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Heterocyclic Compounds from Sugars, XIII. [1] Synthesis of 2-Polyhydroxyalkyl-Δ^4-1,3,4-Thiadiazolines from Aldoses

Gyula Argay [a], René Csuk [b], Zoltán Györgydeák [c*], Alajos Kálmán [c] and Günther Snatzke [† d]

[a] Central Research Institute, Hungarian Academy of Sciences, H-1525 Budapest, Pf 17, Hungary;

[b] Pharmazeutisch-Chemisches Institut, Universität Heidelberg, Im Neuenheimer Feld 364, D-69120 Heidelberg, Germany;

[c] Department of Organic Chemistry, Lajos Kossuth University, H-4010 Debrecen, Pf 20, Hungary;

[d] Lehrstuhl für Strukturchemie der Ruhr-Universität Bochum, D-44780 Bochum, Germany

Abstract.– The reaction between 2-phenylthiobenzhydrazide and aldoses has been investigated; the products obtained in these reactions have the structure of 2-polyhydroxyalkyl-Δ^4-1,3,4-thiadiazolines as shown by spectroscopic evidence and by single crystal X-ray analysis.

INTRODUCTION

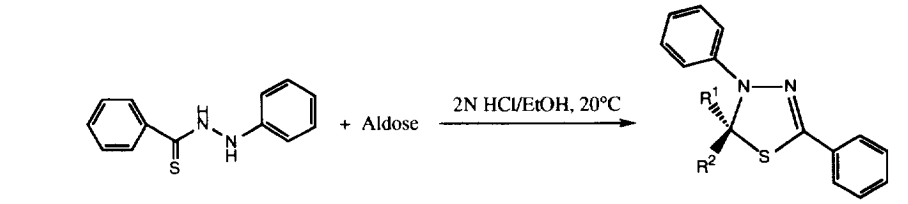
Renewed interest in the formation of heterocycles from carbohydrates led to a reinvestigation of the cyclocondensation reaction between thiobenzhydrazides and carbonyl compounds.[2] It was shown that the products of these reactions are usually obtained as an equilibrated mixture of acyclic thioacylhydrazones or exclusively as the corresponding Δ^4-1,3,4-thiadiazolines (2,3-dihydro-1,3,4-thiadiazoles) which have also been synthesized by several other methods.[3]

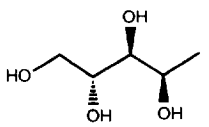
During the study of carbohydrate derived heterocycles and their chirooptical properties we became interested in the cyclocondensation reaction [4] between 2-phenylthiobenzhydrazide (**1**) and aldoses **2**. The previous syntheses of these compounds, however, did not give unambiguous structural proof nor could these investigations provide full analytical data for the obtained compounds. Obviously several products had been obtained previously only as an impure mixture of several components.

RESULTS AND DISCUSSION

The cyclocondensation reaction between **1** and several aldoses **2** according to methods already described in the literature [4, 5] afforded mixtures of several products, for some of which according to the results of elemental analysis and the results of hydrolysis experiments the structure of Δ^4-1,3,4-thiadiazolines had been assigned.[4, 5]

Cyclocondensation reactions using a setup of standardized reaction conditions (all reactions were performed under N_2 inert gas atmosphere using 2N ethanolic hydrochloric acid as the reagent) were carried out and revealed the formation of 2-polyhydroxyalkyl-Δ^4-1,3,4-thiadiazolines **3** as the main products; only these compounds could be isolated from the reaction mixtures. These compounds could be easily characterized by their ^{1}H- and ^{13}C NMR spectra. Thus, in the ^{1}H NMR spectra of **3** the signal for $H(C2)_{thiadiazoline}$ is found between $\delta \approx 3.7$ ppm and in the ^{13}C NMR spectra $C(5)_{thiadiazoline}$ is observed between $\delta \approx 130$-132 ppm and for $C(2)_{thiadiazoline}$ $\delta \approx 60$ ppm is recorded. Characteristic signals in the IR spectra for all thiadiazolines **3** were found at $\nu = 3500$-3200, 1590, 1490, 1440-1450, 1120-1130, 1050, 1030, 760-770, 740 and 690 cm^{-1}.

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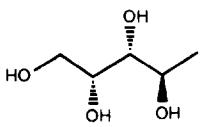
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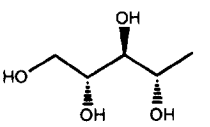
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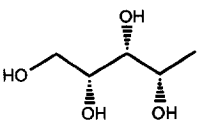
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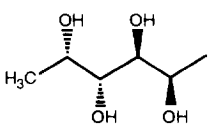
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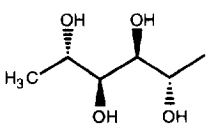
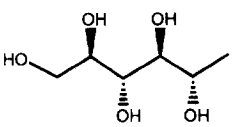

f L-rhamno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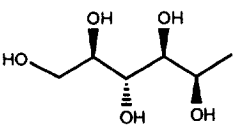
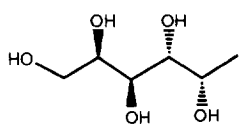

h, D-altro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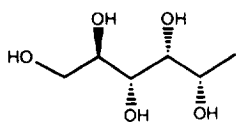
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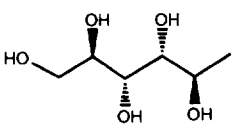
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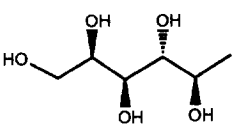

l, D-talo

It was found that the D-aldopentoses D-arabinose (**2a**), D-lyxose (**2b**), D-ribose (**2c**), D-xylose (**2d**) reacted more easily as compared to the aldohexoses L-fucose (**2e**), L-rhamnose (**2f**), D-allose (**2g**), D-altrose (**2h**), D-galactose (**2i**), D-glucose(**2j**), D-mannose (**2k**) and D-talose (**2l**), respectively. The yields of the corresponding thiadiazolines decrease upon applying prolonged reaction times and the formation of dark red deterioration products is observed. This finding can be regarded as the main reason for obtaining diminished yields for **3g** and **3h** – both compounds exhibit a high solubility in the reaction mixture and could not be obtained in crystalline form.

