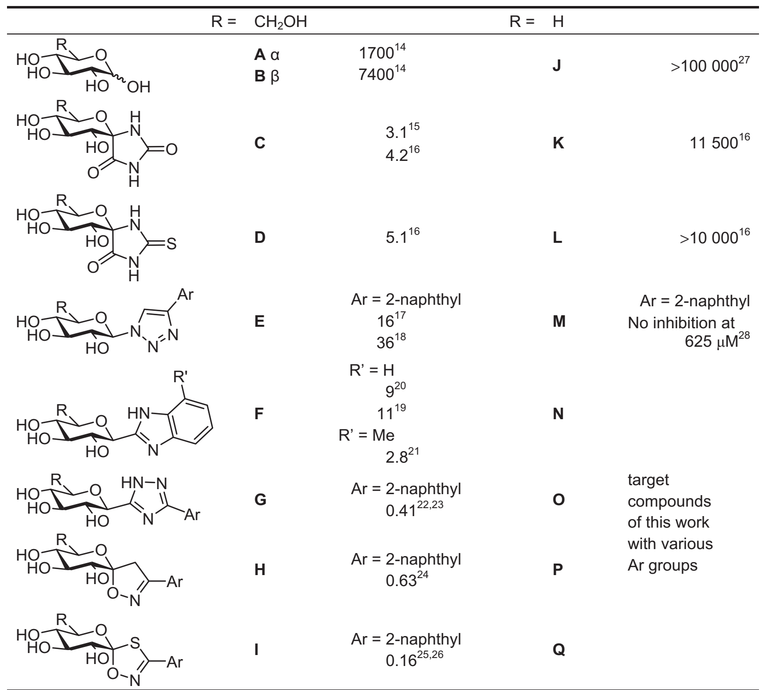


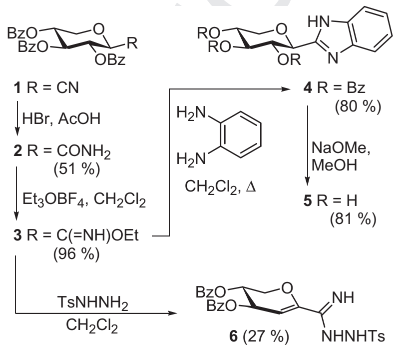
Chart 1. Selected inhibitors of rabbit muscle glycogen phosphorylase *b* (RMGP*b*, K_i [μM]).

and tested against GP to check if the interactions of the aglycon might overbalance the worse binding of the 'truncated' glycon. Up to now xylopyranosylidene-spiro-hydantoins[16] **K** and **L** as well as *N*-(β-D-xylopyranosyl)-1,2,3-triazoles (e.g., **M**) together with similar derivatives of 5-thio-xylose and the related cyclic sulfoxides and sulfones[28] were studied, however, showed no significant effect against RMGP*b*.

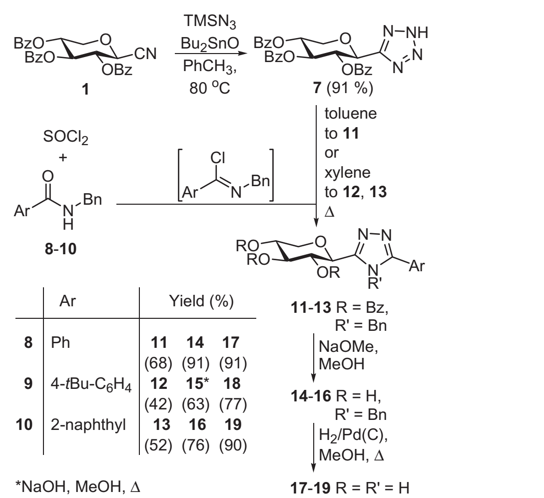
In this paper we report on the synthesis and enzymatic evaluation of xylose derived analogues **N–Q** of the best glucose based inhibitors of rabbit muscle glycogen phosphorylase *b*.

2. Results and discussion

For the preparation of the desired *C*-xylosyl benzimidazole **N**, our recently published reaction sequence was applied.[21] Thus, 2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl cyanide[29] (**1**, Scheme 1) was hydrated to anhydro-aldonamide **2** which, on treatment by $Et_3O{\cdot}BF_4$ gave ethyl imidate **3**. Reaction of **3** with 1,2-diamino-benzene furnished the protected benzimidazole **4** which was *O*-debenzoylated under Zemplén conditions[30] to give the test compound **5**.



Scheme 1. Some transformations starting from *O*-perbenzoylated β-D-xylopyranosyl cyanide **1**.



Scheme 2. Synthesis of 3-(β-D-xylopyranosyl)-5-substituted-1,2,4-triazoles **17–19**.

Structure elucidation of the compounds was straightforward by NMR methods, and it is to be noted that line broadening of some resonances in the ^{13}C spectra, due to fast proton exchange of the two nitrogens, was observed similarly to earlier experiences.[21]

Next, to get an intermediate for the preparation of *C*-xylosyl-1,2,4-triazoles **O**, imidate **3** was reacted with tosylhydrazine,[22,31] however, instead of the expected N^1-tosyl-(*C*-xylopyranosyl)formamidrazone only its benzoic acid elimination product **6** could be isolated.

Therefore, we turned to an alternative route[23] (Scheme 2) and, to this end, **1** was transformed to tetrazole[‡] **7** by $TMSN_3$–Bu_2SnO.[33] Reactions of **7** with non-purified *N*-benzyl-arenecarboximidoyl

‡ The analogous *O*-peracetylated 5-(β-D-xylopyranosyl)tetrazole is known in the lit.[32]

chlorides obtained from the corresponding carboxamides **8–10** gave the O-perbenzoylated *N*-benzyl-1,2,4-triazoles **11–13**. These compounds were first O-deprotected by the Zemplén protocol[30] or NaOH in MeOH to give **14** and **16**, as well as **15**, respectively, followed by catalytic hydrogenation to remove the *N*-benzyl protection to yield the test compounds **17–19**.

For the preparation of xylopyranosylidene-spiro-isoxazolines **P**, O-peracetylated β-D-xylopyranosyl cyanide[34] **20** was transformed to the corresponding anhydro-aldose tosylhydrazone **21** by applying our published method.[35,36] Bamford–Stevens reaction[37] of **21** was performed by thermal decomposition of the intermediate salt[35,38] to give *exo*-xylal **22** in excellent yield. 1,3-Dipolar cycloaddition of **22** and nitrile-oxides,[39] generated in situ by bleach oxidation of the corresponding aromatic aldoximes,[40] gave stereoselectively the protected spiro-isoxazolines **23–28**, which were O-deacetylated under Zemplén conditions[30] to obtain the test compounds **29–34**. The configuration of the spiro-carbon was proven by Nuclear Overhauser Effect (NOE) difference spectra showing spatial vicinity of the isoxazoline methylene protons with H-2′ (but not with H-3′ and H-5′) of the sugar ring. Similar exclusive stereoselectivity was observed in the formation of the glucose-
Q5 derived isoxazolines[24] (Chart 1, **H**) (Scheme 3).

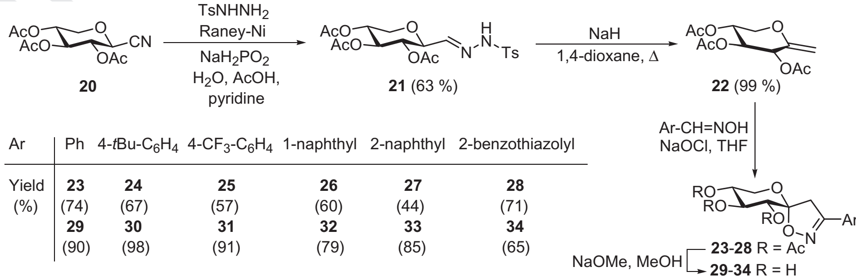
Synthesis of the xylopyranosylidene-spiro-oxathiazoles **Q** was started by the conversion of O-peracetylated 1-thio-β-D-xylopyranose[41] **35** to *S*-β-D-xylopyranosyl thiohydroximates **36–38** (Scheme 4). One of the generally applied methods to get *S*-glycosyl thiohydroximates[42] is the reaction of the corresponding 1-thiosugars with nitrile-oxides. In addition to the above mentioned oxidative processes, a frequently used way to obtain nitrile-oxides in situ is the base-induced dehydrohalogenation of hydroximoyl halides which are isolable after halogenation (by e.g., Cl_2, NCS or NBS) of aldoximes.[39] Because of the sensitivity of thiols to oxidation, nitrile oxides were generated from hydroximoyl chlorides by Et_3N (method *a* in Scheme 4) in the presence of **35**. A recently reported procedure to perform the chlorination and HCl elimination in one continuous operation (method *b*), suggested to be superior especially for the preparation of glycosyl thiohydroximates,[43] was also studied. Although both methods gave good yields of the expected products **36–38**, in our hands the conventional dehydrochlorination of the isolated hydroximoyl chlorides gave better results (compare yields for methods *a* and *b* in Scheme 4). Thiohydroximates **36–38** were deacetylated by the Zemplén method[30] to give the test compounds **39–41**.

Ring closure of the thiohydroximates was effected by NBS under irradiation as reported for the preparation of several glycoenzyme inhibitors of this spiro-oxathiazole type.[26,44,45] Expectedly, the formation of two spiro epimers was observed, however, in contrast to earlier findings with hexopyranose derived compounds where the anomeric configuration of the thiohydroximate was retained in the major cyclized product, in these reactions compounds of the inverted configuration **42–44** were isolated as the main products. The minor products **45** and **47** having the same spiro configuration (1′*S*) as the glucose-derived inhibitors **I** in Chart 1 were deacetylated under Zemplén conditions[30] to obtain the test compounds **48** and **49**.

Structural elucidation of the xylopyranosylidene-spiro-oxathiazoles **42–47** was based on comparisons of their NMR spectral and optical rotation data to those of the D-*gluco* counterparts where at least for one compound (**I** Ar = Ph in Chart 1) the structure was determined by X-ray crystallography.[44] For **42–47** the presence of a xylopyranose ring in the $^4C_1$ conformation was deduced from the vicinal coupling constants in the ^{1}H NMR spectra. To establish the configuration of the spiro centre, characteristic differences observed for the 1′*R* and 1′*S* epimers of the D-*gluco* derivatives (Table 1, **50**, **51** and **52**, **53**, respectively) were sought for in the data of the D-*xylo* compounds. Thus, for the D-*gluco* configured epimeric pairs **50**, **51**, and **52**, **53** the change of the spiro configuration had practically no influence on the chemical shifts of the H-2′ and H-4′ protons, but H-3′ and H-5′ showed ~0.5 and ~0.3 ppm difference, respectively, depending on the presence of an axial S versus O atom in the spiro-heterocycle. The same tendency was also present in the chemical shift values of the respective protons of the D-*xylo* derivatives **42–44** versus **45–47**. The chemical shifts for the spiro carbons were consistently higher for the 1′*R* than for the 1′*S* compounds in both series. Finally, the 1′*R* derivatives were significantly more dextrorotatory than the 1′*S* compounds. The spiro configurations were assigned by utilizing these coincidences.

