Pergamon

Tetrahedron 57 (2001) 5429–5434

TETRAHEDRON

Preparation of 3,5-bis-(β-D-glycopyranosyl)-1,2,4-thiadiazoles from *C*-(β-D-glycopyranosyl)thioformamides

Erzsébet Ősz,[a] Katalin Czifrák,[a] Tamás Deim,[a] László Szilágyi,[a] Attila Bényei[b] and László Somsák[a,*]

[a]*Department of Organic Chemistry, University of Debrecen, H-4010 Debrecen, Hungary*
[b]*Department of Physical Chemistry, Laboratory for X-Ray Diffraction, University of Debrecen, H-4010 Debrecen, Hungary*

Received 18 January 2001; revised 3 April 2001; accepted 20 April 2001

Abstract—Acylated *C*-glycopyranosyl thioformamides of D-*gluco*, D-*galacto*, and D-*xylo* configuration were obtained by treating the corresponding glycosyl cyanides with hydrogen sulfide in the presence of triethylamine. The thioformamides gave 3,5-bis-(β-D-glycopyranosyl)-1,2,4-thiadiazoles in reactions with potassium bromate and sodium dithionite in dichloromethane–water biphasic solvent mixture. Deprotected derivatives were prepared by Zemplén deacylation.

1. Introduction

Recently we have reported a simple, short synthetic sequence for the preparation of glycopyranosylidene-*spiro*-hydantoins and their thio analogues.[1–4] The key step of these preparations was a ring closure of acylated *C*-(1-bromo-1-deoxy-β-D-glycopyranosyl)formamides with cyanate or thiocyanate ions. The D-*gluco spiro*-thiohydantoin proved to be the best available glucose analogue inhibitor of muscle and liver glycogen phosphorylase (GP) *a* and *b* enzymes,[2,3] and was also effective in decreasing liver GP*a* activity in vivo.[5] As a part of this project we set out to prepare the corresponding *spiro*-dithiohydantoins in an analogous way. To this end we investigated the radical-mediated bromination of *C*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)thioformamide (**4a**). The new material obtained from this reaction with high mass recovery contained, however, no bromine, and structure elucidation by NMR methods and X-ray crystallography established its structure as 3,5-bis-(β-D-galactopyranosyl)-1,2,4-thiadiazole **7a**.

It has long been known that two molecules of thioamides can undergo intermolecular cyclization under oxidative conditions to give 3,5-disubstituted-1,2,4-thiadiazoles by a mechanism not well understood as yet.[6,7] The reaction has been considered to be limited mainly to arylthioamides and characterized by variable yields and formation of by-products such as nitriles and isothiocyanates.[7]

Since the first observation was encouraging and the product **7a** had an interesting asymmetric bis-*C*-glycosyl heterocyclic structure the reaction was investigated further and extended to other sugar configurations.

2. Results and discussion

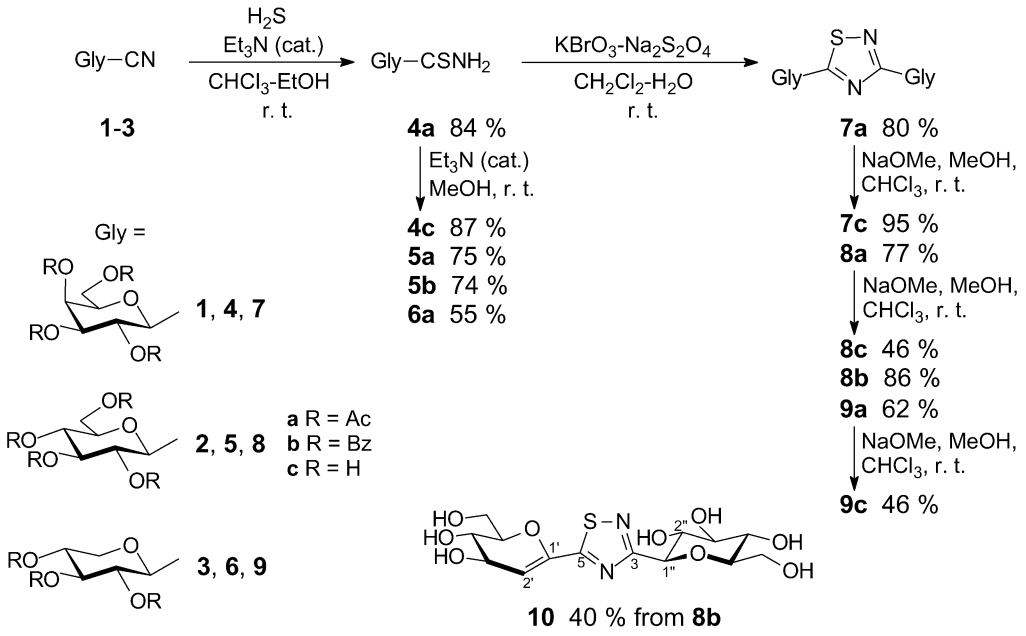
The starting *C*-(β-D-glycopyranosyl)thioformamides **4a**–**6a** and **5b** were prepared from the corresponding acylated β-D-glycopyranosyl cyanides **1a**,[8,9] **2a**,[8,9] **3a**,[10] and **2b**,[4] respectively, by hydrogen sulfide addition in a chloroform–ethanol solvent mixture in the presence of catalytic amounts of triethylamine (Scheme 1). Surprisingly, from *C*-glycosyl thioformamides with pyranoid rings only **6a** and its α-L-arabino analogue have so far been described in the literature using essentially the same procedure with 4-dimethylaminopyridine as the catalyst in 2-propanol for their preparation.[11]