^{1}H NMR spectroscopic investigation of the crude reaction mixtures revealed in many cases the presence of two epimers differing only in the absolute configuration at $C(2)_{thiadiazoline}$. These epimers could

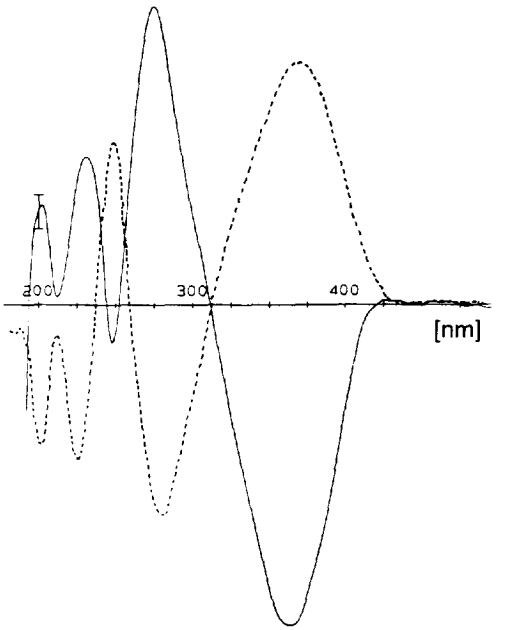
be separated neither by TLC nor by flash chromatography under a variety of different conditions; crystallization of the crude mixtures, however, resulted in the clean separation of the epimers. Interestingly enough, for the reaction of **2a** and **2b** it was shown that even the crude reaction mixtures contained only one of the two possible isomers although the reason for this unexpected stereoselectivity remains unclear und subject for further study.

Tab. 1: CD-spectra for the 3,5-diphenyl-2,3-dihydro-[1,3,4]thiadiazol-2-yl)alkane-polyoles **3** and acetylated analogues **4** in acetonitrile (λ_{max} ($\Delta\varepsilon$))

Comp.	Band I [a]	Band II	Band III	Band IV'	Band IV"
3a [b]	369.2 (-18.1)	278.8 (+16.1)	246.4 (-13.0)	224.0 (+11.4)	
3b [c]	372.0 (+20.4)	279.2 (-11.6)	250.8 (+6.8)	232.0 (-15.6)	199.6 (-2.7)
3c [d]	371.6 (-16.0)	279.6 (+9.1)	250.4 (-5.1)	232.8 (+12.8)	208.4 (+0.9)
(+)-3i	368.4 (+25.9)	280.0 (-22.7)	247.6 (+17.5)	225.2 (-16.8)	201.2 (-15.4)
(-)-3i	363.6 (-8.6)	274.0 (+8.0)	247.2 (-1.0)	230.0 (+4.0)	201.2 (+2.7)
(+)-3k	372.8 (+14.1)	279.2 (-7.9)	251.6 (+4.7)	234.0 (-13.0)	
(-)-3k	358.4 (-11.3)	279.6 (+10.3)	247.2 (-7.3)	225.2 (+5.8)	
4b	364.8 (+25.4)	277.6 (-14.8)	249.2 (+11.0)	229.2 (-18.6)	
4g	365.2 (-20.5)	277.6 (+11.7)	248.8 (-8.3)	230.4 (+16.5)	
(+)-4i	362.2 (+26.9)	276.0 (-23.9)	245.0 (+15.2)	223.6 (-10.7)	198.0 (-14.7)

[a] For a classification of the bands *cf* lit.8; [b] in MeOH
[c] band V 188.4 (+9.5); [d] 187.2 (-11.1)

Fig. 1: CD-spectra for **(+)-3i** (---) and **(-)-3i** (—)



From the ^{1}H and ^{13}C NMR spectroscopic data the presence of an acyclic polyhydroxyalkyl chain was revealed but these data did not allow an assignment of the absolute configuration at $C(2)_{thiadiazoline}$ in an unambiguous manner. Assuming coplanarity of the two aromatic ring systems semiempirical MO calculations (MOPAC)[6] were performed for a set of several possible conformations for each of the respective epimers and from the torsion angle $H(C2)_{thiadiazoline}$-C(1)-H-C(1) and from the estimated electronegativity of the

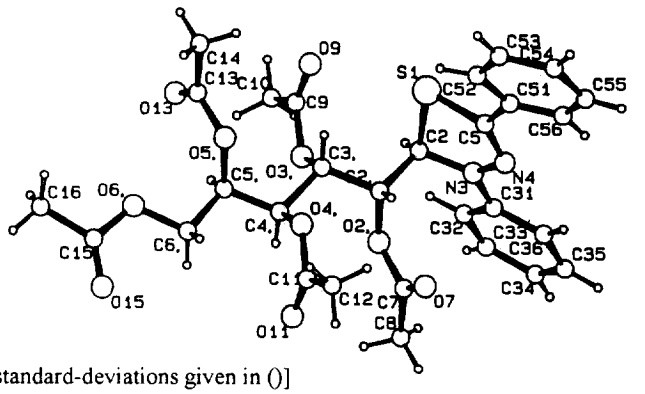
substituents the coupling constants $^3J_{\text{H-C(2)}_{\text{thiadiazoline}},\ \text{H-C(1)}}$ were calculated.[7] The calculated $^3J_{H,H}$ values correlated with the experimentally obtained J values and allowed a classification of the compounds into two different groups showing either $^3J_{\text{H-C(2)}_{\text{thiadiazoline}},\ \text{H-C(1)}}$ = 1–3 Hz and $^3J_{\text{H-C(2)}_{\text{thiadiazoline}},\ \text{H-C(1)}}$ = 9–10 Hz, respectively. Residing on these findings a tentative assignment of the absolute configuration at $\text{C(2)}_{\text{thiadiazoline}}$ can be made (unfortunately, several of the ^{1}H NMR spectra were too crowded to allow an unambiguous determination of these coupling constants) which was confirmed by a comparison of the optical rotations and the CD spectra with analogues from the 2-polyacetoxyalkyl-benzothiazoline series.[8] Analysis of the CD spectra of the D-galacto epimers (+)-**3i** and (-)-**3i** revealed a reversal of sign for all five *Cotton* effects in both spectra. This behavior implicates that the absolute configuration at $\text{C(2)}_{\text{thiadiazoline}}$ seems to be the reason for the reversal of sign of the *Cotton* effects. Interestingly, the $\Delta\varepsilon$ values for (+)-**3i** were found to be three times as large as those measured for (-)-**3i** (Fig. 1).

An unambiguous proof of these tentative assignments can be expected from X ray analysis. However, the crystals of **3a-l** were unsuitable and therefore the thiadiazolines **3a-l** were acetylated (acetic anhydride, pyridine, 6-8 h at 20 °C) to afford the corresponding peracetylated **4a-l**. Alternatively, **4a** and **4i** were obtained by cyclocondensation between **1** and 2,3,4,5-tetra-*O*-acetyl-aldehydo-D-arabinose (**5**) and 2,3,4,5,6-penta-*O*-acetyl-aldehydo-D-galactose, respectively.