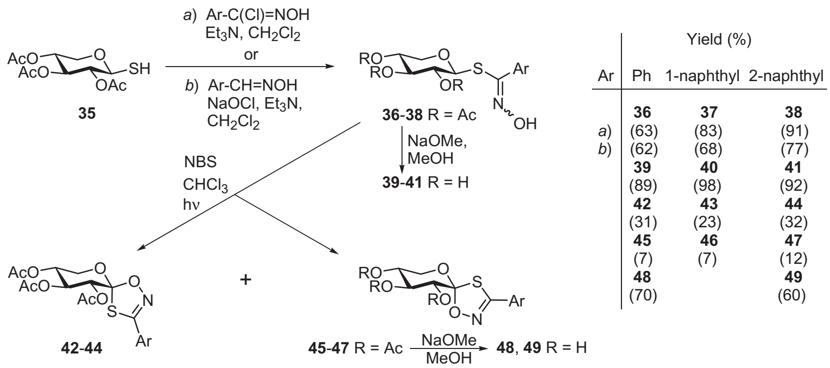
Enzymatic evaluation of the deprotected compounds against rabbit muscle glycogen phosphorylase *b* (RMGP*b*) was carried out as described before.[16] All but one of the deprotected xylose derivatives had no inhibition at 625 μM concentration. The only compound of the series having a moderate effect was 3-(2-naphthyl)-5-(β-D-xylopyranosyl)-1,2,4-triazole (**19**) with an IC_{50} value of 900 μM (calculated[46] K_i = 491 μM). This inhibition is more than three orders of magnitude weaker than that of the D-*gluco* counterpart (**G** in Chart 1, K_i = 0.41 μM). However, a comparison of the ratio of inhibitor constants for the *xylo*/*gluco* hydantoins (Chart 1, compounds **K**/**C** ~2800–3800), thiohydantoins (Chart 1, compounds **L**/**D** ~2300) and 3-(2-naphthyl)-1,2,4-triazoles (Chart 1, compounds **O**(=**19**)/**G** ~1200) shows a clear tendency in making the binding stronger by the aglycons which fit better in the β-channel. Although the findings reveal that the aglycons in these xylose derived compounds (provided that they indeed bind to the catalytic site of GP) still have no strong enough interactions to fully overcompensate the loss of the CH_2OH side chain of the sugar moiety, the above tendency may foreshadow much more efficient xylose-derived inhibitors of GP.

In conclusion, new *C*-xylopyranosyl benzimidazole and 1,2,4-triazoles as well as xylopyranosylidene-spiro-isoxazolines and -oxathiazoles were prepared by adapting procedures used for the syntheses of analogous glucose-derived inhibitors of glycogen phosphorylase. Evaluation of the compounds as inhibitors of rabbit muscle glycogen phosphorylase *b* showed very weak inhibition for 3-(2-naphthyl)-5-(β-D-xylopyranosyl)-1,2,4-triazole only, while all



Ar	Ph	4-*t*Bu-C$_6$H$_4$	4-CF$_3$-C$_6$H$_4$	1-naphthyl	2-naphthyl	2-benzothiazolyl
Yield (%)	**23** (74)	**24** (67)	**25** (57)	**26** (60)	**27** (44)	**28** (71)
	29 (90)	**30** (98)	**31** (91)	**32** (79)	**33** (85)	**34** (65)

Scheme 3. Synthesis of D-xylopyranosylidene-spiro-isoxazolines **29–34**.



Scheme 4. Synthesis of D-xylopyranosylidene-spiro-oxathiazoles **42–49**.

other compounds proved ineffective in a concentration of 625 μM. These observations show that the aglycons rendering their glucose derivatives to nanomolar inhibitors, are not yet capable to completely override the effect of losing the side chain of the glucose moiety. Nevertheless, the increase in the binding strength of the xylose derivatives with the more efficient aglycons may predict strongly binding inhibitors derived from sugars other than glucose.

3. Experimental

3.1. General methods

Melting points were measured on a Kofler hot-stage and are uncorrected. Optical rotations were determined with a Perkin-Elmer 241 polarimeter at rt. NMR spectra were recorded with a Bruker 360 (360/90 MHz for ^{1}H/^{13}C) spectrometer. Chemical shifts are referenced to Me_4Si (^{1}H), or to the residual solvent signals (^{13}C). Microanalyses were performed on an Elementar Vario Micro cube instrument. ESI-MS spectra were measured with a Thermo Scientific LTQ XL spectrometer. TLC was performed on DC-Alurolle Kieselgel 60 F_{254} (Merck) plates, visualized under UV light and by gentle heating. For column chromatography Kieselgel 60 (Merck, particle size 0.063–0.200 mm) was used. CH_2Cl_2, $CHCl_3$, toluene and *m*-xylene were distilled from P_4O_{10} and stored over 4 Å molecular sieves or sodium wires. MeOH was purified by distillation after refluxing for a couple of hours with magnesium turnings and iodine. 1,4-Dioxane was distilled from sodium benzophenone ketyl and stored over sodium wires. 2,3,4-Tri-*O*-benzoyl-β-D-xylopyranosyl cyanide[29] (**1**), *N*-benzyl-arenecarboxamides[23] (**8–10**), 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl-cyanide[34] (**20**), 2,3,4-tri-*O*-acetyl-1-thio-β-D-xylopyranose[41] (**35**), arenecarbaldoximes[47] and *N*-hydroxy-arenecarboximidoyl chlorides[47] were synthesized according to published procedures.

3.2. General procedure I for the Zemplén-deacylation[30]

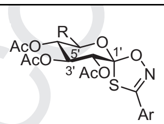
An *O*-acylated compound was dissolved in anhydrous MeOH (5 mL/100 mg, a few drops of $CHCl_3$ were added in case of incomplete dissolution) and a catalytic amount of a NaOMe solution (~1 M in MeOH) was added. The mixture was kept at rt and monitored by TLC (7:3 $CHCl_3$–MeOH). After disappearance of the starting material the mixture was neutralized with a cation exchange resin Amberlyst 15 (H^+ form), then the resin was filtered off and the solvent removed. The residue was purified either by column chromatography or by crystallization.

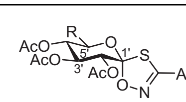
3.3. General procedure II for the synthesis of 4-benzyl-3-(2′,3′,4′-tri-*O*-benzoyl-β-D-xylopyranosyl)-5-substituted-1,2,4-triazoles (11–13)

An *N*-benzyl-arenecarboxamide[23] (**8–10**, 4.63 mmol, 3 equiv) was dissolved in $SOCl_2$ (20 mL), and refluxed for 2 h. After distilling

Table 1
Selected spectral data for spiro-oxathiazoles of D-glucose and D-xylose

Ar (Compound)





	1′*R*					1′*S*				
	R = H			R = CH_2OAc*		R = H			R = CH_2OAc*	
	Ph (**42**)	1-Naphthyl (**43**)	2-Naphthyl (**44**)	Ph (**50**)	1-Naphthyl (**51**)	Ph (**45**)	1-Naphthyl (**46**)	2-Naphthyl (**47**)	Ph (**52**)	1-Naphthyl (**53**)
H-2′	5.52	5.58	5.56	5.60	5.66	5.56	5.59	5.60	5.63	5.67
H-3′	5.13	5.15	5.17	5.10	5.13	5.62	5.68	5.66	5.63	5.67
H-4′	5.07	5.10	5.11	5.27	5.29	5.12	5.14	5.15	5.27	5.29
H-5′$_{ax}$	3.79	3.85	3.83	4.10	4.18	4.04	4.11	4.07	4.42	4.51
H-5′$_{eq}$	4.19	4.28	4.22	–	–	4.00	4.06	4.02	–	–
C-1′	126.6	125.8	126.7	127.3	126.3	122.6	121.9	122.6	122.4	121.8
[α]$_D$	+178	+151	+182	+179	+99	+78	+73	+61	+53	+44

* Data taken from Ref. 44.

off the excess of $SOCl_2$ under reduced pressure, anhydrous toluene (20 mL) was evaporated from the residue. 5-(2,3,4-Tri-*O*-benzoyl-β-D-xylopyranosyl)tetrazole (**7**, 1.54 mmol, 1 equiv) and anhydrous toluene or *m*-xylene (20 mL) were added, the mixture was heated to reflux temperature and the reaction was monitored by TLC (1:1 EtOAc–hexane). After total consumption of the tetrazole the solvent was removed and the residue was purified by column chromatography.

3.4. General procedure III for the removal of benzyl protecting groups

A benzylated compound (0.5 mmol) was dissolved in anhydrous MeOH (25 mL), 10% Pd(C) (20 mg) was added and H_2 gas was bubbled through the reaction mixture at 50 °C. After disappearance of the starting material (monitored by TLC, 7:3 $CHCl_3$–MeOH) the reaction mixture was filtered through a pad of Celite, the solvent was evaporated and the residue was purified by column chromatography.

3.5. General procedure IV for the synthesis of (1′*R*)-2′,3′,4′-tri-*O*-acetyl-1′,5′-anhydro-D-xylitol-spiro[1′,5]-3-aryl-4,5-dihydro-isoxazoles (23–28)

3,4,5-Tri-*O*-acetyl-2,6-anhydro-1-deoxy-D-*xylo*-hex-1-enitol (**22**, 100 mg, 0.37 mmol) and an arenecarbaldoxime (1.85 mmol, 5 equiv) were dissolved in THF (4.8 mL) under N_2 atmosphere. To this stirred solution domestic bleach (5% available chlorine, 3.86 mL) was added with a syringe pump in 5 h at rt. The reaction was stirred for additional 24 h. After complete disappearance of the starting *exo*-xylal (TLC, 1:1 EtOAc–hexane) the reaction was diluted with EtOAc (20 mL), the phases were separated and the organic layer was washed with water (3 × 15 mL), dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (1:3 EtOAc–hexane).

3.6. General procedure V (method *a*) for the synthesis of 2,3,4-tri-*O*-acetyl-1-*S*-(*Z*)-arylhydroximoyl-1-thio-β-D-xylopyranoses (36–38)

2,3,4-Tri-*O*-acetyl-1-thio-β-D-xylopyranose[41] (**35**, 0.29 g, 1 mmol) and the corresponding *N*-hydroxy-arenecarboximidoyl chloride (1.5 mmol) were dissolved in anhydrous CH_2Cl_2 (10 mL), Et_3N was added (3 mmol) and the reaction mixture was stirred at rt under Ar. After completion of the reaction (1.5 h, monitored by TLC, 1:2 EtOAc–hexane) the mixture was treated with 2 M HCl solution (20 mL), then the separated organic phase was washed with water (2 × 20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (1:2 EtOAc–hexane) to give an oil that was crystallized from hexane.

3.7. General procedure VI (method *b*)[43] for the synthesis of 2,3,4-tri-*O*-acetyl-1-*S*-(*Z*)-arylhydroximoyl-1-thio-β-D-xylopyranoses (36–38)

An arenecarbaldoxime (1.5 mmol) was dissolved in CH_2Cl_2 (10 mL) and the solution was extracted with domestic bleach (5% available chlorine, 5 mL). After drying over $MgSO_4$ the organic phase was added dropwise to a solution of 2,3,4-tri-*O*-acetyl-1-thio-β-D-xylopyranose[41] (**35**, 0.29 g, 1 mmol) in CH_2Cl_2 (10 mL). After addition of Et_3N (3 mmol) the reaction mixture was stirred at rt under Ar, and monitored by TLC (1:2 EtOAc–hexane). When the starting material was consumed (1.5 h) the mixture was treated with 2 M HCl solution (20 mL), then the separated organic phase was washed with water (2 × 20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (1:2 EtOAc–hexane) to give an oil that was crystallized from hexane.

3.8. General procedure VII for the synthesis of (1′*S*/1′*R*)-2′,3′,4′-tri-*O*-acetyl-1′,5′-anhydro-D-xylitol-spiro[1′,5]-3-aryl-1,4,2-oxathiazoles (42–47)

A 2,3,4-tri-*O*-acetyl-1-*S*-(*Z*)-arylhydroximoyl-1-thio-β-D-xylopyranose (**36–38**, 1 mmol) and NBS (1.2 mmol) were dissolved in anhydrous $CHCl_3$ (20 mL) and the mixture was boiled and illuminated by a 250 W heat lamp. When TLC (1:2 EtOAc–hexane) showed total consumption of the starting material (1 h) the reaction mixture was diluted with $CHCl_3$ (30 mL), extracted with satd aq $Na_2S_2O_4$ solution (40 mL), satd aq $NaHCO_3$ solution (40 mL) and water (40 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by column chromatography.

