ELSEVIER

Carbohydrate Research 301 (1997) 23–32

CARBOHYDRATE RESEARCH

Synthesis of 4-cyanophenyl 2-azido-2-deoxy- and 3-azido-3-deoxy-1,5-dithio-β-D-xylopyranosides [1,2]

Éva Bozó, Sándor Boros, János Kuszmann *

Institute for Drug Research, P.O.B. 82, H-1325 Budapest, Hungary

Received 30 December 1996; accepted 22 February 1997

Abstract

Azidonitration of 3,4-di-*O*-benzoyl-1,5-anhydro-5-thio-D-*threo*-pent-1-enitol (3,4-di-*O*-benzoyl-5-thio-D-xylal) afforded a 1:1 mixture of 2-azido-3,4-di-*O*-benzoyl-2-deoxy-1-*O*-nitro-5-thio-α-D-xylo- and lyxo-pyranosides, which were converted after separation into their 1-*O*-acetyl derivatives **8** and **11**, respectively. Glycosidation of **8** and **11** with methanol in the presence of trimethylsilyl triflate afforded methyl 2-azido-3,4-di-*O*-benzoyl-2-deoxy-5-thio-α,β-D-xylo- and lyxo-pyranosides in a ratio of 1:1, and 5:2, respectively. When 4-cyanothiophenol was used as acceptor for the glycosidation of **8**, the anomeric thioglycosides were formed in the same ratio (1:1). Deacetylation of the β-isomer afforded 4-cyanophenyl 2-azido-2-deoxy-1,5-dithio-β-D-xylopyranoside **3**. 3-Azido-3-deoxy-5-*S*-benzoyl-1,2-*O*-isopropylidene-α-D-xylofuranose was synthesised from D-glucose in 10 steps and was converted into 1,2,4-tri-*O*-acetyl-3-azido-3-deoxy-5-thio-D-xylopyranose **31**. Glycosidation of **31** with 4-cyanothiophenol in the presence of trimethylsilyl triflate afforded 4-cyanothiophenyl 2,4-di-*O*-acetyl-3-azido-3-deoxy-5-thio-α,β-D-xylopyranoside in a ratio of 1:1.5. Their deacetylation gave 4-cyanophenyl 3-azido-3-deoxy-1,5-dithio-β-D-xylopyranoside **4** and its α-anomer **34**. Reduction of **4** with sodium borohydride-nickel chloride gave the 3-amino derivative **36**, which was converted into the acetamido compound **38**. Compounds **3**, **4**, and **36** possess high oral antithrombotic activity, which decreases on acetylation of the amino group in **38**. The α-anomer **34** was inactive. © 1997 Elsevier Science Ltd.

Keywords: 2-Azido-2-deoxy-5-thio-D-xylose; 3-Azido-3-deoxy-5-thio-D-xylose; Azidonitration reaction; Glycosidation reactions; Thioglycosides; Oral antithrombotic activity

1. Introduction

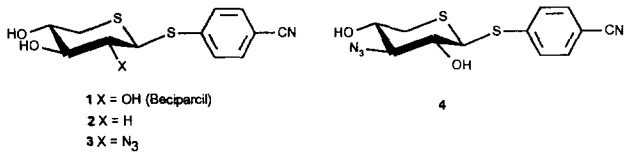
In a previous paper [1], the synthesis of 4-cyanophenyl 2-deoxy-1,5-dithio-β-D-xylopyranoside (**2**), which differed from 4-cyanophenyl 1,5-dithio-β-D-xylopyranoside (beciparcil, **1**) [2] in the absence of the hydroxyl group at C-2 was reported. (See Scheme 1.) As the oral antithrombotic activity was substantially increased by this alteration, exchange of the individual hydroxyl groups of beciparcil by other polar, but aprotic substituents was decided. Among the different candidates the azido group was chosen,

* Corresponding author.

[1] Orally active antithrombotic thioglycosides, Part II. For Part I see [1].

[2] Presented partly at the XVIIIth International Carbohydrate Symposium, Milan, July 21–26, 1996. Abstr. BP090.