Tab.2: Selected bond lengths (Å) for (+)-**4i** [11]

C(5) - C(51)	1.492(9)
N(3) - C(2)	1.446(9)
N(3) - C(31)	1.401(9)
N(3) - N(4)	1.385(8)
N(4) - C(5)	1.257(9)
S(1) - C(2)	1.809(7)
S(1) - C(5)	1.758(7)

Fig. 2: Perspective view of (+)-**4i**



Tab.3: Selected angles (°) for (+)-**4i** [standard-deviations given in ()]

C(2,) - C(3,) - C(4,)	113.2(10)	N(4) - N(3) - C(2)	114.2(9)
C(2) - N(3) - C(31)	126.1(10)	N(4) - N(3) - C(31)	119.3(10)
C(2) - S(1) - C(5)	86.9(5)	S(1) - C(2) - C(2,)	109.1(8)
N(3) - C(2) - C(2,)	112.8(9)	S(1) - C(2) - N(3)	103.3(8)
N(3) - N(4) - C(5)	110.3(10)	S(1) - C(5) - C(51)	120.1(9)
N(4) - C(5) - C(51)	122.3(11)	S(1) - C(5) - N(4)	117.5(9)

Pure crystalline compounds **4** were obtained very easily by recrystallization whereas syrupy compounds **4** could only be purified by repeated flash chromatography. Thus, suitable crystals for (+)-**4i** were grown and subjected to an X ray analysis.

A perspective view of **(+)-4i** is shown in Fig. 2; selected bond lengths, bond angles and torsion angles are compiled in Tab. 1 and Tab. 2 and reveal a significant delocalization of the π-electrons within the C=N-N fragment and the phenyl substituents. The N-N-bond as well as the C-N bonds in **(+)-4i** are longer as compared to the bond lengths found in 2-methyl-3-phenylazo-1,3,4-thiadiazoline.[9] The bond lengths obtained by AM1 calculations[6] show greater deviations (± 10%) than the bond or torsion angles (± 5°) The puckering-parameters for the five membered ring were calculated with Q=0.291(7)Å and φ =3.31.3(1.4)°.

The compounds **3** were tested in *in vitro* screenings against a series of tumor cell lines showing pronounced antitumor activity of the D-*lyxo* configurated **3d** against the non-small cell lung cancer cell line HOP-92, the renal cancer cell line RXF-393 as well as the breast cancer cell line HS578T. *In vivo* screenings, however, using a tumor system of three athymic mouse models each containing one of these three human tumor cell lines in a subcutaneous xenograft, showed that this compound did not exhibit significant *in vivo* antitumor activity on the treatment schedule evaluated in this study and thus a maximal tolerated dose was not achieved. In addition, **3d** was tested against the well established P388 mouse leukemia model for comparison purposes, but again no satisfactory activity was achieved.[10]

The combination using optical, NMR and X ray analytical methods should be very useful also for the determination of the absolute configuration of related heterocyclic polyols.[12,13]

EXPERIMENTAL

Melting points are uncorrected (*Boëtius* hot stage microscope, Fa. Küster), optical rotations were obtained using a Schmidt-Haensch polarimeter (0.5 dm cell), NMR spectra (internal Me_4Si) were recorded using either a Bruker AM400, AM250 or a Varian XL300 instrument (DMSO-d_6, δ given in ppm, *J* in Hz, internal Me_4Si, C' and H' correspond to the atoms of the heterocycle), CD spectra were recorded on a ISA-Jobin-Yvon-Dichrograph (Model 185 and Mark II, concentration 1 mg/ml), IR spectra (film or KBr pellet) on a Perkin-Elmer 298 instrument or on a Perkin-Elmer 1605 FT-IR, MS spectra were taken either on a MAT311A or a Varian-112S instrument; for elemental analysis a Foss-Heraeus Vario EL instrument was used. All experiments were performed under inert gas (N_2).TLC was performed on silica gel (Merck 5554, Kieselgel (Merck 5554) using chloroform:methanol:acetic acid = 70:14:1 (*v/v/v*) as the eluent.

X ray analysis for **(+)-(1R, 2S, 3S, 4R)-1,2,3,4,5-pentaacetoxy-1-[(2R)-1-(3,5-diphenyl)-2,3-dihydro-[1,3,4]thiadiazol-2-yl-)]-pentane-1,2,3,4,5-pentaol (4i)**: Diffraction data were collected at room temperature on a Enraf-Nonius-CAD-4-diffractometer using graphite monochromated Cu K_α radiation (λ= 1.54184 Å, ω-2 ϑ-scan method, 2 ϑ_{max} =150°); crystal size 0.2*0.25*0.35 mm: $C_{29}H_{32}N_2O_{10}S$ (M=600.65); monoklin, space group C2, a=36.247(4)Å, b=11.747(1)Å, c=7.465(1)Å, β=93.24(1)°; V_{calc} = 3174(1)Å^3, Z=4, D_{calc} = 1.26 gcm^{-3}, μ=13.4 cm^{-1} Data were collected for one octant of reciprocal space ($-45 \le h \le 45$, $0 \le k \le 14$, $0 \le l \le 9$) yielding 3446 unique and 2022 significant ($I > 3\ \sigma(I)$) intensities. Lp correction and an empirical absorption correction (max. and min transmission coefficient 1.481 and 0.543, respectively) were applied to the data. The structure was solved by direct methods and refined with least-squares, including isotropic and atomic displacement parameters for all non-hydrogen atoms. H atoms attached to C were

included at calculated positions (Multan-82, R=0.050, R_ω=0.047, $\omega = 1$). A final difference electron density map showed features up to 0.19(4)eÅ^{-3}.[11]

General procedure for the synthesis of 2-polyhydroxyalkyl-Δ^4-1,3,4-thiadiazolines.– 2-Phenylthiobenzhydrazide (2.30 g, 10 mmol) [5c] was dissolved in ethanol (30 *ml*) and a solution of the aldose (10 mmol) in 2N hydrochloric acid (5 *ml*) was slowly added. The product precipitate from the reaction mixture and was filtered off after 3h (**3a** und **3b**) or after 20h (**3c,e,g,i,j,k,l**); for some products it was necessary to remove most of the solvent *in vacuo* and then the product (**3d,f,h**) was filtered off. For purification the crude products were recrystallized (twice, for the solvent: *vide infra*). The products **(-)-3i** und **(+)-3i** were obtained after evaporation of the solvents and recrystallization of the crude product.

General procedure for the synthesis of peracetylated 2-polyhydroxyalkyl-Δ^4-1,3,4-thiadiazolines **4** .–

a) From Δ^4-1,3,4-thiadiazolines 3 (GP2).– To a solution of 2 (1 mmol) in dry pyridine (3.8 ml) acetic anhydride (0.96 ml) was slowly added and the reaction mixture was stirred for 7-10 h at 25 °C. The solvents were evaporated *in vacuo* and the remaining semicrystalline residue (green-brown) was triturated with water and a saturated solution of potassium hydrogensulfate. Several crude products crystallized and were recrystallized. Oily components were dissolved in dry dichloromethane, the solution was dried ($MgSO_4$), the solvent was removed and the residue subjected to flash chromatography (silica gel, toluene: ethyl acetate = 10:3 (*v/v*)).

b) From per-O-acetyl-aldehydo-aldoses.– To a solution of the corresponding per-*O*-acetyl-*aldehydo*-aldose (3.0 mmol) and **1** (0.69 g, 3 mmol) in dry 1,4-dioxane (5.4 *ml*) a saturated solution of dry hydrochloric acid in diethyl ether (0.1 *ml*) was slowly added and the mixture was stirred for 5h. After neutralization with sodium hydrogencarbonate the solvent was removed and the syrupy residue was triturated with hot ethanol, filtered and to the filtrate a few drops of water were added. After standing for several hours at 5 °C **4a** (24.6%) and **(+)-4i** (56%) were filtered off and dried.