3.9. Synthesis and characterization of the compounds

3.9.1. *C*-(2,3,4-Tri-*O*-benzoyl-β-D-xylopyranosyl)formamide (2)

2,3,4-Tri-*O*-benzoyl-β-D-xylopyranosyl cyanide[29] (**1**, 3.0 g, 6.4 mmol) was suspended in a solution of HBr in AcOH (8 mL, 33% m/m) and the mixture was stirred at rt. After disappearance of the starting material (3 h, monitored by TLC, 1:1 EtOAc–hexane) the reaction mixture was poured into ice-water (40 mL) and extracted with $CHCl_3$ (2 × 30 mL). The combined organic phases were washed with satd aq $NaHCO_3$ solution (2 × 30 mL), then with water (30 mL), dried over $MgSO_4$, filtered and the solvent was removed. The remaining oil was crystallized from Et_2O to give 1.58 g (51%) of **2** as a white solid. Mp: 173–175 °C; $[\alpha]_D$ −15 (*c* 0.5, DMSO); ^{1}H NMR (DMSO-d_6) δ (ppm): 7.88–7.38 (17H, m, Ar, $CONH_2$), 5.89, 5.63 (2 × 1H, 2 pseudo t, *J* = 9.2, 9.2 Hz in each, H-2, H-3), 5.40 (1H, ddd, *J* = 10.5, 9.2, 5.5 Hz, H-4), 4.35–4.32 (2H, m, H-1, H-5eq), 3.90 (1H, pseudo t, *J* = 11.2, 10.5 Hz, H-5ax); ^{13}C NMR (DMSO-d_6) δ (ppm): 168.7 ($CONH_2$), 165.1, 164.8, 164.4 (C=O), 133.7–128.6 (Ar), 76.7, 73.2, 70.0, 69.3 (C-1–C-4), 65.3 (C-5). Anal. Calcd for $C_{27}H_{23}NO_8$ (489.47): C, 66.25; H, 4.74; N, 2.86. Found: C, 66.11; H, 4.83; N, 2.73.

3.9.2. Ethyl *C*-(2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl)formimidate (3)

C-(2,3,4-Tri-*O*-benzoyl-β-D-xylopyranosyl)formamide (**2**, 1.0 g, 2.04 mmol) and $Et_3O{\cdot}BF_4$ (1.16 g, 6.13 mmol, 3 equiv) were stirred in anhydrous CH_2Cl_2 (15 mL) at rt under Ar, and monitored by TLC (1:1 EtOAc–hexane). After completion of the reaction (24 h), the mixture was diluted with CH_2Cl_2 (50 mL), extracted with satd aq $NaHCO_3$ solution (40 mL) and then with water (40 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under diminished pressure. The pale yellow amorphous crude product (1.02 g, 96%) was used without further purification. R_f: 0.59 (1:1 EtOAc–hexane); ^{1}H NMR ($CDCl_3$) δ (ppm): 8.00–7.23 (16H, m, Ar, NH), 6.00, 5.59 (2 × 1H, 2 pseudo t, *J* = 9.2, 9.2 Hz in each, H-2, H-3), 5.46 (1H, ddd, *J* = 10.6, 9.2, 5.3 Hz, H-4), 4.53 (1H, dd, *J* = 11.2, 5.3 Hz, H-5eq), 4.14 (1H, d, *J* = 9.2 Hz, H-1), 4.12–3.92 (2H, m, CH_2), 3.71 (1H, pseudo t, *J* = 11.2, 10.6 Hz, H-5ax), 0.86 (3H, t, 7.3 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 167.5, 165.4, 165.1, 164.9 (C=O, C=NH), 133.2–128.0 (Ar), 75.1, 72.6, 70.3, 69.4 (C-1–C-4), 66.0 (C-5), 61.8 (CH_2), 13.2 (CH_3).

3.9.3. 2-(2′,3′,4′-Tri-*O*-benzoyl-β-D-xylopyranosyl)-benzimidazole (4)

Ethyl *C*-(2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl)formimidate (**3**, 0.15 g, 0.29 mmol) and *o*-phenylenediamine (63 mg, 0.58 mmol) were heated in anhydrous CH_2Cl_2 (3 mL) at reflux temperature, and the reaction was monitored by TLC (1:1 EtOAc–hexane). After completion of the reaction (5 h) the solvent was evaporated, and the residue was purified by column chromatography (2:3 EtOAc–hexane) to give 0.13 g (80%) pale yellow solid. Mp: 123–125 °C; $[\alpha]_D$ −96 (c 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 11.17 (1H, br s, NH), 7.97–7.17 (19H, m, Ar), 6.06, 5.85 (2 × 1H, 2 pseudo t, J = 9.4, 9.4 Hz in each, H-2′, H-3′), 5.42 (1H, ddd, J = 9.8, 9.4, 5.4 Hz, H-4′), 5.17 (1H, d, J = 9.4 Hz, H-1′), 4.42 (1H, dd, J = 11.3, 5.4 Hz, H-5′eq), 3.76 (1H, pseudo t, J = 11.3, 9.8 Hz, H-5′ax); ^{13}C NMR ($CDCl_3$) δ (ppm): 165.6, 165.4, 165.3 (C=O), 149.1 (C-2), 138.3 (C-3a, C-7a), 133.3–128.1 (Ar), 122.7 (C-5, C-6), 115.5 (C-4, C-7), 75.4, 73.2, 71.4, 69.7 (C-1′–C-4′), 67.0 (C-5′). Anal. Calcd for $C_{33}H_{26}N_2O_7$ (562.57): C, 70.45; H, 4.66; N, 4.98. Found: C, 70.51; H, 4.80; N, 4.76.

3.9.4. 2-(β-D-Xylopyranosyl)-benzimidazole (5)

From compound **4** (0.22 g, 0.39 mmol) according to General procedure **I** (Section 3.2). Reaction time: 1.5 h. Purified by column chromatography (85:15 $CHCl_3$–MeOH) to yield 79 mg (81%) white amorphous solid. R_f: 0.45 (7:3 $CHCl_3$–MeOH); $[\alpha]_D$ −18 (c 0.5, DMSO); ^{1}H NMR (DMSO-d_6) δ (ppm): 12.53 (1H, s, NH), 7.56–7.48 (2H, m, benzimidazole), 7.17–7.16 (2H, m, benzimidazole), 5.21–5.14 (3H, m, 3 × OH), 4.31 (1H, d, J = 9.2 Hz, H-1′), 3.87 (1H, dd, J = 11.2, 5.3 Hz, H-5′eq), 3.64 (1H, pseudo t, J = 9.2, 9.2 Hz, H-2′ or H-3′), 3.47 (1H, ddd, J = 10.6, 9.2, 5.3 Hz, H-4′), 3.31 (1H, pseudo t, J = 9.2, 9.2 Hz, H-2′ or H-3′), 3.26 (1H, pseudo t, J = 11.2, 10.6 Hz, H-5′ax); ^{13}C NMR (DMSO-d_6) δ (ppm): 152.4 (C-2), 142.5, 134.1 (C-3a, C-7a), 122.1, 121.1, 118.7, 111.3 (C-4–C-7), 78.0, 76.9, 72.8, 70.2 (C-1′–C-4′), 69.6 (C-5′). Anal. Calcd for $C_{12}H_{14}N_2O_4$ (250.25): C, 57.59; H, 5.64; N, 11.19. Found: C, 57.51; H, 5.79; N, 11.13.

3.9.5. *N*[1]-Tosyl-*C*-(3,4-di-*O*-benzoyl-2-deoxy-D-*threo*-pent-1-enopyranosyl)formamidrazone (6)

Ethyl *C*-(2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl)formimidate (**3**, 0.39 g, 0.76 mmol) and *p*-toluenesulfonylhydrazide (0.21 g, 1.13 mmol, 1.5 equiv) were dissolved in anhydrous CH_2Cl_2 (12 mL), stirred at rt and monitored by TLC (1:1 EtOAc–hexane). After completion of the reaction (3 days) the solvent was evaporated, and the residue was purified by column chromatography (4:7 EtOAc–hexane). The resulting pale yellow oil was crystallized from Et_2O to give 0.11 g (27%) white solid. Mp: 120–121 °C; $[\alpha]_D$ −120 (c 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 8.01–7.28 (14H, m, Ar), 5.97, 5.58–5–35 (5H, 3 br signals, H-2, H-3, H-4, NH_2), 4.54, 4.26 (2 × 1H, 2 br signals, H-5eq, H-5ax), 2.37 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 165.3, 165.0 (C=O), 154.5, 148.2, 144.1 (C-1, C=N, Ts-C-1) 134.5-128.3 (Ar), 97.9 (C-2), 67.2 (C-3 or C-4), 65.0 (C-5), 63.9 (C-3 or C-4), 21.5 (CH_3). MS-ESI (*m*/*z*): calcd for $C_{27}H_{26}N_3O_7S^+$ $[M+H]^+$: 536.15. Found: 536.42.

3.9.6. 5-(2′,3′,4′-Tri-*O*-benzoyl-β-D-xylopyranosyl)tetrazole (7)

2,3,4-Tri-*O*-benzoyl-β-D-xylopyranosyl cyanide[29] (**1**, 2.00 g, 4.24 mmol), $TMSN_3$ (2.23 mL, 16.96 mmol) and Bu_2SnO (0.10 g, 0.42 mmol) were dissolved in anhydrous toluene (60 mL) and heated at 80 °C overnight. Toluene was then removed under reduced pressure, and the residue was crystallized from MeOH to yield 1.98 g (91%) white solid. Mp: 176–177 °C; $[\alpha]_D$ −29 (c 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 14.73 (1H, br s, NH), 7.99–7.19 (15H, m, Ar), 6.08, 5.87 (2 × 1H, 2 pseudo t, J = 9.5, 9.4 Hz in each, H-2′, H-3′), 5.61 (1H, ddd, J = 10.8, 9.7, 5.7 Hz, H-4′), 5.26 (1H, d, J = 9.6 Hz, H-1′), 4.56 (1H, dd, J = 11.3, 5.3 Hz, H-5′eq), 3.80 (1H, pseudo t, J = 11.3, 10.8 Hz, H-5′ax); ^{13}C NMR ($CDCl_3$) δ (ppm): 165.9, 165.8, 165.5 (C=O), 152.3 (tetrazole C-5), 133.7-128.3 (Ar), 72.9, 72.2, 71.1, 69.7 (C-1′–C-4′), 67.4 (C-5′). Anal. Calcd for $C_{27}H_{22}N_4O_7$ (514.49): C, 63.03; H, 4.31; N, 10.89. Found: C, 62.99; H, 4.29; N, 10.90.

3.9.7. 4-Benzyl-3-phenyl-5-(2′,3′,4′-tri-*O*-benzoyl-β-D-xylopyranosyl)-1,2,4-triazole (11)

From tetrazole **7** (0.70 g, 1.36 mmol) and *N*-benzyl-benzamide (**8**, 0.86 g, 4.08 mmol) in toluene according to General procedure **II** (Section 3.3). Reaction time: 16 h. Purified by column chromatography (1:1 EtOAc–hexane) to yield 0.65 g (68%) white crystals. Mp: 230–231 °C; $[\alpha]_D$ −33 (c 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 7.96–7.05 (25H, m, Ar), 6.02, 5.92 (2 × 1H, 2 pseudo t, J = 9.4, 9.5 Hz in each, H-2′, H-3′), 5.49 (1H, d, J = 16.3 Hz, $PhCH_2$), 5.41 (1H, ddd, J = 9.8, 9.4, 5.3 Hz, H-4′), 5.33 (1H, d, J = 16.3 Hz, $PhCH_2$), 4.94 (1H, d, J = 9.6 Hz, H-1′), 4.46 (1H, dd, J = 11.1, 5.3 Hz, H-5′eq), 3.60 (1H, pseudo t, J = 11.1, 10.7 Hz, H-5′ax); ^{13}C NMR ($CDCl_3$) δ (ppm): 165.7, 165.4, 164.6 (C=O), 156.4, 150.2 (triazole C-3, C-5), 135.3–126.3 (Ar), 73.3, 73.3, 69.8, 69.7 (C-1′–C-4′), 67.2 (C-5′), 48.0 ($PhCH_2$). Anal. Calcd for $C_{41}H_{33}N_3O_7$ (679.72): C, 72.45; H, 4.89; N, 6.18. Found: C, 72.56; H, 4.94; N, 6.12.