The first experiments were aimed at the radical-mediated bromination[12] of **4a**. In the presence of a catalytic amount of AIBN in bromotrichloromethane at reflux temperature or at room temperature with irradiation only decomposition could be observed. With two equivalents of *N*-bromosuccinimide in the presence of catalytic AIBN in carbon tetrachloride at 60°C the main product was shown to be **7a** by TLC. The best result was achieved with one equivalent of bromine in chloroform solution at room temperature to give **7a** in 80% yield. However, this procedure was not safely reproducible, therefore, other oxidants were sought for. With cerium(IV)ammonium nitrate in aqueous acetonitrile three compounds were isolated: **1a** (16%), *C*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)formamide (31%), and **7a** (44%). Most efficient and convenient was the

Keywords: 1,2,4-thiadiazole; thioamide; bromination; carbohydrates; oxidation.

* Corresponding author. Tel.: +36-52-512-900; fax: +36-52-453-836; e-mail: somsak@tigris.klte.hu

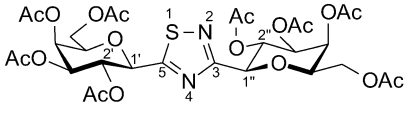
0040–4020/01/$ - see front matter
PII: S0040-4020(01)00444-6



Scheme 1.

preparation of **7a** with the reagent system $KBrO_3$–$Na_2S_2O_4$ in dichloromethane–water biphasic solvent, a mixture similar to the ones proposed recently for benzylic brominations (actually $NaBrO_3$–$NaHSO_3$ was used in EtOAc–H_2O)[13] as well as for deprotection of benzylated carbohydrate derivatives ($NaBrO_3$–$Na_2S_2O_4$ in EtOAc–H_2O).[14] In this way crude **7a** was obtained as a chromatographically homogeneous product in 94% yield. The analogous **8a**, **8b**, and **9a** were isolated in 77, 86, and 62% yields, respectively, after recrystallization of the crude product. Deprotection was performed by the Zemplén method to give **7c**–**9c**. Applying the same protocol to **8b** at room temperature left one of the benzoyl groups untouched even after prolonged reaction time. In refluxing methanol **10** was obtained in a concurrent elimination reaction.

Table 1. Long-range ^{13}C–^{1}H and ^{15}N–^{1}H HMBC correlations in **7a**



$^{13}C/^{15}N$ atom	C-3	C-5	N-2	N-4
^{1}H	H-1″	H-1′	H-1″	H-1′
^{1}H	H-2″	H-2′		H-1″

The structure of **7a** could be established by thorough NMR investigations. The presence of two series of resonances in the ^{1}H and ^{13}C spectra indicated an asymmetric dimeric structure. The proton assignment was based on a ^{1}H–^{1}H COSY experiment. Using ^{13}C–^{1}H HSQC and ^{13}C–^{1}H HMBC spectra two carbon atoms (C-3 and C-5) attached to the anomeric carbons (C-1′ and C-1″) could be assigned, while the ^{15}N–^{1}H HMBC spectrum indicated the presence of two tertiary nitrogen atoms (N-2 and N-4) displaying long-range couplings to the anomeric carbons belonging to a hetero-bond or ring. Long-range ^{15}C–^{1}H and ^{15}N–^{1}H HMBC correlations crucial for the structure determination of **7a** are listed in Table 1. These observations are compatible with the presence of a 3,5-disubstituted-1,2,4-thiadiazole moiety as the bridging element in the dimeric structure. The high values (9.9 and 9.8 Hz) of the $^{3}J_{H\text{-}1',H\text{-}2'}$ and $^{3}J_{H\text{-}1'',H\text{-}2''}$ coupling constants are characteristic for β(D) configurations at both anomeric centres. Single crystal X-ray structure determination provided further confirmation of the structure of compound **7a** (Fig. 1). Each of the other 1,2,4-thiadiazole derivatives **7**–**9**, either protected or