(1 *S*, 2*R*, *3* R)-1-[(2 *S*)-(3,5-Diphenyl-2,3-dihydro-[1,3,4]thiadiazol-2-yl)]-butane-1,2,3,4-tetraol (D-*arabino*) (3a).– 3.31 g (92%), mp 234-235°C (1,4-dioxane), lit [5a]: 220-225°C (for the L-isomer), $[\alpha]_D^{25}$ = -1079.0° (*c* 0.5, pyridine), lit:[5a] +698° (for the L-isomer); IR (KBr): 3500-3200*br*, 3050*w*, 3020*w*, 2960*w*, 2920*w*, 2880*w*, 1590*s*, 1540*m*, 1485*s*, 1445*s*, 1340*s*, 1260*m*, 1240*s*, 1180*w*, 1130*s*, 1120*m*, 1100*m*, 1085*m*, 10045*s*, 1030*m*, 1015*m*, 1000w, 995*w*, 975*m*, 905*s*, 870*m*, 845*m*, 810*m*, 770*s*, 740*s*, 705*s*, 690*s*; ^{1}H NMR (250 MHz): δ 6.90-7.70 (*m*, 1 H), 5.93 (*d*, *J* = 9.7 Hz, 1 H), 5.34 (*d*, *J* = 6.6 Hz, 1 H), 4.71 (*d*, *J* = 7.9 Hz, 1 H), 4.35 (*m*, 2 H), 3.65-3.35 (*m*, 5 H); Anal. calcd. for $C_{18}H_{20}N_2O_4S$ (360.43): C, 59.98; H, 5.59; N, 7.77; S, 8.90; found: C, 59.67; H, 5.35; N, 7.58; S, 9.04. By acetylation according to GP2 the tetra-acetate **4a** was obtained.– 1.35 g (85%); mp 134-135°C; $[\alpha]_D^{25}$ = -758° (*c* 0.5, $CHCl_3$); Anal. calcd. for $C_{26}H_{28}N_2O_8S$ (528.58): C, 59.08; H, 5.34; N, 5.30; S, 6.07; found: C, 58.87; H, 5.60; N, 5.31; S, 6.30.

(1R, 2S, 3R)-1-[(2R)-(3,5-Diphenyl-2,3-dihydro-[1,3,4]thiadiazol-2-yl)]-butane-1,2,3,4-tetraol (D-*lyxo*) (3b).– 3.1 g (86%); mp 153-154°C (EtOH), lit:[5a] 151-153°C; $[\alpha]_D^{25}$ = +1001.5° (*c* 0.5, pyridine), lit [5a]: $[\alpha]_D^{25}$ +977°; IR (KBr): 3610*br s*, 3500-3200 *br s*, 3050*w*, 2050*w*, 2920*w*, 1595*s*, 1550*s*, 1495*s*, 1440*m*, 1370*s*, 1335*m*, 1310*w*, 1260*s*, 1180*w*, 1125*s*, 1100*m*, 1070*s*, 1050*s*, 1030*m*, 1010*m*, 1000*m*, 970*s*, 920*w*,

910*w*, 885*w*, 870*w*, 860*w*, 810*w*, 770*s*, 750*s*, 710*w*, 690*s*, 675*m*, 650*w*; ^{1}H NMR (250 MHz, DMSO-d_6): δ 6.90-7.60 (*m*, 10 H), 6.4 (*d*, *J* = 9.0 Hz, 1 H), 5.90 (*d*, *J* = 9.0 Hz, 1 H), 5.50 (*d*, *J* = 3.2 Hz, 1 H), 4.70 (d, *J* = 5.0 Hz, 1 H), 4.51 (*d*, J = 5.1 Hz, 1 H), 4.36 (*m*, 1 H), 3.28-3.85 (*m*, 4 H); ^{13}C-NMR (50 MHz, DMSO-d_6): δ 143.81 (*s*), 142.54 (*s*), 131.18 (*s*), 129.36, 129.24, 128.81, 126.24, 119.32 (each *d*), 113.53 (*d*,), 74.26, 69.86, 69.52, 68.01 (each *d*), 62.64 (*t*); Anal. calcd. for $C_{18}H_{20}N_2O_4S$ (360.43): C, 59.97; H, 5.59; N, 7.77; S, 8.90; found: C, 59.68; H, 5.63; N, 7.79; S, 8.76. By acetylation according to GP2 the tetra-acetate **4b** was obtained.– 0.51 g (96%); mp 117-118°C; $[\alpha]_D^{25}$ = +782° (*c* 0.5, $CHCl_3$). Anal. calcd. for $C_{26}H_{28}N_2O_8S$ (528.58): C, 59.08; H, 5.34; N, 5.30; S, 6.07; found: C, 59.46; H, 5.24; N, 5.36; S, 5.99.

(1R, 2R, 3R)-1-[(2S)-(3,5-Diphenyl-2,3-dihydro-[1,3,4]thiadiazol-2-yl-)-butane-1,2,3,4-tetraol (D-*ribo*) (3c).– 3.17 g (88%); mp 171-172.5°C (EtOH); lit:[5a] 169-171°C; $[\alpha]_D^{25}$ = -1072.0° (*c* 0.5, pyridine); lit.[5a]: -1060°; IR (KBr): 3450-3200 *br s*, 3040*w*, 3020*w*, 2900*m*, 2960*w*, 2930*w*, 1590*s*, 1550*s*, 1490*s*, 1470*w*, 1450*s*, 1360*s*, 1335*m*, 1255*s*, 1200*w*, 1190*m*, 1175*m*, 1150*w*, 1125*s*, 1075*s*, 1050*s*, 1030*s*, 995*m*, 965*s*, 920*m*, 760*s*, 740*s*, 710*m*, 690*s*, 670*m*; ^{1}H NMR (250 MHz, DMSO-d_6): δ 6.85-7.65 (*m*, 10 H), 6.39 (*d*, *J* = 1.5 Hz, 1 H), 5.13 (*d*, *J* = 6.0 Hz, 1 H), 5.07 (*d*, *J* = 6.2 Hz, 1 H), 4.79 (*d*, *J* = 4.9 Hz, 1 H), 4.45 (*t*, *J* = 5.5 Hz, 1 H), 4.12 (*m*, 1 H), 3.40-3.60 (*m*, 4 H); ^{13}C-NMR (50 MHz, DMSO-d_6): δ 143.86 (*s*), 143.10 (*s*), 131.12 (*s*), 129.51, 129.38, 129.25, 129.04, 128.80, 126.19, 119.34 (each *d*), 113.39 (*d*), 73.80, 73.42, 71.93, 69.28 (each *d*), 62.54 (t, C(5)); Anal. calcd. for $C_{18}H_{20}N_2O_4S$ (360.43): C, 59.98; H, 5.59; N, 7.77; S, 8.90; found: C, 60.28; H, 5.56; N, 7.68; S, 8.77. By acetylation according to GP2 the tetra-acetate **4c** was obtained.– 0.43 g (81%); mp 103-105°C; $[\alpha]_D^{25}$ = -683° (*c* 0.5, $CHCl_3$). Anal. calcd. for $C_{26}H_{28}N_2O_8S$ (528.58): C, 59.08; H, 5.34; N, 5.30; S, 6.07; found: C, 59.14; H, 5.43; N, 5.32; S, 6.45.