3.9.8. 4-Benzyl-3-(4-*tert*-butylphenyl)-5-(2′,3′,4′-tri-*O*-benzoyl-β-D-xylopyranosyl)-1,2,4-triazole (12)

From tetrazole **7** (1.00 g, 1.94 mmol) and *N*-benzyl-4-*tert*-butylbenzamide (**9**, 1.56 g, 5.83 mmol) in *m*-xylene according to General procedure **II** (Section 3.3). Reaction time: 4 h. Purified by column chromatography (2:3 EtOAc–hexane) to yield 0.60 g (42%) white crystals. Mp: 234–236 °C; $[\alpha]_D$ −18 (c 0.52, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 7.96–7.07 (24H, m, Ar), 6.00, 5.90 (2 × 1H, 2 pseudo t, J = 9.4 Hz in each, H-2′, H-3′), 5.47 (1H, d, J = 16.5 Hz, $PhCH_2$), 5.41–5.33 (2H, m, H-4′, $PhCH_2$), 4.89 (1H, d, J = 9.7 Hz, H-1′), 4.44 (1H, dd, J = 11.2, 5.1 Hz, H-5′eq), 3.57 (1H, pseudo t, J = 11.2, 10.7 Hz, H-5′ax), 1.30 (9H, s, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ (ppm): 165.8, 165.4, 164.5 (C=O), 156.5, 153.4 (triazole C-3, C-5), 150.0, 135.5–123.7 (Ar), 73.4, 73.2, 69.8, 69.7 (C-1′–C-4′), 67.2 (C-5′), 48.0 ($PhCH_2$), 34.8 ($C(CH_3)_3$), 31.1 ($C(CH_3)_3$). Anal. Calcd for $C_{45}H_{41}N_3O_7$ (735.82): C, 73.45; H, 5.62; N, 5.71. Found: C, 73.50; H, 5.59; N, 5.67.

3.9.9. 4-Benzyl-3-(2-naphthyl)-5-(2′,3′,4′-tri-*O*-benzoyl-β-D-xylopyranosyl)-1,2,4-triazole (13)

From tetrazole **7** (1.00 g, 1.94 mmol) and *N*-benzyl-naphthalene-2-carboxamide (**10**, 1.52 g, 5.82 mmol) in *m*-xylene according to General procedure **II** (Section 3.3). Reaction time: 3 h. Purified by column chromatography (1:1 EtOAc–hexane) to yield 0.73 g (52%) white crystals. Mp: 226–227 °C; $[\alpha]_D$ −39 (c 0.47, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 7.97–7.08 (27H, m, Ar), 6.04, 5.95 (2 × 1H, 2 pseudo t, J = 9.5, 9.4 Hz in each, H-2′, H-3′), 5.55 (1H, d, J = 16.4 Hz, $PhCH_2$), 5.45–5.38 (2H, m, H-4′, $PhCH_2$), 5.00 (1H, d, J = 9.6 Hz, H-1′), 4.47 (1H, dd, J = 11.2, 5.3 Hz, H-5′eq), 3.62 (1H, pseudo t, J = 11.2, 10.7 Hz, H-5′ax); ^{13}C NMR ($CDCl_3$) δ (ppm): 165.7, 165.4, 164.7 (C=O), 156.5, 150.3 (triazole C-3, C-5), 135.3–123.8 (Ar), 73.3, 73.2, 69.9, 69.7 (C-1′–C-4′), 67.2 (C-5′), 48.2 ($PhCH_2$). Anal. Calcd for $C_{45}H_{35}N_3O_7$ (729.78): C, 74.06; H, 4.83; N, 5.76. Found: C, 74.11; H, 4.85; N, 5.72.

3.9.10. 4-Benzyl-3-phenyl-5-(β-D-xylopyranosyl)-1,2,4-triazole (14)

From compound **11** (0.44 g, 0.63 mmol) according to General procedure **I** (Section 3.2). Reaction time: 4 h. Purified by column chromatography (9:1 $CHCl_3$–MeOH) to yield 0.21 g (91%) white amorphous solid. R_f: 0.46 (4:1 $CHCl_3$–MeOH); $[\alpha]_D$ −15 (c 0.50, DMSO); ^{1}H NMR (DMSO-d_6) δ (ppm): 7.49–7.41 (5H, m, Ar), 7.23–7.22 (3H, m, Ar), 6.94 (2H, d, J = 6.3 Hz, Ar), 5.38 (1H, d, J = 19.2 Hz, $PhCH_2$), 5.32 (1H, d, J = 18.2 Hz, $PhCH_2$), 4.31 (1H, d, J = 9.6 Hz, H-1′), 3.86 (1H, pseudo t, J = 9.1, 8.9 Hz, H-2′ or H-3′), 3.73 (1H, dd, J = 10.7, 5.8 Hz, H-5′eq), 3.43 (1H, ddd, J = 10.6, 9.4, 5.8 Hz, H-4′), 3.26 (1H, pseudo t, J = 9.1, 8.7 Hz, H-2′ or H-3′), 3.16 (1H, pseudo t, J = 10.7, 10.6 Hz, H-5′ax); ^{13}C NMR (DMSO-d_6) δ (ppm): 154.8, 153.5 (triazole C-3, C-5), 136.2, 130.2, 129.0, 128.8, 128.7, 127.9, 127.3, 126.5 (Ar), 78.1, 73.3, 71.8, 69.5 (C-1′–C-4′), 70.2 (C-5′), 47.0 (PhCH$_2$). Anal. Calcd for $C_{20}H_{21}N_3O_4$ (367.40): C, 65.38; H, 5.76; N, 11.44. Found: C, 65.30; H, 5.78; N, 11.45.

3.9.11. 4-Benzyl-3-(4-*tert*-butylphenyl)-5-(β-D-xylopyranosyl)-1,2,4-triazole (15)

Triazole **12** (0.53 g, 0.63 mmol) was dissolved in anhydrous MeOH (4 mL), 1 M NaOH/MeOH (3 mL) was added and the mixture was refluxed for 1 h. The excess of NaOH was neutralized by AcOH. After evaporation the crude product was purified by column chromatography (9:1 $CHCl_3$–MeOH) to yield 0.19 g (63%) white amorphous solid. R_f: 0.56 (4:1 $CHCl_3$–MeOH); $[\alpha]_D$ −15.0 (*c* 0.50, DMSO); ^{1}H NMR (DMSO-d_6) δ (ppm): 7.42 (4H, m, Ar), 7.26–7.24 (3H, m, Ar), 6.96 (2H, d, *J* = 6.5 Hz, Ar), 5.37 (1H, d, *J* = 18.1 Hz, PhCH$_2$), 5.32 (1H, d, *J* = 17.8 Hz, PhCH$_2$), 4.23 (1H, d, *J* = 9.6 Hz, H-1′), 3.83 (1H, pseudo t, *J* = 9.1, 9.0 Hz, H-2′ or H-3′), 3.72 (1H, dd, *J* = 10.6, 4.7 Hz, H-5′eq), 3.40 (1H, ddd, *J* = 10.6, 9.1, 4.7 Hz, H-4′), 3.21 (1H, pseudo t, *J* = 8.7, 8.7 Hz, H-2′ or H-3′), 3.12 (1H, pseudo t, *J* = 10.7, 10.6 Hz, H-5′ax), 1.25 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR (DMSO-d_6) δ (ppm): 154.6, 153.3 (triazole C-3, C-5), 152.8, 136.2, 128.8, 128.4, 127.8, 126.3, 125.8, 124.4 (Ar), 78.0, 73.3, 71.7, 69.4 (C-1′–C-4′), 70.1 (C-5′), 46.8 (PhCH$_2$), 34.7 (*C*(CH$_3$)$_3$), 31.0 (C(*C*H$_3$)$_3$). Anal. Calcd for $C_{24}H_{29}N_3O_4$ (423.50): C, 68.06; H, 6.90; N, 9.92. Found: 68.19; H, 6.92; N, 9.91.

3.9.12. 4-Benzyl-3-(2-naphthyl)-5-(β-D-xylopyranosyl)-1,2,4-triazole (16)

From compound **13** (0.34 g, 0.47 mmol) according to General procedure **I** (Section 3.2). Reaction time: 3 h. Purified by column chromatography (9:1 $CHCl_3$–MeOH) to yield 0.15 g (76%) white amorphous solid. R_f: 0.40 (4:1 $CHCl_3$–MeOH); $[\alpha]_D$ −14 (*c* 0.50, DMSO); ^{1}H NMR (DMSO-d_6) δ (ppm): 8.04–6.97 (12H, m Ar), 5.49 (1H, d, *J* = 18.3 Hz, PhCH$_2$), 5.44 (1H, d, *J* = 18.3 Hz, PhCH$_2$), 4.39 (1H, d, *J* = 9.6 Hz, H-1′), 3.91 (1H, pseudo t, *J* = 9.1, 9.0 Hz, H-2′ or H-3′), 3.78 (1H, dd, *J* = 10.7, 4.8 Hz, H-5′eq), 3.45 (1H, ddd, *J* = 9.6, 9.0, 5.1 Hz, H-4′), 3.29 (1H, pseudo t, *J* = 8.8, 8.7 Hz, H-2′ or H-3′), 3.13 (1H, pseudo t, *J* = 10.8, 10.8 Hz, H-5′ax); ^{13}C NMR (DMSO-d_6) δ (ppm): 154.7, 153.8 (triazole C-3, C-5), 136.3–124.7 (Ar), 78.1, 73.4, 71.8, 69.5 (C-1′–C-4′), 70.2 (C-5′), 47.2 (PhCH$_2$). Anal. Calcd for $C_{24}H_{23}N_3O_4$ (417.46): C, 69.05; H, 5.55; N, 10.07. Found: C, 68.99; H, 5.49; N, 10.12.

3.9.13. 3-Phenyl-5-(β-D-xylopyranosyl)-1,2,4-triazole (17)

From compound **14** (0.20 g, 0.54 mmol) according to General procedure **III** (Section 3.4). Reaction time: 2 h. Purified by column chromatography (9:1 $CHCl_3$–MeOH) to yield 0.14 g (91%) white amorphous solid. R_f: 0.30 (4:1 $CHCl_3$–MeOH); $[\alpha]_D$ −24 (*c* 0.48, MeOH); ^{1}H NMR (CD$_3$OD) δ (ppm): 7.90 (2H, br s, Ar), 7.40 (3H, m, Ar), 4.37 (1H, d, *J* = 9.6 Hz, H-1′), 4.00 (1H, dd, *J* = 11.1, 5.3 Hz, H-5′eq), 3.80 (1H, br s, H-2′ or H-3′), 3.68 (1H, ddd, *J* = 10.1, 9.0, 5.3 Hz, H-4′), 3.49 (1H, pseudo t, *J* = 9.0, 9.0 Hz, H-2′ or H-3′), 3.36 (1H, pseudo t, *J* = 11.1, 10.8 Hz, H-5′ax); ^{13}C NMR (CD$_3$OD) δ (ppm): 163.0, 156.9 (triazole C-3, C-5), 131.1, 129.9, 127.5 (Ar), 79.5, 77.2, 74.2, 71.1 (C-1′–C-4′), 71.5 (C-5′). Anal. Calcd for $C_{13}H_{15}N_3O_4$ (277.28): C, 56.31; H, 5.45; N, 15.15. Found: C, 56.43; H, 5.49; N, 15.07.