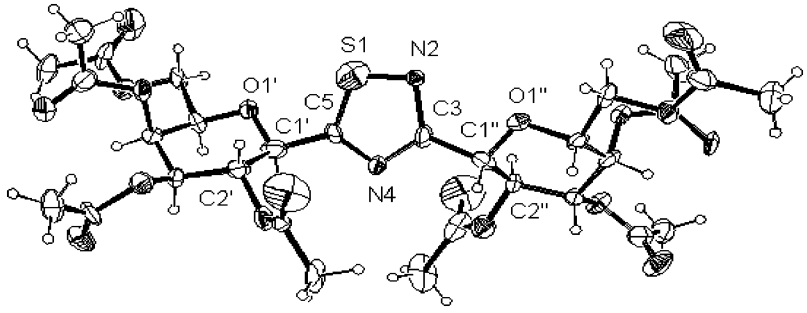


Figure 1. ORTEP drawing of thiadiazole **7a**.

unprotected, had similar characteristics with respect to the anomeric protons as well as the carbons of the heterocycle in the ^{1}H and ^{13}C spectra (see Section 4). In compound **10** a $^{13}C-^{1}H$ HMBC measurement indicated that the unsaturated sugar moiety was attached to C-5 and the β-D-glucopyranosyl residue to C-3.

Some of the deprotected derivatives were assayed as inhibitors of glycosidase enzymes and showed moderate effects with K_i values in the millimolar range (**7c**: *Escherichia coli* β-D-galactosidase 0.3 mM; **9c**: *Aspergillus carbonarius* β-D-xylosidase 12 mM).

3. Conclusion

The described method introduces a new reagent system for the preparation of 1,2,4-thiadiazoles from thioamides, and offers an easy access to interesting 3,5-bis-*C*-glycosyl-1,2,4-thiadiazoles from readily available per-*O*-acylated *C*-(β-D-glycosyl)thioformamides. Some literature examples of similar but symmetric dimeric structures can be found with the D-*gluco* configuration having a triazin-2,4,6-trione as the bridging element.[15] Although these compounds proved moderate inhibitors of glycosidase enzymes, because of the well known biological activities of 1,2,4-thiadiazole derivatives[6] they may deserve further attention.

4. Experimental

Melting points were measured in open capillary tubes or on a Kofler hot-stage and are uncorrected. Optical rotations were determined with a Perkin-Elmer 241 polarimeter at room temperature. NMR spectra were recorded with Bruker WP 200 SY (200/50 MHz for $^{1}H/^{13}C$) or Avance DRX 500 (500/125/50 MHz for $^{1}H/^{13}C/^{15}N$) spectrometers. Chemical shifts are referenced to Me_4Si (^{1}H), to the residual solvent signals (^{13}C) or to NH_4Cl as external standard (^{15}N). TLC was performed on DC-Alurolle Kieselgel 60 F_{254} (Merck), and the plates were visualised by gentle heating. For column chromatography Kieselgel 60 (Merck, particle size 0.063–0.200 mm) was used. Organic solutions were dried over anhydrous $MgSO_4$ and concentrated in vacuo at 40–50°C (water bath).

4.1. General procedure I: preparation of per-*O*-acylated *C*-(β-D-glycopyranosyl)thioformamides 4a–6a, and 5b

A glycopyranosyl cyanide (**1a**–**3a**, or **2b**, 2.8 mmol) was dissolved in chloroform (10 ml) and ethanol (5 ml) was added. Dry hydrogen sulfide was bubbled through the reaction mixture at room temperature for 45–50 min to saturation. Triethylamine (0.1 ml, 0.78 mmol) was then added and the introduction of hydrogen sulfide continued for another 3–3.5 h (until no more starting material could be detected by TLC, eluent ethyl acetate–hexane 1:1). The reaction mixture was evaporated under reduced pressure and the residue crystallised from ethanol.

4.1.1. *C*-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-thioformamide 4a. By *general procedure I* from **1a**: pale yellowish crystals, yield 84%; mp 134–135°C; $[\alpha]_D=+17$ (*c* 1.29, $CHCl_3$); ν_{max} (KBr) 3428, 3320, 3218, 2968, 1746, 1632, 1448, 1368, 1220, 1098, 1064 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.75 (1H, bs, NH_2), 7.60 (1H, bs, NH_2), 5.50 (1H, dd, J=3.3, ~1 Hz, H-4), 5.29 (1H, quasi t, J=10.2, 9.6 Hz, H-2), 5.15 (1H, dd, J=10.2, 3.3 Hz, H-3), 4.39 (1H, d, J=9.6 Hz, H-1), 4.26 (1H, dd, J=11.5, 7.1 Hz, H-6), 4.11 (1H, dd, J=11.5, 5.6 Hz, H-6′), 4.04 (1H, ~td, J=7.1, 5.6, ~1 Hz, H-5), 2.18, 2.08, 2.07, 1.99 (12H, 4s, 4×OAc); ^{13}C NMR ($CDCl_3$): δ 200.0 ($CSNH_2$, $^{3}J_{H\text{-}1,CSNH2}$=2.8 Hz), 170.3, 169.9, 169.8, 169.7 (C=O), 83.0 (C-1), 74.0, 71.2, 67.5, 67.2 (C-2 to C-5), 61.4 (C-6), 20.9, 20.5, 20.4, 20.3 (CH_3); ^{15}N NMR (DMSO-d_6): δ 151.7 (NH_2). Anal. calcd for $C_{15}H_{21}NO_9S$ (391.40): C, 46.03; H, 5.41; N, 3.58; S, 8.19; found: C, 46.40; H, 5.46; N, 3.86; S, 8.42.