PII S0008-6215(97)00079-7



1 X = OH (Beciparcil)
2 X = H
3 X = N_3

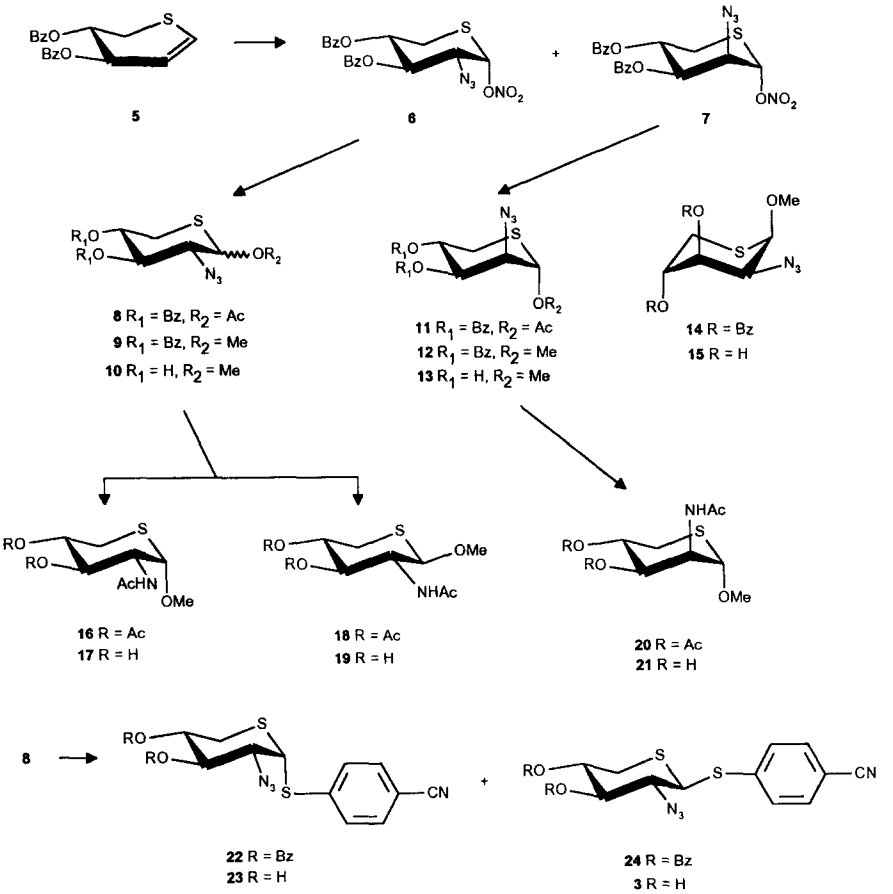
4

Scheme 1.

because such substitution may cause a dramatic change in the properties of biologically important carbohydrate derivatives. One outstanding example is 3′-azido-3′-deoxy-thymidin [3] which, in contrast with thymidin, possesses a well documented anti-HIV activity [4]. In the present paper, the synthesis of the 2-azido-2-deoxy- (**3**) and 3-azido-3-deoxy (**4**) analogs of beciparcil is described.

2. Results and discussion

*Synthesis of 4-cyanophenyl 2-deoxy-2-azido-1,5-dithio-β-*D*-xylopyranoside* (**3**).—For the synthesis of **3**, a properly substituted 2-azido-2-deoxy-5-thio-D-xylopyranose was needed as donor molecule, which could be obtained from 3,4-di-*O*-benzoyl-1,5-anhydro-5-thio-D-*threo*-pent-1-enitol (3,4-di-*O*-benzoyl-5-thio-D-xylal, **5**) [1] by applying the conditions of the azidonitration reaction, which was introduced by Lemieux and Ratcliffe [5] for the conversion of 3,4,6-tri-*O*-acetyl-1,5-anhydro-D-*lyxo*-hex-1-enitol into the corresponding 1-*O*-nitro-2-azido derivatives. (See Scheme 2.) Treatment of a solution of **5** in acetonitrile with sodium azide and subsequently with ceric ammonium nitrate at −20 °C afforded a 1:1 mixture of the D-*xylo* (**6**) and the D-*lyxo* derivative (**7**), separable by column chromatography. According to NMR spectroscopy, both isomers adopted the $^4C_1$-D conformation and contained an α-oriented nitro group. They could be converted into the corresponding 1-*O*-acetyl derivatives **8** and **11**, respectively, on treatment with sodium acetate in acetic acid at elevated temperature (100 °C). Nevertheless, the yield of this conversion was much lower (29%) in the case of **7** affording the α-acetate **11** exclusively, than for **6** (65%) from which a 1:1 mixture of **8α** and **8β** was formed. The lower yield of **11** was probably due to the instability of **7** which decomposed on standing at room temperature, whereas the exclusive formation of the α-anomer may be the consequence of the



5

6

7

8 R_1 = Bz, R_2 = Ac
9 R_1 = Bz, R_2 = Me
10 R_1 = H, R_2 = Me

11 R_1 = Bz, R_2 = Ac
12 R_1 = Bz, R_2 = Me
13 R_1 = H, R_2 = Me

14 R = Bz
15 R = H

16 R = Ac
17 R = H

18 R = Ac
19 R = H

20 R = Ac
21 R = H

22 R = Bz
23 R = H

24 R = Bz
3 R = H

Scheme 2.

axially oriented azido group at C-2 which would hinder the attack from the β-side and destabilize the corresponding β-acetate by an unfavorable gauche effect.