3.9.14. 3-(4-*tert*-Butylphenyl)-5-(β-D-xylopyranosyl)-1,2,4-triazole (18)

From compound **15** (0.18 g, 0.43 mmol) according to General procedure **III** (Section 3.4). Reaction time: 2 h. Purified by column chromatography (9:1 $CHCl_3$–MeOH) to yield 0.11 g (77%) white amorphous solid. R_f: 0.43 (4:1 $CHCl_3$–MeOH); $[\alpha]_D$ −24 (*c* 0.49, MeOH); ^{1}H NMR (CD$_3$OD) δ (ppm): 7.88 (2H, d, *J* = 8.2 Hz, Ar), 7.47 (2H, d, *J* = 8.2 Hz, Ar), 4.38 (1H, d, *J* = 9.7 Hz, H-1′), 4.01 (1H, dd, *J* = 11.1, 5.3 Hz, H-5′eq), 3.83 (1H, pseudo t, *J* = 8.6, 8.3 Hz, H-2′ or H-3′), 3.68 (1H, ddd, *J* = 10.0, 9.2, 5.3 Hz, H-4′), 3.50 (1H, pseudo t, *J* = 9.0, 9.0 Hz, H-2′ or H-3′), 3.37 (1H, pseudo t, *J* = 11.1, 10.0 Hz, H-5′ax), 1.29 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR (CD$_3$OD) δ (ppm): 162.1, 158.4 (triazole C-3, C-5), 154.6, 127.4, 126.9 (Ar), 79.5, 77.3, 74.2, 71.1 (C-1′–C-4′), 71.5 (C-5′), 35.6 (*C*(CH$_3$)$_3$), 31.6 (C(*C*H$_3$)$_3$). Anal. Calcd for $C_{17}H_{23}N_3O_4$ (333.38): C, 61.25; H, 6.95; N, 12.60. Found: C, 61.20; H, 6.96; N, 12.54.

3.9.15. 3-(2-Naphthyl)-5-(β-D-xylopyranosyl)-1,2,4-triazole (19)

From compound **16** (0.14 g, 0.33 mmol) according to General procedure **III** (Section 3.4). Reaction time: 16 h. Purified by column chromatography (9:1 $CHCl_3$–MeOH) to yield 0.10 g (90%) white amorphous solid. R_f: 0.44 (4:1 $CHCl_3$–MeOH); $[\alpha]_D$ −22 (*c* 0.47, MeOH); ^{1}H NMR (CD$_3$OD) δ (ppm): 8.36 (1H, s, Ar), 7.93 (1H, d, *J* = 8.2 Hz, Ar), 7.78–7.69 (3H, m, Ar), 7.38–7.35 (2H, m, Ar), 4.40 (1H, d, *J* = 9.7 Hz, H-1′), 4.00 (1H, dd, *J* = 11.0, 5.3 Hz, H-5′eq), 3.84 (1H, pseudo t, *J* = 8.9, 8.7 Hz, H-2′ or H-3′), 3.71 (1H, ddd, *J* = 9.9, 9.5, 5.3 Hz, H-4′), 3.51 (1H, pseudo t, *J* = 8.9, 8.9 Hz, H-2′ or H-3′), 3.37 (1H, pseudo t, *J* = 11.0, 9.9 Hz, H-5′ax); ^{13}C NMR (CD$_3$OD) δ (ppm): 160.7, 159.0 (triazole C-3, C-5), 138.8, 135.3, 134.4, 129.7, 129.5, 128.7, 128.1, 127.7, 127.2, 124.5 (Ar), 79.5, 77.2, 74.3, 71.1 (C-1′–C-4′), 71.5 (C-5′). Anal. Calcd for $C_{17}H_{17}N_3O_4$ (327.33): C, 62.38; H, 5.23; N, 12.84. Found: C, 62.40; H, 5.19; N, 12.80.

3.9.16. *C*-(2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl)formaldehyde-tosylhydrazone (21)

To a vigorously stirred solution of pyridine (10 mL), AcOH (6 mL) and water (6 mL) an aqueous suspension of Raney-Ni (2.60 g) was added at rt. 2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl-cyanide[34] (**20**, 0.50 g, 1.75 mmol), *p*-toluenesulfonylhydrazide (0.39 g, 4.43 mmol) and NaH$_2$PO$_2$ (1.30 g, 15 mmol) were then added to the mixture. When the reaction was complete (TLC, 1:1 EtOAc–hexane) the insoluble materials were filtered off, and washed with EtOAc (40 mL). The organic layer of the filtrate was separated, washed with 10% aq HCl solution (3 × 10 mL), satd aq NaHCO$_3$ solution (3 × 10 mL), water (10 mL) and then dried over MgSO$_4$. The solution was concentrated under reduced pressure, the residue was purified by column chromatography (1:1 EtOAc–hexane) to give 0.50 g (63%) white crystals. Mp: 143–147 °C; $[\alpha]_D$ −14 (*c* 0.98, CHCl$_3$); ^{1}H NMR (CDCl$_3$) δ (ppm): 9.20 (1H, s, NH), 7.79 (2H, d, *J* = 8.1 Hz, Ph), 7.32 (2H, d, *J* = 8.0 Hz, Ph), 7.00 (1H, d, *J* = 6.4 Hz, CH), 5.25 (1H, pseudo t, *J* = 9.5, 9.5 Hz, H-2 or H-3), 4.98 (1H, ddd, *J* = 11.1, 9.6, 5.5 Hz, H-4), 4.92 (1H, pseudo t, *J* = 9.6, 9.6 Hz, H-2 or H-3), 4.10 (1H, dd, *J* = 11.1, 5.5 Hz, H-5eq), 3.90 (1H, dd, *J* = 9.7, 6.4 Hz, H-1), 3.32 (1H, pseudo t, *J* = 11.0, 10.9 Hz, H-5ax), 2.41 (3H, s, CH$_3$), 2.04 (6H, s, 2 × CH$_3$) 1.75, (3H, s, CH$_3$); ^{13}C NMR (CDCl$_3$) δ (ppm): 170.5, 170.1, 169.9 (C=O), 143.9 (CH=N), 135.1, 127.7, 129.5 (Ar), 77.9, 72.4, 69.5, 68.7 (C-1–C-4), 66.3 (C-5), 21.3, 20.5 (2 × CH$_3$), 20.1 (CH$_3$). Anal. Calcd for $C_{19}H_{24}N_2O_9S$ (456.47): C, 49.99; H, 5.30; N, 6.14. Found: C, 50.06; H, 5.38; N, 6.19.

3.9.17. 3,4,5-Tri-*O*-acetyl-2,6-anhydro-1-deoxy-D-*xylo*-hex-1-enitol (22)

In a flame-dried three-necked flask NaH (95%, 44 mg, 1.75 mmol) was added to anhydrous 1,4-dioxane. This stirred suspension was heated to reflux and a solution of **21** (200 mg, 0.44 mmol) in anhydrous 1,4-dioxane (13 mL) was added dropwise during 1.5 h. The reaction was refluxed until the complete disappearance of the starting material (TLC, 1:1 EtOAc–hexane). After cooling to rt the insoluble material was filtered off and washed with anhydrous 1,4-dioxane (10 mL). The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (1:1 EtOAc–hexane) to yield 118 mg (99%) white amorphous solid. R_f: 0.59 (1:1 EtOAc–hexane); $[\alpha]_D$ +8 (*c* 0.51, CHCl$_3$); ^{1}H NMR (CDCl$_3$) δ (ppm): 5.38 (1H, ddd, *J* = 8.0, <1 Hz, H-3), 5.11 (1H, pseudo t, J = 7.9, 7.8 Hz, H-4), 5.03 (1H, ddd, J = 8.4, 7.9, 4.8 Hz, H-5), 4.73 (1H, pseudo t, J = 1.5, 1.5 Hz, H-1a), 4.47 (1H, pseudo t, J = 1.5, 1.5 Hz, H-1b), 4.18 (1H, dd, J = 11.1, 4.8 Hz, H-6eq), 3.55 (1H, dd, J = 11.1, 8.4 Hz, H-6ax), 2.04 (3H, s, CH_3), 2.09 (6H, s, 2 × CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 169.7 (2), 169.2 (C=O), 153.5 (C-2), 95.9 (C-1), 72.1, 68.7 (2) (C-3–C-5), 66.9 (C-6), 20.7 (3 × CH_3). Anal. Calcd for $C_{12}H_{16}O_7$ (272.25): C, 52.94; H, 5.92. Found: C, 53.07; H, 5.99.

3.9.18. (1′R)-2′,3′,4′-Tri-O-acetyl-1′,5′-anhydro-D-xylitol-spiro[1′,5]-3-phenyl-4,5-dihydro-isoxazole (23)

From compound **22** (100 mg, 0.37 mmol) and benzaldoxime (222 mg, 1.85 mmol) according to General procedure **IV** (Section 3.5) to yield 105 mg (74%) white amorphous solid. R_f: 0.38 (1:2 EtOAc–hexane); $[\alpha]_D$ +34 (c 0.79, $CHCl_3$); ^1H NMR ($CDCl_3$) δ (ppm): 7.59–7.19 (5H, m, Ar), 5.49 (1H, pseudo t, J = 10.6, 9.2 Hz, H-3′), 5.29 (1H, d, J = 10.6 Hz, H-2′), 5.00 (1H, ddd, J = 10.6, 9.2, 6.6 Hz, H-4′), 3.92–3.78 (2H, m, H-5′ax, H-5′eq), 3.25 (2H, br s, CH_2), 1.98 (9H, m, 3 × CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 170.3, 169.9, 169.7 (C=O), 157.7 (C=N), 130.8, 128.8, 128.3, 126.8 (Ar), 107.0 (C-1′), 71.1, 69.4, 68.9 (C-2′–C-4′), 60.2 (C-5′), 43.2 (CH_2), 20.6 (3 × CH_3). Anal. Calcd for $C_{19}H_{21}NO_8$ (391.38): C, 58.31; H, 5.41; N, 3.58. Found: C, 58.42; H, 5.54; N, 3.62.

3.9.19. (1′R)-2′,3′,4′-Tri-O-acetyl-1′,5′-anhydro-D-xylitol-spiro[1′,5]-3-(4-*tert*-butylphenyl)-4,5-dihydro-isoxazole (24)

From compound **22** (100 mg, 0.37 mmol) and 4-*tert*-butylbenzaldoxime (327 mg, 1.85 mmol) according to General procedure **IV** (Section 3.5) to yield 110 mg (67%) white amorphous solid. R_f: 0.54 (1:2 EtOAc–hexane); $[\alpha]_D$ +29 (c 1.95, $CHCl_3$); ^1H NMR ($CDCl_3$) δ (ppm): 7.59 (2H, d, J = 8.5 Hz, Ar), 7.44 (2H, d, J = 8.5 Hz, Ar), 5.56 (1H, pseudo t, J = 9.9, 9.8 Hz, H-3′), 5.36 (1H, d, J = 10.1 Hz, H-2′), 5.08 (1H, ddd, J = 10.5, 9.8, 6.2 Hz, H-4′), 3.96 (1H, pseudo t, J = 11.0, 10.9 Hz, H-5′ax), 3.73 (1H, dd, J = 11.2, 6.2 Hz, H-5′eq), 3.31 (2H, s, CH_2), 2.06–2.04 (9H, m, 3 × CH_3), 1.33 (9H, s, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ (ppm): 170.3, 170.0, 169.7 (C=O), 157.5 (C=N), 125.5, 125.8, 126.6, 154.3 (Ar), 106.9 (C-1′), 71.1, 69.4, 68.9 (C-2′–C-4′), 60.2 (C-5′), 43.4 (CH_2), 34.9 ($C(CH_3)_3$), 31.1 ($C(CH_3)_3$), 20.6 (3 × CH_3). Anal. Calcd for $C_{23}H_{29}NO_8$ (447.48): C, 61.73; H, 6.53; N, 3.13. Found: C, 61.80; H, 6.61; N, 3.24.