4.1.2. *C*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)thioformamide 5a. By *general procedure I* from **2a**: pale yellowish crystals, yield 75%; mp 138–140°C; $[\alpha]_D=-15$ (*c* 0.95, $CHCl_3$); ν_{max} (KBr) 3376, 3330, 3178, 2950, 1752, 1716, 1628, 1430, 1374, 1230, 1210, 1094, 1036 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.00 (1H, bs, NH_2), 7.80 (1H, bs, NH_2), 5.24–5.04 (3H, 3×t, H-2,3,4), 4.34 (1H, d, J=9.5 Hz, H-1), 4.24 (1H, dd, J=12.1, 4.4 Hz, H-6), 4.08 (1H, dd, J=12.1, 2.2 Hz, H-6′) 3.77 (1H, m, H-5), 2.04, 2.00, 1.98, 1.94 (12H, 4s, 4×OAc); ^{13}C NMR ($CDCl_3$): δ 199.6 ($CSNH_2$), 170.0, 169.8, 169.4 (C=O), 82.8 (C-1), 75.0, 73.2, 70.0, 67.6 (C-2 to C-5) 61.9 (C-6), 20.9, 20.6, 20.3 (CH_3). Anal. calcd for $C_{15}H_{21}NO_9S$ (391.40): C, 46.03; H, 5.41; N, 3.58; found: C, 46.22; H, 5.29; N, 3.65.

4.1.3. *C*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)thioformamide 5b. By *general procedure I* from **2b**: pale yellowish crystals, yield 74%; mp 198–200°C; $[\alpha]_D=-18$ (*c* 1.02, $CHCl_3$); ν_{max} (KBr) 3420, 3331, 3250, 3100, 1732, 1602, 1316, 1268, 1178, 1094, 1068, 708 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.1–7.8 (10H, m, aromatic+NH_2), 7.6–7.2 (12H, m, aromatic), 5.97 (1H, t, J=9.5, 9.5 Hz), 5.72 (1H, t, J=9.5, ~10 Hz), 5.62 (1H, t, J=9.5, 9.5 Hz) (H-2 to H-4), 4.74 (1H, d, J=9.5 Hz, H-1), 4.69 (1H, dd, J=12.6, 2.6 Hz, H-6), 4.55 (1H, dd, J=12.6, 5.3 Hz, H-6′), 4.24 (1H, dd, J=9.5, 5.3, 2.6 Hz, H-5); ^{13}C NMR ($CDCl_3$): δ 190.6 ($CSNH_2$), 166.3, 165.5, 165.4, 165.1 (C=O), 133–128 (aromatic signals), 82.7(C-1), 75.9, 73.4, 71.2, 69.0 (C-2 to C-5), 62.8 (C-6). Anal. calcd for $C_{35}H_{29}NO_9S$ (639.67): C, 65.72; H, 4.54; N, 2.19; found: C, 65.44; H, 4.46; N, 2.41.

4.1.4. *C*-(2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl)thioformamide 6a. By *general procedure I* from **3a**: pale yellowish crystals, yield 55%; mp 179–181°C (lit.[11] mp 179–181°C).

4.2. General procedure II: preparation of per-*O*-acylated 3,5-bis-(β-D-glycopyranosyl)-1,2,4-thiadiazoles 7a–9a and 8b

A per-*O*-acylated *C*-(β-D-glycopyranosyl)thioformamide (**4a**–**6a**, or **5b**, 0.5 mmol) was dissolved in dichloromethane (12 ml), a solution of $KBrO_3$ (0.42 g, 2.5 mmol) in water (6 ml) was added and the two phase mixture was vigorously stirred. A solution of $Na_2S_2O_4$ (0.49 g, 2.8 mmol) in water (6 ml) was added dropwise during ~10 min and stirring

continued until disappearance of the starting material (TLC, eluent ethyl acetate–hexane 1:1, ~0.5 h). Dichloromethane (30 ml) was then added, and the organic phase washed with 5% aq. $Na_2S_2O_3$ (20 ml), and water (20 ml), dried, and the solvent evaporated. The syrupy crude product was crystallized from 96% EtOH.