(1R, 2S, 3R)-1-[(2R)-(3,5-Diphenyl-2,3-dihydro-[1,3,4]thiadiazol-2-yl)]-butane-1,2,3,4-tetraol (D-*xylo*) (3d).– 2.23 g (62%); mp 163-164.5°C (EtOH), lit:[5a]: 162-164°C; $[\alpha]_D^{25}$ = +1432° (*c* 0.5, pyridine); lit.[5a]: +1450°; IR (KBr): 3500-3200 *br s*, 3045*w*, 3020*w*, 2960*w*, 2920*w*, 2880*w*, 1590*s*, 1550*m*, 1490*s*, 1445*s*, 1335*s*, 1260*m*, 1240*s*, 1180*w*, 1130*s*, 1115*m*, 1105*m*, 1080*m*, 1050*s*, 1030*m*, 1015*m*, 1000*w*, 995*w*, 975*m*, 960*s*, 915*m*, 875*m*, 845*m*, 810*m*, 765*s*, 740*s*, 705*s*, 690*s*; ^{1}H NMR (250 MHz, DMSO-d_6): δ 6.8-7.8 (*m*, 10 H), 5.99 (*d*, *J* = 9.8 Hz, 1 H), 5.52 (*d*, *J* = 5.8 Hz, 1 H), 4.63 (*d*, *J* = 6.8 Hz, 1 H), 4.56 (*d*, *J* = 4.7 Hz, 1 H), 4.46 (*t*, *J* = 5.5 Hz, 1 H), 3.25-3.80 (*m*, 5 H); ^{13}C-NMR (50 MHz, DMSO-d_6): δ 146.78 (*s*), 146.72 (*s*), 130.89 (*d*), 130.44 (*s*), 129.22, 128.94, 127.18, 120.56 (each *d*), 114.80 (*d*), 74.76, 73.72, 72.99, 69.24 (each *d*), 62.44 (*t*, C(5)); Anal. calcd. for $C_{18}H_{20}N_2O_4S$ (360.43): C, 59.98; H, 5.59; N, 7.77; S, 8.90; found: C, 59.90; H, 6.26; N, 7.71; S, 9.02. By acetylation according to GP2 the tetra-acetate **4d** was obtained.– 0.38 g (72%), foam; $[\alpha]_D^{25}$ = +690° (*c* 0.5, $CHCl_3$). Anal. calcd. for $C_{26}H_{28}N_2O_8S$ (528.58): C, 59.08; H, 5.34; N, 5.30; S, 6.07; found: C, 59.28; H, 5.49; N, 5.01; S, 6.19.

(1S, 2R, 3R, 4S)-1-[(2S)-(3,5-Diphenyl-2,3-dihydro-[1,3,4]thiadiazol-2-yl-)]-pentane-1,2,3,4-tetraol (L-*fuco*) (3e).– 3.63 g (87%); mp 199°C (EtOH), lit:[5a]: 193-194°C; $[\alpha]_D^{25}$ = -1341° (*c* 0.5, pyridine); lit.[5a] -624°; IR (KBr): 3500-3300*br*, 3040*w*, 3015*w*, 2910*m*, 2960*w*, 2940*w*, 1590*s*, 1540*s*, 1490*s*, 1470*w*, 1450*s*, 1360*s*, 1335*m*, 1250*s*, 1205*w*, 1195*m*, 1180*m*, 1145*w*, 1125*s*, 1075*s*, 1050*s*, 1025*s*, 995*m*, 960*s*, 920*m*, 760*s*, 740*s*, 710*m*, 690*s*, 670*s*; ^{1}H NMR (250 MHz, DMSO-d_6): δ 6.90-7.8 (*m*, 1 H), 5.95 (*d*, *J* = 10.2 Hz, 1 H), 5.28 (*d*, *J* = 6.6 Hz, 1 H), 4.68 (*d*, *J* = 8.1 Hz, 1 H), 4.15 (*d*, *J* = 7.1 Hz, 1 H), 3.50-4. (*m*, 5 H), 1.12 (*d*, *J* = 6.7 Hz, 3 H); Anal. calcd. for $C_{19}H_{22}N_2O_4S$ (374.46): C, 60.94; H, 5.92; N, 7.48; S, 8.56; found: C, 61.29;

H, 5.96; N, 7.61; S, 9.03. By acetylation according to GP2 the tetra-acetate **4e** was obtained.– 0.37 g (68%); mp 170-172°C, $[\alpha]_D^{25}$ = -370° (*c* 0.5, $CHCl_3$). Anal. calcd. for $C_{27}H_{30}N_2O_8S$ (542.61): C, 59.77; H, 5.57; N, 5.16; S, 5.91; found: C, 59.49; H, 5.23; N, 5.26; S, 5.86.

(1R, 2R, 3S, 4S)-1-[(2S)-(3,5-Diphenyl-2,3-dihydro-[1,3,4]thiadiazol-2-yl-)]-pentane-1,2,3,4-tetraol (L-*rhamno*) (3f).– 2.36 g (63%); mp 181-182°C (50% aqu. EtOH); lit.[5a] 175-176°C; $[\alpha]_D^{25}$ = -975° (*c* 0.5, pyridine); lit:[5a] -936°; IR (KBr): 3450-3250*br*, 3040*w*, 3020*w*, 2910*m*, 2960*w*, 2940*w*, 1590*s*, 1540*s*, 1490*s*, 1470*w*, 1450*s*, 1360*s*, 1340*m*, 1250*s*, 1200*w*, 1190*m*, 1180*m*, 1150*w*, 1130*s*, 1075*s*, 1050*s*, 1030*s*, 995*m*, 960*s*, 920*m*, 760*s*, 740*s*, 710*m*, 690*s*, 670*s*; ^{1}H NMR (250 MHz, DMSO-d_6): δ 6.80-7.75 (*m*, 10 H), 6.48 (*d*, *J* = 1.3 Hz, 1 H), 5.0 (*br s*, 1 H), 4.10 (*br d*, *J* = 9.0 Hz, 1 H), 3.25-3.70 (*m*, 6 H), 1.11 (*d*, *J* = 6.1 Hz, Me); Anal. calcd. for $C_{19}H_{22}N_2O_4S$ (374.46): C, 60.94; H, 5.92; N, 7.48; S, 8.56; found: C, 61.48; H, 5.87; N, 7.69; S, 8.80. By acetylation according to GP2 the tetra-acetate **4f** was obtained.– 0.52 g (95%) as an oil; $[\alpha]_D^{25}$ = -359° (*c* 0.5, $CHCl_3$). Anal. calcd. for $C_{27}H_{30}N_2O_8S$ (542.61): C, 59.76; H, 5.57; N, 5.16; S, 5.91; found: C, 59.88; H, 5.33; N, 5.28; S, 6.21.