3.9.20. (1′R)-2′,3′,4′-Tri-O-acetyl-1′,5′-anhydro-D-xylitol-spiro[1′,5]-3-(4-trifluoromethylphenyl)-4,5-dihydro-isoxazole (25)

From compound **22** (100 mg, 0.37 mmol) and 4-(trifluoromethyl)benzaldoxime (327 mg, 1.85 mmol) according to General procedure **IV** (Section 3.5) to yield 96 mg (57%) white amorphous solid. R_f: 0.49 (1:2 EtOAc–hexane); $[\alpha]_D$ +29 (c 2.07, $CHCl_3$); ^1H NMR ($CDCl_3$) δ (ppm): 7.79–7.67 (4H, m, Ar) 5.58 (1H, pseudo t, J = 9.8, 9.8 Hz, H-3′), 5.38 (1H, d, J = 10.1 Hz, H-2′), 5.09 (1H, ddd, J = 10.0, 9.8, 6.5 Hz, H-4′), 3.96 (1H, pseudo t, J = 11.1, 11.0 Hz, H-5′ax), 3.91 (1H, dd, J = 11.2, 6.5 Hz, H-5′eq), 3.34 (2H, s, CH_2), 2.07–2.05 (9H, m, 3 × CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 170.3, 170.0, 169.7 (C=O), 156.7 (C=N), 131.8, 127.1, 125.8 (Ar), 123.5 (q, $^1J_{(C,F)}$ = 271.3, CF_3), 107.5 (C-1′), 70.9, 69.4, 68.8 (C-2′–C-4′), 60.3 (C-5′), 42.6 (CH_2), 20.6 (3 × CH_3). Anal. Calcd for $C_{20}H_{20}F_3NO_8$ (459.37): C, 52.29; H, 4.39; N, 3.05. Found: C, 52.21; H, 4.52; N, 2.96.

3.9.21. (1′R)-2′,3′,4′-Tri-O-acetyl-1′,5′-anhydro-D-xylitol-spiro[1′,5]-3-(1-naphthyl)-4,5-dihydro-isoxazole (26)

From compound **22** (100 mg, 0.37 mmol) and 1-naphthaldoxime (316 mg, 1.85 mmol) according to General procedure **IV** (Section 3.5) to yield 100 mg (60%) white amorphous solid. R_f: 0.40 (1:2 EtOAc–hexane); $[\alpha]_D$ +46 (c 0.81, $CHCl_3$); ^1H NMR ($CDCl_3$) δ (ppm): 8.98–7.45 (7H, m, Ar), 5.63 (1H, pseudo t, J = 9.9, 9.8 Hz, H-3′), 5.42 (1H, d, J = 10.1 Hz, H-2′), 5.12 (1H, ddd, J = 10.2, 9.8, 6.2 Hz, H-4′), 4.04 (1H, pseudo t, J = 11.0, 10.9 Hz, H-5′ax), 3.93 (1H, dd, 1H, J = 11.0, 6.1 Hz, H-5′eq), 3.53 (2H, s, CH_2), 2.07–2.06 (9H, m, 3 × CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 170.3, 170.0, 169.8 (C=O), 158.5 (C=N), 133.9–124.7 (Ar), 106.0 (C-1′), 71.2, 69.4, 69.0 (C-2′–C-4′), 60.3 (C-5′), 46.1 (CH_2), 20.7 (3 × CH_3). Anal. Calcd for $C_{23}H_{23}NO_8$ (441.44): C, 62.58; H, 5.25; N, 3.17. Found: C, 62.66; H, 5.31; N, 3.23.

3.9.22. (1′R)-2,3,4-Tri-O-acetyl-1′,5′-anhydro-D-xylitol-spiro[1′,5]-3-(2-naphthyl)-4,5-dihydro-isoxazole (27)

From compound **22** (100 mg, 0.37 mmol) and 2-naphthaldoxime (316 mg, 1.85 mmol) according to General procedure **IV** (Section 3.5) to yield 71 mg (44%) white amorphous solid. R_f: 0.42 (1:2 EtOAc–hexane); $[\alpha]_D$ +12 (c 0.86, $CHCl_3$); ^1H NMR ($CDCl_3$) δ (ppm): 7.98–7.46 (7H, m, Ar), 5.61 (1H, pseudo t, J = 9.9, 9.8 Hz, H-3′), 5.41 (1H, d, J = 10.1 Hz, H-2′), 5.12 (1H, ddd, J = 10.3, 6.2 Hz, H-4′), 4.00 (1H, pseudo t, J = 11.0, 10.9 Hz, H-5′ax), 3.90 (1H, dd, J = 11.1, 6.1 Hz, H-5′eq), 3.45 (2H, br s, CH_2), 2.06–2.05 (9H, m, 3 × CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 170.3, 169.9, 169.7 (C=O), 157.8 (C=N), 134.2–123.0 (Ar), 107.1 (C-1′), 71.1, 69.4, 68.9 (C-2′–C-4′), 60.2 (C-5′), 43.2 (CH_2), 20.6 (3 × CH_3). Anal. Calcd for $C_{23}H_{23}NO_8$ (441.44): C, 62.58; H, 5.25; N, 3.17. Found: C, 62.51; H, 5.19; N, 3.26.

3.9.23. (1′R)-2′,3′,4′-Tri-O-acetyl-1′,5′-anhydro-D-xylitol-spiro[1′,5]-3-(2-benzothiazolyl)-4,5-dihydro-isoxazole (28)

From compound **22** (100 mg, 0.37 mmol) and benzothiazole-2-carbaldoxime (329 mg, 1.85 mmol) according to General procedure **IV** (Section 3.5) to yield 117 mg (71%) yellow amorphous solid. R_f: 0.40 (1:2 EtOAc–hexane); $[\alpha]_D$ +1 (c 1.83, $CHCl_3$); ^1H NMR ($CDCl_3$) δ (ppm): 8.05–7.45 (4H, m, Ar), 5.59 (1H, pseudo t, J = 9.8, 9.8 Hz, H-3′), 5.43 (1H, d, J = 10.1 Hz, H-2′), 5.17–5.09 (1H, m, H-4′), 3.98–3.95 (2H, m, H-5′ax, H-5′eq), 3.63 (1H, d, J = 18.4 Hz, CH_2a), 3.56 (1H, d, J = 18.5 Hz, CH_2b), 2.07–2.06, (9H, m, 3 × CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 169.8, 169.7, 169.6 (C=O), 156.4, 155.5, 152.7 (C=N, C—N), 126.7, 126.5, 123.7, 121.7 (Ar), 108.3, (C-1′), 68.5, 69.1, 70.8 (C-2′–C-4′), 60.4 (C-5′), 42.6 (CH_2), 20.4 (3 × CH_3). Anal. Calcd for $C_{20}H_{20}N_2O_8S$ (448.45): C, 53.57; H, 4.50; N, 6.25. Found: C, 53.63; H, 4.57; N, 6.31.

3.9.24. (1′R)-1′,5′-Anhydro-D-xylitol-spiro[1′,5]-3-phenyl-4,5-dihydro-isoxazole (29)

From compound **23** (100 mg, 0.26 mmol) according to General procedure **I** (Section 3.2). The crude product was crystallized from EtOH to yield 61 mg (90%) white crystals. Mp: 180–183 °C; $[\alpha]_D$ +70 (c 0.90, MeOH); ^1H NMR (CD_3OD) δ (ppm): 7.69–7.67 (2H, m, Ph), 7.44–7.43 (3H, m, Ph), 3.76–3.56 (6H, m, H-2′, H-3′, H-4′, H-5′ax, H-5′eq, CH_2a), 3.25 (1H, d, J = 17.7 Hz, CH_2b); ^{13}C NMR (CD_3OD) δ (ppm): 159.8 (C=N), 131.7, 130.3, 130.0, 127.8 (Ar), 110.9 (C-1′), 76.4, 73.0, 71.2 (C-2′–C-4′), 64.9 (C-5′), 44.2 (CH_2). Anal. Calcd for $C_{13}H_{15}NO_5$ (265.26): C, 58.86; H, 5.70; N, 5.28. Found: C, 58.92; H, 5.59; N, 5.21.

3.9.25. (1′R)-1′,5′-Anhydro-D-xylitol-spiro[1′,5]-3-(4-*tert*-butylphenyl)-4,5-dihydro-isoxazole (30)

From compound **24** (100 mg, 0.23 mmol) according to General procedure **I** (Section 3.2). The crude product was crystallized from EtOH to yield 69 mg (98%) white crystals. Mp: 238–242 °C; $[\alpha]_D$ +63 (c 2.50, DMSO); ^1H NMR (DMSO-d_6) δ (ppm): 7.59 (2H, d, J = 7.9 Hz, Ar), 7.46 (2H, d, J = 8.0 Hz, Ar), 5.33 (1H, br s, OH), 5.08 (2H, m, 2 × OH), 3.58 (1H, d, J = 17.8 Hz, CH_2a), 3.53–3.36 (5H, m, H-2′, H-3′, H-4′, H-5′ax, H-5′eq), 3.18 (1H, d, J = 17.7 Hz, CH_2b), 1.28 (9H, s, $C(CH_3)_3$); ^{13}C NMR (DMSO-d_6) δ (ppm): 157.0 (C=N), 153.0, 126.3, 125.6 (Ar), 109.6 (C-1′), 74.4, 71.4, 69.6

(C-2′–C-4′), 63.7 (C-5′), 42.7 (CH_2), 34.5 ($C(CH_3)_3$), 30.8 ($C(CH_3)_3$). Anal. Calcd for $C_{17}H_{23}NO_5$ (321.37): C, 63.54; H, 7.21; N, 4.36. Found: C, 63.61; H, 7.10; N, 4.42.

3.9.26. (1′*R*)-1′,5′-Anhydro-D-xylitol-spiro[1′,5]-3-(4-trifluoromethylphenyl)-4,5-dihydro-isoxazole (31)

From compound **25** (100 mg, 0.23 mmol) according to General procedure **I** (Section 3.2). The crude product was crystallized from EtOH to yield 66 mg (91%) white crystals. Mp: 197–198 °C; $[\alpha]_D$ +47 (*c* 0.36, MeOH); ^{1}H NMR (CD_3OD) δ (ppm): 7.79–7.62 (4H, m, Ar), 3.71–3.49 (7H, m, H-2′, H-3′, H-4′, H-5′ax, H-5′eq, CH_2);^{13}C NMR (CD_3OD) δ (ppm): 158.4 (C═N), 134.2, 128.3, 126.7 (Ar), 111.5 (C-1′), 76.3, 73.1, 71.1 (C-2′–C-4′), 65.0 (C-5′), 43.8 (CH_2). Anal. Calcd for $C_{14}H_{14}F_3NO_5$ (333.26): C, 50.46; H, 4.23; N, 4.20. Found: C, 50.39; H, 4.33; N, 4.26.

3.9.27. (1′*R*)-1′,5′-Anhydro-D-xylitol-spiro[1′,5]-3-(1-naphthyl)-4,5-dihydro-isoxazole (32)

From compound **26** (100 mg, 0.23 mmol) according to General procedure **I** (Section 3.2). The crude product was crystallized from EtOH to yield 57 mg (79%) white crystals. Mp: 179–180 °C; $[\alpha]_D$ +66 (*c* 0.95, MeOH); ^{1}H NMR (CD_3OD) δ (ppm): 8.73–8.71 (1H, m, Ar), 7.81–7.79 (2H, m, Ar), 7.48–7.36 (4H, m, Ar), 3.82 (1H, d, *J* = 17.6 Hz, CH_2a), 3.76–3.56 (6H, m, H-2′, H-3′, H-4′, H-5′ax, H-5′eq, CH_2b); ^{13}C NMR (CD_3OD) δ (ppm): 160.3 (C═N), 135.4–126.1 (Ar), 109.9 (C-1′), 76.5, 73.0, 71.3 (C-2′–C-4′), 65.0 (C-5′), 47.2 (CH_2). Anal. Calcd for $C_{17}H_{17}NO_5$ (315.32): C, 64.75; H, 5.43; N, 4.44. Found: C, 64.89; H, 5.37; N, 4.39.