4.2.1. 3,5-Bis-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-1,2,4-thiadiazole 7a. To a solution of **4a** (0.1 g, ~0.26 mmol) in chloroform (6 ml) bromine (0.13 ml, ~0.26 mmol) was added with stirring at room temperature. The reaction mixture was then immediately evaporated under reduced pressure, and the yellowish residue crystallised from ethanol to yield crude **7a**. Recrystallisation from hot ethanol gave the title compound **7a** (0.077 g, 80%) as white crystals; mp 203–204°C; $[\alpha]_D$=+23 (*c* 2.10, $CHCl_3$); ν_{max} (KBr) 2976, 1756, 1434, 1370, 1234, 1116, 1054 cm^{-1}; ^1H NMR (C_6D_6): δ 6.09 (1H, quasi t, *J*=10.2, 9.9 Hz, H-2′), 5.79 (1H, quasi t, *J*=10.2, 10.0 Hz, H-2″), 5.66 (1H, d, *J*=3.3, <1 Hz, H-4′), 5.60 (1H, d, *J*=3.3, <1 Hz, H-4″), 5.42 (1H, dd, *J*=10.2, 3.3 Hz, H-3′), 5.34 (1H, dd, *J*=10.2, 3.3 Hz, H-3″), 4.90 (1H, d, *J*=10.2 Hz, H-1′), 4.61 (1H, d, *J*=10.2 Hz, H-1″), 4.26 (2H, strongly coupled AB spinsystem, *J*=6.5 Hz, H-6a′,6b′), 4.15 (2H, strongly coupled AB spinsystem, *J*=6.5 Hz, H-6a″,6b″), 3.59 (1H, quasi t, *J*=6.5, <1 Hz, H-5′), 3.40 (1H, quasi t, *J*=6.5, <1 Hz, H-5″); in C_6D_6–$CDCl_3$=1:1 solvent mixture the signals of the H-6a,6b′ and H-6a,6b″ protons are distinguished: δ 4.17 (1H, dd, *J*=11.4, 6.5 Hz, H-6a′), 4.11 (1H, dd, *J*=11.4, 6.5 Hz, H-6b′), 4.09 (1H, dd, *J*=11.4, 6.7 Hz, H-6a″), 4.06 (1H, dd, *J*=11.4, 6.2 Hz, H-6b″), 2.12, 1.76, 1.73, 1.67, 1.62, 1.61, 1.60, 1.56 (24H, 8s, 8×CH_3); ^{13}C NMR (C_6D_6): δ 189.9 (C-5), 171.8 (C-3), 170.5, 170.3, 170.1, 170.0, 169.9, 169.7, 169.1 (C=O), 77.7 (C-1′), 77.4 (C-1″), 75.5 (C-5′), 75.5 (C-5″), 72.9 (C-3′), 72.2 (C-3″), 69.3 (C-2′), 69.2 (C-2″), 68.4 (C-4′), 67.8 (C-4″), 62.1 (CH_2′), 61.5 (CH_2″), 21.1, 20.7, 20.5, 20.48, 20.42, 20.3, 20.1 (CH_3); ^{15}N NMR (DMSO-d_6): δ 274.6 (N-4), 240.9 (N-2). Anal. calcd for $C_{30}H_{38}N_2O_{18}S$ (746.70): C, 48.26; H, 5.13; N, 3.75; S, 4.29; found: C, 47.75; H, 5.15; N, 3.81; S, 4.52.By *general procedure II* from **4a**: yield 94%, mp 197–198°C, recrystallization from EtOH with 85% recovery; mp 203–204°C.

4.2.2. 3,5-Bis-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,4-thiadiazole 8a. By *general procedure II* from **5a**: white crystals, yield 77%; mp 189–191°C; $[\alpha]_D$=−3 (*c* 1.04, $CHCl_3$); ν_{max} (KBr) 2948, 1752, 1434, 1370, 1226, 1104, 1036 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.40–5.06 (6H, m, H-2′ to H-4′ and H-2″ to H-4″), 4.88 (1H, d, *J*=9.5 Hz, H-1′), 4.76 (1H, d, *J*=9.5 Hz, H-1″), 4.32–4.02 (4H, H-6a′, H-6b′, H-6a″, H-6b″), 3.84 (2H, m, H-5′, H-5″), 2.12, 2.05, 2.04, 2.00, 1.95, 1.80 (24H, 6s, 8×OAc); ^{13}C NMR ($CDCl_3$): δ 188.7 (C-5), 170.4, 170.3, 170.2, 170.1, 169.9, 169.3, 168.8, 168,7 (C=O), 169.3 (C-3), 76.8 (C-1′), 76.5 (C-1″), 76.3, 76.2, 73.9, 73.2, 70.9 two carbons, 68.0, 67.9 (C-2′ to C-5′ and C-2″ to C-5″), 62.1, 61.7 (C-6′, C-6″), 20.5, 20.4, 20.1 (CH_3); Anal. calcd for $C_{30}H_{38}N_2O_{18}S$ (746.69): C, 48.25; H, 5.09; N, 3.75; S, 4.28; found: C, 48.42; H, 4.98; N, 3.77; S, 4.30.