(1R, 2R, 3R, 4R)-1-[(2S)-1-(3,5-Diphenyl-2,3-dihydro-[1,3,4]thiadiazol-2-yl-)]-pentane-1,2,3,4,5-pentaol (D-*allo*) (3g).– 2.58 g (66%); mp 172°C (ethyl acetate); $[\alpha]_D^{25}$ = -974° (*c* 0.5, pyridine); IR (KBr): 3500-3245*brs*, 2925*m*, 2920*m*, 2880*s*, 1590*s*, 1500*s*, 1450*s*, 1350*m*, 1250*m*, 1140*m*, 1070*s*, 1040*s*, 1030*s*, 970*s*, 890*s*, 760*s*, 730*s*, 690*s*; ^{1}H NMR (250 MHz, DMSO-d_6): δ 6.85-7.70 (*m*, 10 H), 6.40 (*d*, *J* = 1.45 Hz, 1 H), 5.02 (*d*, *J* = 5.9 Hz, 1 H), 4.99 (*d*, *J* = 5.9 Hz, 1 H), 4.76 (*d*, *J* = 4.0 Hz, 1 H), 4.51 (*d*, *J* = 4.3 Hz, 1 H), 4.30 (*m*, 2 H), 3.35-3.70 (*m*, 5 H); Anal. calcd. for $C_{19}H_{22}N_2O_5S$ (390.46): C, 58.44; H, 5.68; N, 7.17; S, 8.21; found: C, 58.21; H, 5.82; N, 7.19; S, 8.40. By acetylation according to GP2 the penta-acetate **4g** was obtained.– 0.34 g (56%); mp 120-122°C; $[\alpha]_D^{25}$ = -626° (*c* 0.5, $CHCl_3$). Anal. calcd. for $C_{29}H_{32}N_2O_{10}S$ (600.65): C, 57.99; H, 5.37; N, 4.66; S, 5.34; found: C, 58.19; H, 5.69; N, 4.48; S, 5.48.

(1S, 2R, 3R, 4R)-1-[(2S)-1-(3,5-Diphenyl-2,3-dihydro-[1,3,4]thiadiazol-2-yl-)]-pentane-1,2,3,4,5-pentaol (D-*altro*) (3 h).– 2.97 g (79%); mp 150-152°C (50% aqu. EtOH); $[\alpha]_D^{25}$ = -955° (*c* 0.5, pyridine); IR (KBr): 3450-3200*brs*, 2930*m*, 2920*m*, 2885*w*, 1590*s*, 1505*s*, 1450*s*, 1345*m*, 1245*m*, 1140*m*, 1070*s*, 1035*s*, 1020*s*, 975*s*, 895*s*, 755*s*, 735*s*, 690*s*; ^{1}H NMR (250 MHz, DMSO-d_6): δ 6.9-7.8 (*m*, 10 H), 6.35 (*d*, *J* = 3.1 Hz, 1 H), 5.20 (*d*, *J* = 5.9 Hz, 1 H), 4.10-4.80 (*m*, 5 H), 3.25-3.90 (*m*, 5 H); ^{13}C NMR (50 MHz, DMSO-d_6): d 148.20 (*s*), 143.90 (*s*), 131.20 (*s*), 130.10, 129.80, 128.70, 128.65, 126.85, 126.01 (each *d*), 114.03 (*d*), 74.25, 71.80, 71.10, 71.05, 67.13 (each *d*), 64.12 (*t*); Anal. calcd. for $C_{19}H_{22}N_2O_4S$ (390.46): C, 58.44; H, 5.68; N, 7.17; S, 8.21; found: C, 58.17; H, 5.70; N, 7.09; S, 8.45.

(-)-(1R, 2S, 3S, 4R)-1-[(2S)-1-(3,5-Diphenyl-2,3-dihydro-[1,3,4]thiadiazol-2-yl-)]-pentane-1,2,3,4,5-pentaol [(-)-D-*galacto*] [(-)-3i].– 0.8 g (20%); mp 170°C (EtOH), $[\alpha]_D^{25}$ = -426° (*c* 0.5, pyridine); IR (KBr) 3680*s*, 3120br *s*, 3080*w*, 2960*w*, 2940*m*, 2920*w*, 1560*w*, 1495*s*, 1490*s*, 1445*s*, 1360*m*, 1335*m*, 1290*w*, 1250*m*, 1180*m*, 1150*m*, 1105*s*, 1070*s*, 1040*s*, 960*s*, 910*w*, 840*m*, 715*s*, 690*m*, 660*m*; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.90-7.80 (*m*, 10 H), 6.10 (*m*, 1 H), 5.30 (*m*, 1 H), 5.05 (*d*, *J* = 7.4 Hz, 1 H), 4.92 (*t*, *J* = 4.4 Hz, 1 H), 4.50 (*d*, *J* = 7.9 Hz, 1 H)), 4.45 (*m*, 1 H), 4.38 (*d*, *J* = 5.5 Hz, 1 H), 4.20 (*m*, 1 H), 3.30-3.90 (*m*, 4 H); ^{13}C-NMR (50 MHz, DMSO-d_6): δ 147.56 (*s*), 145.56 (*s*), 130.29 (*s*), 129.45, 129.21, 128.96, 127.00, 120.31 (each *d*), 114.13 (*d*), 75.69, 75.31, 70.16, 70.02, 69.09 (each *d*), 60.93 (*t*); Anal. calcd. for

$C_{19}H_{22}N_2O_5S$ (390.46): C, 58.45; H, 5.68; N, 7.17; S, 8.21; found: C, 58.78; H, 5.67; N, 7.09; S, 8.45. By acetylation according to GP2 the penta-acetate **(2S) (-4i)** was obtained.– 0.57 g (95%); mp 105-106°C; $[\alpha]_D^{25}$ = -253° (*c* 1.4, $CHCl_3$). Anal. calcd. for $C_{29}H_{32}N_2O_{10}S$ (600.65): C, 57.99; H, 5.37; N, 4.66; S, 5.34; found: C, 58.17; H, 5.61; N, 4.48; S, 5.12.