3.9.28. (1′*R*)-1′,5′-Anhydro-D-xylitol-spiro[1′,5]-3-(2-naphthyl)-4,5-dihydro-isoxazole (33)

From compound **27** (100 mg, 0.23 mmol) according to General procedure **I** (Section 3.2). The crude product was crystallized from EtOH to yield 61 mg (85%) white crystals. Mp: 191–194 °C; $[\alpha]_D$ +44 (*c* 1.07, DMSO); ^{1}H NMR (DMSO-d_6) δ (ppm): 8.14–7.58 (7H, m, Ar), 5.41 (1H, br s, OH), 5.14–5.11 (2H, m, 2 × OH), 3.73 (1H, d, *J* = 17.6 Hz, CH_2a), 3.56–3.38 (6H, m, H-2′, H-3′, H-4′, H-5′ax, H-5′eq, CH_2b); ^{13}C NMR (DMSO-d_6) δ (ppm): 157.4 (C═N), 133.5–122.8 (Ar), 109.9 (C-1′), 74.4, 71.5, 69.5 (C-2′–C-4′), 63.8 (C-5′), 42.6 (CH_2). Anal. Calcd for $C_{17}H_{17}NO_5$ (315.32): C, 64.75; H, 5.43; N, 4.44. Found: C, 64.89; H, 5.42; N, 4.36.

3.9.29. (1′*R*)-1′,5′-Anhydro-D-xylitol-spiro[1′,5]-3-(2-benzothiazolyl)-4,5-dihydro-isoxazole (34)

From compound **28** (100 mg, 0.23 mmol) according to General procedure **I** (Section 3.2). The crude product was crystallized from EtOH to yield 47 mg (65%) white crystals. Mp: 225–230 °C; $[\alpha]_D$ +47 (*c* 1.15, MeOH); ^{1}H NMR (CD_3OD) δ (ppm): 7.88–7.73 (2H, m, Ar), 7.46–7.33 (2H, m, Ar), 3.79–3.67 (7H, m, H-2′, H-3′, H-4′, H-5′ax, H-5′eq, CH_2);^{13}C NMR (CD_3OD) δ (ppm): 158.5, 156.7, 153.0 (C═N, C—N), 135.3, 128.3, 128.0, 124.0, 123.0 (Ar), 112.5 (C-1′), 75.7, 72.5, 70.4 (C-2′–C-4′), 64.9 (C-5′), 43.3 (CH_2). Anal. Calcd for $C_{14}H_{14}N_2O_5S$ (322.33): C, 52.17; H, 4.38; N, 8.69. Found: C, 52.25; H, 4.45; N, 8.75.

3.9.30. 2,3,4-Tri-*O*-acetyl-1-*S*-(*Z*)-benzhydroximoyl-1-thio-β-D-xylopyranose (36)

A: From compound **35** (1.61 g, 5.51 mmol) and *N*-hydroxy-benzenecarboximidoyl chloride (1.29 g, 8.27 mmol) according to General procedure **V** (Section 3.6). Yield: 1.43 g (63%).

B: From compound **35** (1.00 g, 3.42 mmol) and benzaldoxime (0.62 g, 5.14 mmol) according to General procedure **VI** (Section 3.7). Yield: 0.88 g (62%), white crystals. Mp: 165–168 °C; $[\alpha]_D$ +14 (*c* 0.46, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 9.10 (1H, s, OH), 7.52–7.40 (5H, m, Ar), 5.02–4.97 (2H, m, H-2, H-3), 4.86 (1H, ddd, *J* = 8.7, 8.3, 4.9 Hz, H-4), 4.60 (1H, strongly coupled m, H-1), 4.06 (1H, dd, *J* = 11.8, 4.9 Hz, H-5eq), 2.88 (1H, dd, *J* = 11.8, 8.7 Hz, H-5ax), 2.04, 2.03, 1.98 (3 × 3H, 3 s, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 169.9, 169.7, 169.3 (C═O), 152.5 (C═N), 132.3, 130.0, 128.9, 128.5 (Ar), 81.8 (C-1), 71.7, 69.8, 68.1 (C-2–C-4), 64.9 (C-5), 20.6 (3 × CH_3). Anal. Calcd for $C_{18}H_{21}NO_8S$ (411.43): C, 52.55; H, 5.14; N, 3.40. Found: C, 52.39; H, 5.17; N, 3.49.

3.9.31. 2,3,4-Tri-*O*-acetyl-1-*S*-(*Z*)-1-naphthhydroximoyl-1-thio-β-D-xylopyranose (37)

A: From compound **35** (0.93 g, 3.17 mmol) and *N*-hydroxy-1-naphthalenecarboximidoyl chloride (0.98 g, 4.75 mmol) according to General procedure **V** (Section 3.6). Yield: 1.22 g (83%).

B: From compound **35** (1.50 g, 5.14 mmol) and 1-naphthaldoxime (1.32 g, 7.71 mmol) according to General procedure **VI** (Section 3.7). Yield: 1.62 g (68%), white amorphous solid. R_f: 0.57 (1:1 EtOAc–hexane); $[\alpha]_D$ +22 (*c* 0.52, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 9.24 (1H, br s, OH), 7.98–7.51 (7H, m, Ar), 4.91 (1H, pseudo t, *J* = 8.6, 8.4 Hz, H-2 or H-3), 4.78–4.69 (2H, m, H-2 or H-3, H-4), 4.03 (1H, d, *J* = 8.6 Hz, H-1), 3.66 (1H, dd, *J* = 11.9, 4.6 Hz, H-5eq), 2.23 (1H, dd, *J* = 11.9, 8.7 Hz, H-5ax), 1.97, 1.94, 1.89 (3 × 3H, 3 s, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 169.9, 169.6, 169.1 (C═O), 152.5 (C═N), 133.2, 131.8, 130.3, 128.7, 128.2, 126.9, 126.6, 125.1, 124.7 (Ar), 81.4 (C-1), 71.9, 69.2, 68.1 (C-2–C-4), 64.7 (C-5), 20.6 (3 × CH_3). Anal. Calcd for $C_{22}H_{23}NO_8S$ (461.48): C, 57.26; H, 5.02; N, 3.04. Found: C, 57.32; H, 5.14; N, 2.93.

3.9.32. 2,3,4-Tri-*O*-acetyl-1-*S*-(*Z*)-2-naphthhydroximoyl-1-thio-β-D-xylopyranose (38)

A: From compound **35** (0.86 g, 2.96 mmol) and *N*-hydroxy-2-naphthalenecarboximidoyl chloride (0.91 g, 4.43 mmol) according to General procedure **V** (Section 3.6). Yield: 1.23 g (91%).

B: From compound **35** (1.71 g, 5.84 mmol) 2-naphthaldoxime (1.50 g, 8.76 mmol) according to General procedure **VI** (Section 3.7). Yield: 2.10 g (77%), white crystals. Mp: 169–172 °C; $[\alpha]_D$ +17 (*c* 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 9.09 (1H, s, OH), 8.06–7.52 (7H, m, Ar), 5.04, 4.97 (2 × 1H, 2 pseudo t, *J* = 8.0, 8.0 Hz in each, H-2, H-3), 4.87 (1H, ddd, *J* = 8.6, 8.0, 4.9 Hz, H-4), 4.70 (1H, d, *J* = 8.0 Hz, H-1), 4.08 (1H, dd, *J* = 11.7, 4.9 Hz, H-5eq), 2.88 (1H, dd, *J* = 11.7, 8.6 Hz, H-5ax), 2.05, 2.03, 1.95 (3 × 3H, 3 s, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 169.8, 169.7, 169.3 (C═O), 152.4 (C═N), 133.8, 132.7, 129.8, 129.0, 128.5, 128.2, 127.7, 127.3, 126.7, 125.5 (Ar), 81.8 (C-1), 71.5, 69.8, 68.1 (C-2–C-4), 64.8 (C-5), 20.7 (3 × CH_3). Anal. Calcd for $C_{22}H_{23}NO_8S$ (461.48): C, 57.26; H, 5.02; N, 3.04. Found: C, 57.34; H, 4.89; N, 3.10.

3.9.33. 1-*S*-(*Z*)-Benzhydroximoyl-1-thio-β-D-xylopyranose (39)

From compound **36** (0.20 g, 0.49 mmol) according to General procedure **I** (Section 3.2). Purified by column chromatography (9:1 $CHCl_3$–MeOH) to yield 0.12 g (89%) white solid. Mp: 174–178 °C; $[\alpha]_D$ −5 (*c* 0.50, DMSO); ^{1}H NMR (DMSO-d_6) δ (ppm): 7.44–7.43 (5H, m, Ar), 5.41, 5.12, 4.90 (3 × 1H, 3 d, OH), 4.12 (1H, d, *J* = 9.2 Hz, H-1), 3.57 (1H, dd, *J* = 11.2, 4.9 Hz, H-5eq), 3.23 (1H, m, H-4), 3.07, 2.91 (2 × 1H, 2 m, H-2, H-3), 2.38 (1H, pseudo t, *J* = 11.2, 9.9 Hz, H-5ax); ^{13}C NMR (DMSO-d_6) δ (ppm): 151.1 (C═N), 133.6, 129.0, 128.5, 128.0 (Ar), 84.2 (C-1), 77.6, 72.5, 69.1 (C-2–C-4), 68.9 (C-5). Anal. Calcd for $C_{12}H_{15}NO_5S$ (285.32): C, 50.52; H, 5.30; N, 4.91. Found: 50.46; H, 5.52; N, 4.87.

3.9.34. 1-*S*-(*Z*)-1-Naphthhydroximoyl-1-thio-β-D-xylopyranose (40)

From compound **37** (0.20 g, 0.43 mmol) according to General procedure **I** (Section 3.2). Purified by column chromatography (9:1 $CHCl_3$–MeOH) to yield 0.14 g (98%) brownish solid. Mp: 198–202 °C; $[\alpha]_D$ +16 (*c* 0.53, DMSO); ^{1}H NMR (CD_3OD) δ (ppm): 8.04–7.51 (7H, m, Ar), 3.72 (1H, d, *J* = 9.7 Hz, H-1), 3.31–3.25 (2H, m, H-4, H-5eq), 3.20 (1H, pseudo t, *J* = 9.7, 8.7 Hz, H-2 or H-3), 2.83 (1H, pseudo t, *J* = 8.7, 8.3 Hz, H-2 or H-3), 1.91 (1H, strongly coupled m, H-5ax); ^{13}C NMR (CD_3OD) δ (ppm): 154.1 (C=N), 134.7, 133.5, 131.3, 130.9, 129.5, 129.1, 127.7, 127.4, 126.8, 125.8 (Ar), 85.6 (C-1), 79.2, 73.5, 70.6 (C-2–C-4), 69.9 (C-5). Anal. Calcd for $C_{16}H_{17}NO_5S$ (335.37): C, 57.30; H, 5.11; N, 4.18. Found: C, 57.34; H, 5.26; N, 4.09.

3.9.35. 1-*S*-(*Z*)-2-Naphthhydroximoyl-1-thio-β-D-xylopyranose (41)

From compound **38** (0.20 g, 0.43 mmol) according to General procedure **I** (Section 3.2). Purified by column chromatography (9:1 $CHCl_3$–MeOH) to yield 0.13 g (92%) pale yellow solid. Mp: 185–188 °C; $[\alpha]_D$ +1 (*c* 0.46, DMSO); ^{1}H NMR (CD_3OD) δ (ppm): 8.05–7.51 (7H, m, Ar), 4.26 (1H, d, *J* = 9.7 Hz, H-1), 3.68 (1H, dd, *J* = 11.7, 5.3 Hz, H-5eq), 3.41 (1H, ddd, *J* = 10.2, 8.7, 5.3 Hz, H-4), 3.29 (1H, pseudo t, *J* = 9.7, 8.7 Hz, H-2 or H-3), 3.04 (1H, t, *J* = 8.7 Hz, H-2 or H-3), 2.43 (1H, pseudo t, *J* = 11.2, 10.2 Hz, H-5ax); ^{13}C NMR (CD_3OD) δ (ppm): 154.1 (C=N), 135.0, 134.1, 132.3, 130.0, 129.4, 128.8, 128.1, 127.7, 127.3 (Ar), 85.9 (C-1), 79.2, 74.1, 70.6 (C-2 – C-4), 70.3 (C-5). Anal. Calcd for $C_{16}H_{17}NO_5S$ (335.37): C, 57.30; H, 5.11; N, 4.18. Found: C, 57.40; H, 5.03; N, 4.27.