4.2.3. 3,5-Bis-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,2,4-thiadiazole 8b. By *general procedure II* from **5b**: white crystals, yield 86%; mp 280–282°C; $[\alpha]_D$=−10 (*c* 0.98, $CHCl_3$); ν_{max} (KBr) 3066, 2954, 2884, 1740, 1602, 1584, 1492, 1452, 1316, 1264, 1178, 1108, 1094, 708 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.1–7.1 (40H, m, aromatic), 6.06–5.33 (6H, 6×t, H-2′ to H-4′ and H-2″ to H-4″), 5.24 (1H, d, *J*=9.5 Hz, H-1′), 4.95 (1H, d, *J*=9.5 Hz, H-1″), 4.72 (1H, dd, *J*=12.6, 2.6 Hz, H-6a′ or H-6a″), 4.53 (1H, dd, *J*=12.6, 4.7 Hz, H-6b′ or H-6b″), 4.42 (1H, dd, *J*=12.6, 2.6 Hz. H-6a′ or H-6a″), 4.40–4.28 (2H, m, H-5′ or H-5″ and H-6b′ or H-6b″), 4.13 (1H, ddd, *J*=9.5, 4.7, 2.6 Hz, H-5′ or H-5″); ^{13}C NMR ($CDCl_3$): δ 188.4 (C-5), 170.5 (C-3), 166.1, 166.0, 165.7, 165.1, 165.0, 164.8, 164.2 (C=O), 134–128 (aromatic signals), 77.0 (C-1′), 76.9 (C-1″), 76.8, 76.4, 74.5, 73.5, 71.9, 71.4, 69.6, 69.2 (C-2′ to C-5′ and C-2″ to C-5″), 63.9, 62.7 (C-6′, C-6″); Anal. calcd for $C_{70}H_{54}N_2O_{18}S$ (1242.56): C, 67.63; H, 4.35; N, 2.25; S, 2.57; found: C, 67.09; H, 4.36; N, 2.35; S, 2.56.

4.2.4. 3,5-Bis-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-1,2,4-thiadiazole 9a. By *general procedure II* from **6a**: white crystals, yield 62%; mp 198–199°C; $[\alpha]_D$=−53 (*c* 0.50 $CHCl_3$); ν_{max} (KBr) 2940, 2860, 1752, 1628, 1430, 1374, 1226, 1112, 1088, 1058, 1036 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.42–4.98 (6H, m, H-2′, H-2″, H-3, H-3″, H-5a, H-5a″), 4.77 (1H, d, *J*=9.5 Hz, H-1′), 4.67 (1H, d, *J*=9.5 Hz, H-1″), 4.25 (2H, m, H-4′, H-4″) 3.56–3.40 (2H, m, H-5b′ or H-5b″), 2.03, 2.01, 1.97, 1.82 (18H, 4s, 6×OAc); ^{13}C NMR ($CDCl_3$): δ 189.0 (C-5), 170.5, 170.1, 169.9, 169.6, 169.2, 168.8 (C=O), 168.6 (C-3), 76.7 (C-1′, C-1″), 73.0, 72.5, 71.0, 70.8, 68.6, 68.5 (C-2′ to C-4′ and C-2″ to C-4″), 66.9, 66.8, (C-5′,C-5″), 20.5, 20.4, 20.2 (CH_3); Anal. calcd for $C_{24}H_{30}N_2O_{14}S$ (616.56): C, 46.75; H, 4.90; N, 4.54; S, 5.20; found: C, 46.13; H, 4.98; N, 4.45; S, 5.11.

4.3. General procedure III: preparation of the deprotected 3,5-bis-(β-D-glycopyranosyl)-1,2,4-thiadiazoles 7c–9c

A per-*O*-acylated 3,5-bis-(β-D-glycopyranosyl)-1,2,4-thiadiazole (**7a**–**9a** or **8b**, 0.16 mmol) was dissolved in a mixture of chloroform (20 ml) and methanol (10 ml), and 20 drops of a 1 M solution of NaOMe in MeOH were added. The solution was kept at room temperature for deacetylations or refluxed for debenzoylation until completion of the transformation (TLC, eluent chloroform–methanol 2:1). Then the solution was treated with Amberlyst 15 (H^+ form) filtered and the solvent evaporated. The syrupy residue was purified by column chromatography with chloroform–methanol 2:1 if necessary.

4.3.1. 3,5-Bis-(β-D-galactopyranosyl)-1,2,4-thiadiazole 7c. By *general procedure III* from **7a**: white crystals, yield 95%; mp 150–152°C; $[\alpha]_D$=+53 (*c* 1.1, MeOH); ^1H NMR (CD_3OD): δ 4.64 (1H, d, *J*=9.6 Hz, H-1′), 4.46 (1H, d, *J*=9.6 Hz, H-1″), 4.16 (1H, t, *J*=9.6, 9.5 Hz, H-2′ or H-2″), 3.93 (2H, t, *J*=3.20 Hz, H-3′, H-3″), 3.86-3.55 (9H, m, H-2′, H-4′, H-4″,H-5′, H-5″, H-6a′, H-6a″, H-6b′, H-6b″); ^{13}C NMR (CD_3OD): δ 192.3 (C-5), 173.6 (C-3), 81.4 (C-1′), 81.3 (C-1″), 80.0, 79.7, 75.9, 75.6, 72.4, 71.5,70.9, 70.5 (C-2′ to C-5′ and C-2″ to C-5″), 62.8, 62.7 (C-6′, C-6″); Anal. calcd for $C_{14}H_{22}N_2O_{10}S$ (410.34):

C, 40.97; H, 5.36; N, 6.83; found: C, 40.51; H, 5.46; N, 6.91.