(+)-(1R, 2S, 3S, 4R)-1-[(2R)-1-(3,5-Diphenyl)-2,3-dihydro-[1,3,4]thiadiazol-2-yl-)]-pentane-1,2,3,4,5-pentaol [(+)-D-*galacto*] [(+)-3i].– 1.3 g (33 %); mp 182-184°C lit.:[5a] 180-182°C, $[\alpha]_D^{25}$ +1613 (c 0.5, pyridine), lit:[5a] +1360° (c 0.5, pyridine); IR (KBr) 3690*s*, 3130br *s*, 3085*w*, 2970*w*, 2940*m*, 2920*w*, 1565*w*, 1490*s*, 14850*s*, 1445*s*, 1365*m*, 1335*m*, 1290*w*, 1250*m*, 1185*m*, 1150*m*, 1105*s*, 1075*s*, 1045*s*, 960*s*, 915*w*, 845*m*, 715*s*, 690*m*, 660*m*; ^1H NMR (300 MHz, DMSO-d_6): δ 6.80-7.82 (*m*, 10 H), 5.95 (*m*, 1 H), 5.29 (*d*, *J* = 6.7 Hz, 1 H), 4.65 (*t*, *J* = 8.3 Hz, 1 H), 4.18 (*d*, *J* = 6.7 Hz, 1 H), 4.02 (*d*, *J* = 7.8 Hz, 1 H), 3.40-3.92 (*m*, 7 H); ^{13}C-NMR (50 MHz, DMSO-d_6): δ 146.87 (*s*), 146.66 (*s*), 130.94 (*s*), 130.40, 129.21, 128.80, 127.12, 120.41 (each *d*), 114.77 (*d*), 73.28, 73.02, 69.92, 69.22, 68.47 (each *d*), 63.46 (*t*); Anal. calcd. for $C_{19}H_{22}N_2O_5S$ (390.46): C, 58.45; H, 5.68; N, 7.18; S, 8.21; found: C, 58.74; H, 5.67; N, 7.09; S, 8.21. By acetylation according to GP2 the penta-acetate **(+)-4i** was obtained.– 1.64 g (91%); mp 155-156°C; $[\alpha]_D^{25}$ +820° (c 0.5, $CHCl_3$). Anal. calcd. for $C_{29}H_{32}N_2O_{10}S$ (600.65): C, 57.99; H, 5.34; N, 4.66; S, 5.34; found: C, 58.20; H, 5.19; N, 4.78; S, 5.60.

(-)(1R, 2S, 3R, 4R)-1-[(2S)-1-(3,5-Diphenyl-2,3-dihydro-[1,3,4]thiadiazol-2-yl-)]-pentane-1,2,3,4,5-pentaol (D-*gluco*) [(-)-3j].– 3.12 g (80 %); mp 155-156°C, lit:[5a] 135-140°; $[\alpha]_D^{25}$ = -307° (*c* 0.5, pyridine), lit:[5a] -287°; IR (KBr): 3500-3240 *br s*, 2930*m*, 2920*m*, 2880*w*, 1590*s*, 1500*s*, 1445*s*, 1350*m*, 1250*m*, 1140*m*, 1080*s*, 1070*s*, 1040*s*, 1030*s*, 1000*w*, 970*s*, 880*s*, 760*s*, 740*s*, 690*s*; ^1H NMR (300 MHz, DMSO-d_6): δ 6.80-7.80 (*m*, 10 H), 6.27 (*d*, *J* = 2.6 Hz, 1 H), 5.16 (*d*, *J* = 5.8 Hz, 1 H), 4.10-4.65 (*m*, 5 H), 3.25-3.95 (*m*, 5 H); ^{13}C-NMR (50 MHz, DMSO-d_6): δ 146.51 (*s*), 144.22 (*s*), 131.06 (*s*), 129.55, 129.16, 128.83, 128.71, 126.93, 126.33 (each *d*), 113.51 (*d*), 73.08, 71.38, 71.31, 70.91, 69.99 (each *d*), 63.43 (*t*); Anal. calcd. for $C_{19}H_{22}N_2O_4S$ (390.46): C, 58.45; H, 5.68; N, 7.17; S, 8.21; found: C, 58.20; H, 5.17; N, 7.03; S, 8.23. By acetylation according to GP2 the penta-acetate **(-)-4j** was obtained.– 0.53 g (88%) as an oil; $[\alpha]_D^{25}$ = -47° (*c* 0.6, $CHCl_3$). Anal. calcd. for $C_{29}H_{32}N_2O_{10}S$ (600.65): C, 57.99; H, 5.37; N, 4.66; S, 5.34; found: C, 58.14; H, 5.49; N, 4.37; S, 5.57

(+)-(1R, 2S, 3R, 4R)-1-[(2R)-1-(3,5-Diphenyl-2,3-dihydro-[1,3,4]thiadiazol-2-yl-)]-pentane-1,2,3,4,5-pentaol (D-*gluco*) [(+)-3j].– 0.2 g (5%); mp 156-158°C; lit:[5a] 154-155°C; $[\alpha]_D^{25}$ = +1340° (*c* 0.5, pyridine), lit:[5a] +1233°; IR (KBr): 3500-3245*brs*, 2930*m*, 2925*m*, 2885*w*, 1595*s*, 1505*s*, 1445*s*, 1350*m*, 1245*m*, 1140*m*, 1075*s*, 1070*s*, 1040*s*, 1030*s*, 970*s*, 890*s*, 765*s*, 735*s*, 690*s*; ^1H NMR (250 MHz, DMSO-d_6): δ 6.90-7.80 (*m*, 10 H), 6.30 (*d*, *J* = 2.8 Hz, 1 H), 5.15 (*d*, *J* = 5.9 Hz, 1 H), 4.10-4.75 (*m*, 5 H), 3.27-3.98 (*m*, 5 H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 147.13 (*s*, C(5)), 144.28 (*s*, *ipso*-N-Ph), 130.90 (*s*, *ipso*-C-Ph), 129.60, 129.20, 128.85, 128.70, 126.86, 126.29 (each *d*), 113.59 (*d*, *ortho*-N-Ph), 73.20, 71.40, 71.21, 70.10, 69.75 (each *d*), 62.21 (*t*, C(6)); Anal. calcd. for $C_{19}H_{22}N_2O_4S$ (390.46): C, 58.45; H, 5.68; N, 7.18; S, 8.21; found: C, 58.62; H, 5.74; N, 7.15; S, 8.23. By acetylation according to GP2 the penta-acetate **(+)4j** was obtained.– 0.50 g (83%) as an oil; $[\alpha]_D^{25}$ = +383° (*c* 0.5, $CHCl_3$). Anal. calcd. for $C_{29}H_{32}N_2O_{10}S$ (600.65): C, 57.99; H, 5.37; N, 4.66; S, 5.34; found: C, 57.69; H, 5.41; N, 4.86; S, 5.50.