3.9.36. (1′*R*)-2′,3′,4′-Tri-*O*-acetyl-1′,5′-anhydro-D-xylitol-spiro[1′,5]-3-phenyl-1,4,2-oxathiazole (42) and (1′*S*)-2′,3′,4′-tri-*O*-acetyl-1′,5′-anhydro-D-xylitol-spiro[1′,5]-3-phenyl-1,4,2-oxathiazole (45)

From compound **36** (1.00 g, 2.43 mmol) according to General procedure **VII** (Section 3.8). Purified by column chromatography (1:4 EtOAc–hexane) to give **45** as the first and **42** as the second fraction.

*Compound **42**:* Yield: 310 mg (31%), white solid. Mp: 158–161 °C; $[\alpha]_D$ +178 (*c* 1.68, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 7.70–7.41 (7H, m, Ar), 5.52 (1H, d, *J* = 8.7 Hz, H-2′), 5.13 (1H, pseudo t, *J* = 8.7, 8.3 Hz, H-3′), 5.07 (1H, ddd, *J* = 8.7, 8.3, 4.9 Hz, H-4′), 4.19 (1H, dd, *J* = 12.1, 4.9 Hz, H-5′eq), 3.79 (1H, dd, *J* = 12.1, 8.7 Hz, H-5′ax), 2.08 (2), 2.07 (9H, 2 s, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 169.4 (2), 168.4 (C=O), 155.5 (C=N), 131.4, 128.8, 127.7, 127.1 (Ar), 126.6 (C-1′), 71.7, 68.3, 67.3 (C-2′–C-4′), 61.1 (C-5′), 20.4 (3 × CH_3). Anal. Calcd for $C_{18}H_{19}NO_8S$ (409.41): C, 52.81; H, 4.68; N, 3.42. Found: C, 52.96; H, 4.64; N, 3.33.

*Compound **45**:* Yield: 71 mg (7%), pale yellow solid. Mp: 122–124 °C; $[\alpha]_D$ +78 (*c* 0.26, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 7.67–7.41 (5H, m, Ar), 5.62 (1H, pseudo t, *J* = 9.8, 9.2 Hz, H-3′), 5.56 (1H, d, *J* = 9.8 Hz, H-2′), 5.12 (1H, ddd, *J* = 9.7, 9.2, 6.8 Hz, H-4′), 4.04 (1H, pseudo t, *J* = 11.2, 9.7 Hz, H-5′ax), 4.00 (1H, dd, *J* = 11.2, 6.8 Hz, H-5′eq), 2.08, 2.07, 2.06 (3 × 3H, 3 s, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 169.7, 169.4 (2) (C=O), 156.2 (C=N), 131.5, 128.9, 127.9, 127.0 (Ar), 122.6 (C-1′), 70.4, 68.4, 68.1 (C-2′–C-4′), 61.2 (C-5′), 20.5 (3 × CH_3). Anal. Calcd for $C_{18}H_{19}NO_8S$ (409.41): C, 52.81; H, 4.68; N, 3.45. Found: C, 52.63; H, 4.75; N, 3.57.

3.9.37. (1′*R*)-2′,3′,4′-Tri-*O*-acetyl-1′,5′-anhydro-D-xylitol-spiro[1′,5]-3-(1-naphthyl)-1,4,2-oxathiazole (43) and (1′*S*)-2′,3′,4′-tri-*O*-acetyl-1′,5′-anhydro-D-xylitol-spiro[1′,5]-3-(1-naphthyl)-1,4,2-oxathiazole (46)

From compound **37** (1.00 g, 2.17 mmol) according to General procedure **VII** (Section 3.8). Purified by column chromatography (1:4 EtOAc–hexane) to give **46** as the first and **43** as the second fraction.

*Compound **43**:* Yield: 233 mg (23%), pale yellow solid. Mp: 153–156 °C; $[\alpha]_D$ +151 (*c* 1.18, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 8.61–7.47 (7H, m, Ar), 5.58 (1H, d, *J* = 8.3 Hz, H-2′), 5.15 (1H, pseudo t, *J* = 8.3, 7.8 Hz, H-3′), 5.10 (1H, ddd, *J* = 8.7, 7.8, 3.9 Hz, H-4′), 4.28 (1H, dd, *J* = 11.2, 3.9 Hz, H-5′eq), 3.85 (1H, dd, *J* = 11.2, 8.7 Hz, H-5′ax), 2.13, 2.10, 2.08 (3 × 3H, 3 s, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 169.5 (2), 168.5 (C=O), 154.9 (C=N), 133.6, 131.9, 130.2, 129.5, 128.4, 127.6, 126.6 (Ar), 125.8 (C-1′), 125.5, 124.7, 123.7 (Ar), 71.6, 68.5, 67.3 (C-2′–C-4′), 61.2 (C-5′), 20.5 (3 × CH_3). Anal. Calcd for $C_{22}H_{21}NO_8S$ (459.47): C, 57.51; H, 4.61; N, 3.05. Found: C, 57.68; H, 4.56; N, 3.13.

*Compound **46**:* Yield: 66 mg (7%), pale yellow solid. Mp: 145–148 °C; $[\alpha]_D$ +73 (*c* 0.23, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ ppm: 8.65–7.46 (7H, m, Ar), 5.68 (1H, pseudo t, *J* = 9.7, 9.2 Hz, H-3′), 5.59 (1H, d, *J* = 9.7 Hz, H-2′), 5.14 (1H, ddd, *J* = 10.2, 9.2, 6.3 Hz, H-4′), 4.11 (1H, dd, *J* = 11.2, 10.2 Hz, H-5′ax), 4.06 (1H, dd, *J* = 11.2, 6.3 Hz, H-5′eq), 2.13, 2.08, 2.07 (3 × 3H, 3 s, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 169.8, 169.5, 169.4 (C=O), 155.6 (C=N), 133.7, 132.0, 130.3, 129.8, 128.5, 127.8, 126.7, 125.6, 124.8, 123.6 (Ar), 121.9 (C-1′), 70.5, 68.4, 68.2 (C-2′–C-4′), 61.3 (C-5′), 20.6 (3 × CH_3). Anal. Calcd for $C_{22}H_{21}NO_8S$ (459.47): C, 57.51; H, 4.61; N, 3.05. Found: C, 57.62; H, 4.70; N, 2.94.

3.9.38. (1′*R*)-2′,3′,4′-Tri-*O*-acetyl-1′,5′-anhydro-D-xylitol-spiro[1′,5]-3-(2-naphthyl)-1,4,2-oxathiazole (44) and (1′*S*)-2′,3′,4′-tri-*O*-acetyl-1′,5′-anhydro-D-xylitol-spiro[1′,5]-3-(2-naphthyl)-1,4,2-oxathiazole (47)

From compound **38** (1.00 g, 2.17 mmol) according to General procedure **VII** (Section 3.8). Purified by column chromatography (1:4 EtOAc–hexane) to give **47** as the first and **44** as the second fraction.

*Compound **44**:* Yield: 315 mg (32%), white powder. Mp:181–184 °C, $[\alpha]_D$ +182 (*c* 0.85, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm): 8.04–7.53 (7H, m, Ar), 5.56 (1H, d, *J* = 8.7 Hz, H-2′), 5.17 (1H, pseudo t, *J* = 8.7, 8.3 Hz, H-3′), 5.11 (1H, ddd, *J* = 8.7, 8.3, 4.9 Hz, H-4′), 4.22 (1H, dd, *J* = 12.1, 4.9 Hz, H-5′eq), 3.83 (1H, dd, *J* = 12.1, 8.7 Hz, H-5′ax), 2.09, 2.08 (9H, 2 s, CH_3); ^{13}C NMR ($CDCl_3$) δ ppm: 169.5 (2), 168.4 (C=O), 155.7 (C=N), 134.4, 132.6, 129.0, 128.6, 128.4, 127.7, 126.9 (Ar), 126.7 (C-1′), 124.6, 123.5 (Ar), 71.8, 68.4, 67.3 (C-2′–C-4′), 61.2 (C-5′), 20.5 (3 × CH_3). Anal. Calcd for $C_{22}H_{21}NO_8S$ (459.47): C, 57.51; H, 4.61; N, 3.05. Found: C, 57.57; H, 4.49; N, 3.01.

*Compound **47**:* Yield: 120 mg (12%), pale yellow solid, Mp: 140–143 °C, $[\alpha]_D$ +61 (*c* 0.28, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm: 7.98–7.50 (7H, m, Ar), 5.66 (1H, pseudo t, *J* = 9.7, 8.7 Hz, H-3′), 5.60 (1H, d, *J* = 9.7 Hz, H-2′), 5.15 (1H, ddd, *J* = 9.7, 8.7, 6.8 Hz, H-4′), 4.07 (1H, dd, *J* = 11.2, 9.7 Hz, H-5′ax), 4.02 (1H, dd, *J* = 11.2, 6.8 Hz, H-5′eq), 2.09, 2.07 (2) (9H, 2 s, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 169.7, 169.4 (2) (C=O), 156.2 (C=N), 134.5, 132.6, 129.2, 128.7, 128.5, 127.8, 127.0, 124.5, 123.4 (Ar), 122.6 (C-1′), 70.4, 68.3, 68.1 (C-2′–C-4′), 61.2 (C-5′), 20.5 (3 × CH_3). Anal. Calcd for $C_{22}H_{21}NO_8S$ (459.47): C, 57.51; H, 4.61; N, 3.05. Found: C, 57.37; H, 4.65; N, 3.21.

3.9.39. (1′*S*)-1′,5′-Anhydro-D-xylitol-spiro[1′,5]-3-phenyl-1,4,2-oxathiazole (48)

From compound **45** (50 mg, 0.12 mmol) according to General procedure **I** (Section 3.2). Reaction time: 10 min. Purified by column chromatography (4:1 $CHCl_3$–MeOH) to yield 24 mg (70%) white crystals. Mp: 123–126 °C; $[\alpha]_D$ +64 (*c* 0.25, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ (ppm): 7.66–7.49 (5H, m, Ar), 5.76, 5.42, 5.24 (3 × 1H, 3 d, OH), 3.78–3.68 (2H, m, H-2′, H-5′a), 3.59 (1H, m, H-5′b), 3.52–3.40 (2H, m, H-3′, H-4′); ^{13}C NMR (DMSO-d_6) δ (ppm): 155.3 (C=N), 131.4, 129.2, 127.3, 126.6 (Ar), 125.1 (C-1′), 73.9, 71.2, 68.6 (C-2′–C-4′), 64.7 (C-5′). Anal. Calcd for $C_{12}H_{13}NO_5S$ (283.30): C, 50.87; H, 4.63; N, 4.94. Found: C, 50.96; H, 4.74; N, 4.88.

3.9.40. (1′*S*)-1′,5′-Anhydro-D-xylitol-spiro[1′,5]-3-(2-naphthyl)-1,4,2-oxathiazole (49)

From compound **47** (80 mg, 0.17 mmol) according to General procedure **I** (Section 3.2). Reaction time: 10 min. Purified by

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column chromatography (4:1 $CHCl_3$–MeOH) to yield 35 mg (60%) white solid. Mp: 175–178 °C, $[\alpha]_D$ +25 (*c* 0.25, $CHCl_3$); ^1H NMR (DMSO-d_6) δ (ppm): 8.14–7.57 (7H, m, Ar), 5.80, 5.47, 5.28 (3 × 1H, 3 d, OH), 3.81 (1H, m, H-2′), 3.74 (1H, m, H-5′a), 3.64 (1H, m, H-5′b), 3.58–3.46 (2H, m, H-3′, H-4′); ^{13}C NMR (DMSO-d_6) δ (ppm): 155.7 (C=N), 134.2, 132.8, 129.0, 128.7, 128.1, 127.9, 127.4, 126.8, 125.2, 123.3 (Ar), 123.5 (C-1′), 73.9, 71.4, 68.8 (C-2′–C-4′), 64.9 (C-5′). Anal. Calcd for $C_{16}H_{15}NO_5S$ (333.07): C, 57.65; H, 4.54; N, 4.20. Found: C, 57.73; H, 4.61; N, 4.06.

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