4.3.2. 3,5-Bis-(β-D-glucopyranosyl)-1,2,4-thiadiazole 8c. By *general procedure III* from **8a**: yield 46%, colourless syrup; (R_f=0.24, chloroform–methanol 1:1); $[\alpha]_D$=+23 (*c* 0.95, MeOH); ^{1}H NMR (CD_3OD): δ 4.72 (1H, d, *J*=9.4 Hz, H-1′), 4.57 (1H, d, *J*=9.4 Hz, H-1″), 3.92 (1H, dd, *J*=12.1 Hz, H-6a′ or H-6a″), 3.90–3.82 (2H, m, H-6a′ or H-6a″, H-2′or H-2″), 3.76–3.65 (2H, m, H-2′ or H-2″, H-3′ or H-3″, 3.56–3.44 (5H, m, H-3′ or H-3″, H-4′, H-4″, H-5′, H-5″), 3.40 (2H, m, H-6b′, H-6b″); ^{13}C NMR (CD_3OD): δ 191.9 (C-5), 173.6 (C-3), 82.7 (C-1′), 82.6 (C-1″), 79.6, 79.3, 79.2, 79.1, 75.4, 74.2, 71.5, 71.3 (C-2′ to C-5′ and C-2″ to C-5″), 63.0, 62.9 (C-6′, C-6″); Anal. calcd for $C_{14}H_{22}N_2O_{10}S$ (410.39): C, 40.97; H, 5.36; N, 6.83; found: C, 40.47; H, 5.45; N, 6.75.

4.3.3. 3,5-Bis-(β-D-xylopyranosyl)-1,2,4-thiadiazole 9c. By *general procedure III* from **9a**: colourless syrup, yield 46%; (R_f=0.24, chloroform–methanol 2:1); $[\alpha]_D$=−4 (*c* 1.0, MeOH); ^{1}H NMR (CD_3OD): δ 4.67 (1H, d, *J*=9.5 Hz, H-1′), 4.50 (1H, d, *J*=9.5 Hz, H-1″), 4.08 (1H, dd, *J*=11.1, 5.3 Hz, H-5a′ or H-5a″), 3.99 (1H, dd, *J*=11.1, 5.3 Hz, H-5a′ or H-5a″), 3.93 (1H, t, *J*=9.5, 9.5 Hz), 3.70–3.62 (2H, m, H-4′, H-4″), 3.54–3.32 (5H, m); ^{13}C NMR (CD_3OD): δ 192.3 (C-5), 174.0 (C-3), 80.3 (C-1′), 80.1 (C-1″), 79.4, 79.0, 75.7, 74.4, 71.2, 70.7 (C-2′ to C-4′ and C-2″ to C-4″), 71.6, 71.5 (C-5′, C-5″); Anal. calcd for $C_{12}H_{18}N_2O_8S$ (350.34): C, 41.14; H, 5.14; N, 8.00; found: C, 41.31; H, 5.03; N, 8.12.

4.4. *C*-(β-D-Galactopyranosyl)thioformamide 4c

Compound **4a** (0.1 g, 2.55 mmol) was dissolved in MeOH (10 ml) and triethylamine (~10 drops) was added. The mixture was kept at room temperature for 1 d, and then overnight at 35–40°C. After solvent removal the residue was purified by column chromatography (chloroform–methanol–ethyl acetate 2:1:1) to give **4c** as white crystals: yield 87%; mp 165–167°C; $[\alpha]_D$=+114 (*c* 1.06, MeOH); ^{1}H NMR (CD_3OD): δ 4.01 (1H, d, *J*=9.1 Hz, H-1), 3.89 (1H, dd, *J*=3.2, ~1 Hz, H-4), 3.83 (1H, dd, *J*=11.6, 7.4 Hz, H-6), 3.72–3.63 (3H, m,H-2,5,6′), 3.66 (1H, dd, *J*=9.2, 3.2 Hz, H-3); ^{13}C NMR (CD_3OD): δ 204.7 ($CSNH_2$), 84.7 (C-1), 79.9, 75.7, 71.6, 70.3 (C-2 to C-5), 62.9 (C-6). Anal. calcd for $C_7H_{13}NO_5S$ (223.28): C, 37.67; H, 5.83; N, 6.28; found: C, 36.91; H, 5.86; N, 6.24.