(+)-(1S, 2S, 3R, 4R)-1-[(2R)-1-(3,5-Diphenyl-2,3-dihydro-[1,3,4]thiadiazol-2-yl-)]-pentane-1,2,3,4,5-pentaol (D-*manno*) [(+)3k].– 2.89 g (74%); mp 203°C (EtOH), lit:[5a] 201-203°C; $[\alpha]_D^{25}$ = +958° (*c* 0.5, pyridine), lit:[5a] +894°; IR (KBr): 3500-3250*br s*, 3050*w*, 3020*w*, 2940*w*, 2920*w*, 1595*s*, 1555*m*, 1500*s*, 1490*s*, 1440*m*, 1370*s*, 1330*w*, 1310*w*, 1260*s*, 1190*m*, 1135*s*, 1100*m*, 1070*s*, 1040*m*, 1020*m*, 1015*s*, 965*s*, 950*s*, 840*m*, 760*s*, 740*s*, 690*s*; ^{1}H NMR (300 MHz, DMSOo-d_6): δ 6.85-7.72 (*m*, 10 H), 6.48 (*d*, *J* = 1.5, 1 H), 4.96 (*d*, *J* = 6.6 Hz, 1 H), 4.66 (*d*, *J* = 8.2 Hz, 1 H), 4.41 (*d*, *J* = 5.3 Hz, 1 H), 4.34 (*t*, *J* = 5.6 Hz, 1 H), 4.25 (*d*, *J* = 7.2 Hz, 1 H), 4.10 (*m*, 1 H), 4.35-4.70 (*m*, 5 H); ^{13}C-NMR (50 MHz, DMSO-d_6): δ 144.08 (*s*), 142.88 (*s*), 131.42 (*s*), 129.63, 129.51, 129.06, 126.50 (each *d*), 113.70 (*d*), 74.59, 71.37, 69.69, 69.67, 68.33 (each *d*), 64.20 (*t*); Anal. calcd. for $C_{19}H_{22}N_2O_4S$ (390.46): C, 58.45; H, 5.68; N, 7.18; S, 8.21; found: C, 58.62; H, 5.75; N, 6.95; S, 8.52. By acetylation according to GP2 the penta-acetate **4k** was obtained.– 0.57 g (95%); mp 127-129°C; $[\alpha]_D^{25}$ = +700° (*c* 0.5, $CHCl_3$). Anal. calcd. for $C_{29}H_{32}N_2O_{10}S$ (600.65): C, 57.99; H, 5.37; N, 4.66; S, 5.34; found: C, 57.82; H, 5.44; N, 4.64; S, 5.69.

(-)-(1S, 2S, 3R, 4R)-1-[(2S)-1-(3,5-Diphenyl-2,3-dihydro-[1,3,4]thiadiazol-2-yl-)]-pentane-1,2,3,4,5-pentaol (D-*manno*) [(-)3k].– 0.8 g (20%); mp 202-203°C (EtOH); $[\alpha]_D^{25}$ -462° (c 0.5, pyridine); IR (KBr): 3500-3250*brs*, 3045*w*, 3025*w*, 2940*w*, 2920*w*, 1590*s*, 1550*m*, 1500*s*, 1490*s*, 1440*m*, 1365*s*, 1330*w*, 1315*w*, 1265*s*, 1185*m*, 1135*s*, 1100*m*, 1070*s*, 1040*m*, 1020*m*, 1015*s*, 965*s*, 950*s*, 840*m*, 760*s*, 745*s*, 690*s*; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.85-7.75 (*m*, 10 H), 6.40 (*d*, *J* = 8.0 Hz, 1 H), 4.90 (*d*, *J* = 7.3 Hz, 1 H), 4.55-4.62 (*m*, 3 H), 4.32 (*d*, *J* = 6.2 Hz, 1 H), 4.13 (*m*, 1 H), 4.39-4.72 (*m*, 5 H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 146.03 (*s*, C(5)), 143.90 (*s*, *ipso*-N-Ph), 131.50 (*s*, *ipso*-C-Ph), 130.03, 129.60, 129.04, 126.42 (each *d*), 113.75 (*d*, *ortho*-N-Ph), 75.20, 72.01, 69.70, 69.52, 68.20 (each *d*), 64.13 (*t*, C(6)); Anal. calcd. for $C_{19}H_{22}N_2O_{10}S$ (390.46): C, 58.45; H, 5.68; N, 7.17; S, 8.21; found: C, 58.22; H, 5.67; N, 7.24; S, 8.19.

(1S, 2R, 3R, 4R)-1-[(2R)-1-(3,5-Diphenyl-2,3-dihydro-[1,3,4]thiadiazol-2-yl-)]-pentane-1,2,3,4,5-pentaol (D-*talo*) (3l).– 3.12 g (80%); mp 183-184°C (EtOH); $[\alpha]_D^{25}$ = +917° (*c* 0.5, pyridine); IR (KBr): 3580*brs*, *3140brs*, 3085*w*, 2980*w*, 2940*m*, 2920*w*, 1565*w*, 1490*s*, 1480*s*, 1445*s*, 1360*m*, 1340*m*, 1290*m*, 1250*m*, 1185*m*, 1155*m*, 1100*s*, 1080*s*, 1045*s*, 960*s*, 915*w*, 845*m*, 720*s*, 690*m*, 660*m*; ^{1}H NMR (250 MHz, DMSO-d_6): δ 6.80-7.75 (*m*, 10 H), 6.40 (*d*, *J* = 1.3 Hz, 1 H), 5.15-5.30 (*m*, 2 H), 4.42-4.72 (*m*, 3 H), 4.18 (*m*, 1 H), 3.28.-3.70 (*m*, 5 H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 146.90 (*s*, C(5)), 145.02, 129.90 (each *s*), 132.01, 130.21, 129.02, 126.90, 120.50 (each *d*), 114.30 (*d*, *ortho*-N-Ph), 74.30, 72.09, 70.03, 70.01, 68.90 (each *d*), 62.49 (*t*, C(6)); Anal. calcd. for $C_{19}H_{22}N_2O_4S$ (390.46): C, 58.45; H, 5.68; N, 7.18; S, 8.21; found: C, 58.65; H, 5.73; N, 6.90; S, 8.34. By acetylation according to GP2 the penta-acetate **4l** was obtained.– 0.52 g (87%) as an oil; $[\alpha]_D^{25}$ = +363° (*c* 0.5, $CHCl_3$). Anal. calcd. for $C_{29}H_{32}N_2O_{10}S$ (600.65): C, 57.99; H, 5.37; N, 4.66; S, 5.34; found: C, 58.13; H, 5.42; N, 4.50; S, 5.48.

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