4.5. 3-(β-D-Glucopyranosyl)-5-(2-deoxy-D-arabino-hex-1-enopyranosyl)-1,2,4-thiadiazole 10

By *general procedure III* from **8b**: colourless syrup, yield 40%; (R_f=0.28, chloroform–methanol 2:1); $[\alpha]_D$=+21 (*c* 0.8, MeOH); ^{1}H NMR (CD_3OD): δ 6.10 (1H, t, *J*=2.6, <1 Hz, H-2′), 4.59 (1H, d, *J*=9.5 Hz, H-1″), 4.36 (1H, dd,*J*=7.4, 2.6 Hz, H-3′), 4.08 (1H, ddd, *J*=8.9, 4.7, 2.1 Hz, H-5a′ or H-5a″), 4.04–3.68 (6H, m, H-2″, H-3″, H-4′, H-4″, H-6a′ or H-6a″, H-6b′ or H-6b″), 3.58–3.44 (3H, m, H-5′or H-5″, H-6a′ or H-6a″, H-6b′ or H-6b″); ^{13}C NMR (CD_3OD): δ 185.5 (C-5), 174.8 (C-3), 145.9 (C-1′), 107.6 (C-2′), 82.4 (C-1″), 82.2, 79.5, 79.3, 74.5, 71.3, 70.1, 70.0 (C-3′ to C-5′ and C-2″ to C-5″), 62.6, 61.8 (C-6′, C-6″); Anal. calcd for $C_{14}H_{20}N_2O_9S$ (392.38): C, 42.85; H, 5.14; N 7.14; found: C, 42.92; H, 5.34; N 7.22.

4.6. X-Ray crystallography† of 7a

Colourless prism crystals (0.44×0.3×0.23 mm) of $C_{30}H_{38}N_2O_{18}S$, grown from ethanol *M*=746.68, orthorhombic, *a*=8,912(1) Å, *b*=8,905(1) Å, *c*=46,308(1) Å, *V*=3675,1(6) Å^3, *Z*=4, space group: $P2_12_12_1$, ρ_{calc}=1.35 g cm^{-3}. Data were collected at 293(1) K, Enraf Nonius MACH3 diffractometer, Mo Kα radiation λ=0.71073 Å, ω–2θ motion, θ_{max}=25.47°, 3052 reflections of which 1531 were unique with $I>2\sigma(I)$, decay: 1%. The structure was solved using the SIR-92 software[16] and refined on *F*[17] using SHELX-97[17] program, publication material was prepared with the WINGX-97 suite,[18] $R(F)$=0.10 and $wR(F^2)$=0.31 for 3052 reflections, 461 parameters.

Acknowledgements

This work was supported by the Hungarian Scientific Research Fund (Grants: OTKA T23814, T32124, D25136) and the Ministry of Education (Grant: FKFP 423/2000). Professor László Kiss is thanked for the enzyme assays.

References

1. Ősz, E.; Sós, E.; Somsák, L.; Szilágyi, L.; Dinya, Z. *Tetrahedron* **1997**, *53*, 5813–5824.
2. Ősz, E.; Somsák, L.; Szilágyi, L.; Kovács, L.; Docsa, T.; Tóth, B.; Gergely, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1385–1390.
3. Somsák, L.; Kovács, L.; Tóth, M.; Ősz, E.; Szilágyi, L.; Györgydeák, Z.; Dinya, Z.; Docsa, T.; Tóth, B.; Gergely, P. *J. Med. Chem.*, accepted for publication.
4. Somsák, L.; Nagy, V. *Tetrahedron: Asymmetry* **2000**, *11*, 1719–1727, Corrigendum 2247.
5. Somsák, L.; Nagy, V.; Docsa, T.; Tóth, B.; Gergely, P. *Tetrahedron: Asymmetry* **2000**, *11*, 405–408.
6. Kurzer, F. *Adv. Heterocycl. Chem.* **1982**, *32*, 285–398.
7. Wilkins, D. J.; Bradley, P. A. In *Comprehensive Heterocyclic Chemistry II*, Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Exeter, 1996; Vol. 4, pp 307–354.
8. Myers, R. W.; Lee, Y. C. *Carbohydr. Res.* **1984**, *132*, 61–85.
9. Myers, R. W.; Lee, Y. C. *Carbohydr. Res.* **1986**, *154*, 145–163.
10. Helferich, B.; Ost, W. *Chem. Ber.* **1962**, *95*, 2612–2615.
11. Kovács, L.; Herczegh, P.; Batta, G.; Farkas, I. *Tetrahedron* **1991**, *47*, 5539–5548.
12. Somsák, L.; Ferrier, R. J. *Adv. Carbohydr. Chem. Biochem.* **1991**, *49*, 37–92.
13. Kikuchi, D.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1998**, *63*, 6023–6026.
14. Adinolfi, M.; Barone, G.; Guariniello, L.; Iadonisi, A. *Tetrahedron Lett.* **1999**, *40*, 8439–8441.

† Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 156556.

15. Jochims, J. C.; von Voithenberg, H.; Wegner, G. *Chem. Ber.* **1978**, *111*, 1693–1708.
16. Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A. *J. Appl. Crystallogr.* **1993**, *26*, 343–350.
17. Sheldrick, G. M. *SHELXL-97*; Universität Göttingen, Germany.
18. Farrugia, L. J. *WINGX-97 system*; University of Glasgow, UK.