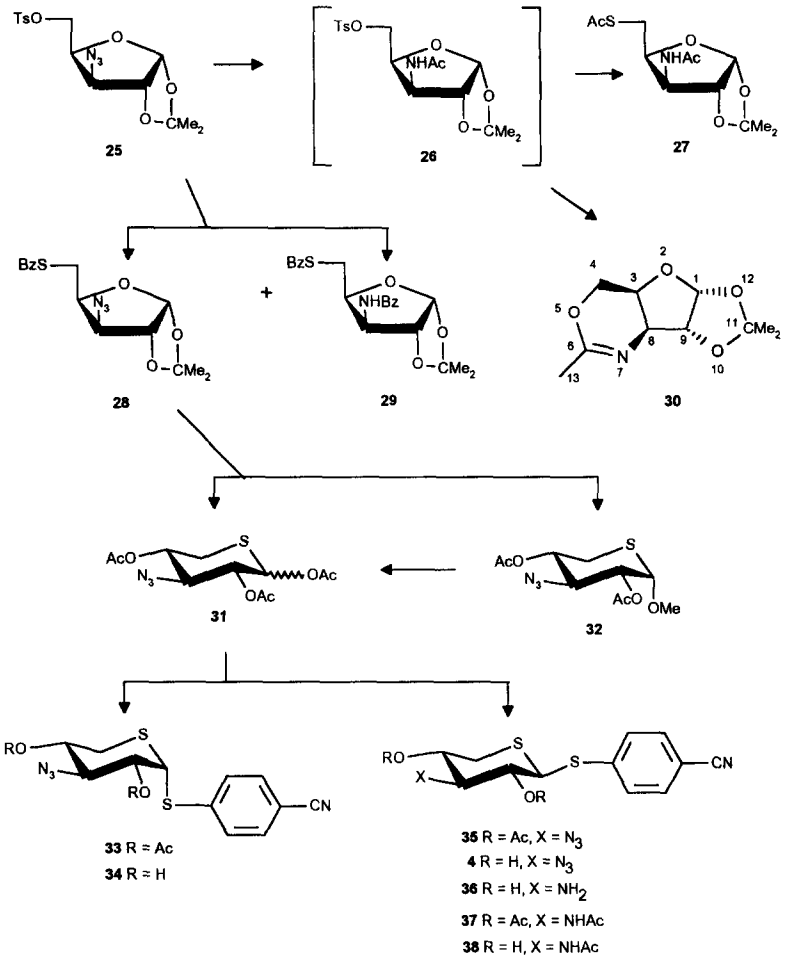
As no glycosidation reactions with 2-azido-5-thio sugars were carried out so far, before attempting the synthesis of the aimed thioglycosides it was decided to study the behavior of triacetates **8** and **11** in model experiments using methanol as acceptor and trimethylsilyl triflate as promoter. The reactions, carried out in dichloromethane at 5 °C, afforded in the case of the *xylo* derivative **8** an inseparable mixture of the two anomers (**9**) in 62% yield. According to NMR spectroscopy, the $\alpha:\beta$ ratio was 1:1 and both anomers adopted the $^4C_1$-D conformation. After Zemplén deacetylation, the azido groups of the obtained mixture (**10**) could be reduced with sodium borohydride in the presence of nickel chloride to give, after acetylation, the two anomeric acetamido glycosides **16** and **18** in crystalline state. According to NMR spectroscopy, **16** adopts in solution the $^4C_1$-D conformation, while both **18** and **19** are present in an equilibrium of the $^4C_1$-D and $^1C_4$-D conformations. In $CDCl_3$ solution, this equilibrium is slightly shifted towards the $^1C_4$-D conformation in the case of **18** ($^4C_1$ 40%; $^1C_4$ 60%), whereas **19** adopts predominantly the $^4C_1$-D conformation ($^4C_1$ 80%; $^1C_4$ 20%) in Me_2SO-d_6 solution in which no intramolecular H-bridges are formed.

When the same glycosidation reaction was carried out with the *lyxo* derivative **11**, the mixture of the two anomers (**12** and **14**) was obtained in similar yield (60%), but the $\alpha:\beta$ ratio was 5:2. In both anomers the methoxy group adopts the axial position, consequently **12** adopts the $^4C_1$-D and **14** the $^1C_4$-D conformation. This mixture was submitted to the same reaction sequence mentioned above; i.e. deacetylation gave a mixture of **13** and **15**, from which after reduction and subsequent acetylation only the α-anomer **20** could be separated in crystalline state. Zemplén deacetylation of **20** gave the acetamido derivative **21**.

For the synthesis of the target-compound **3**, the *xylo* ester **8** was used as donor, 4-cyanothiophenol as acceptor and the glycosidation was carried out as described above for the methyl 5-thio-glycosides. The mixture of resulting 5-thio-xylopyranosides contained the α- (**22**) and the β-anomer (**24**) (1:1 ratio) which could be separated by column chromatography. Debenzoylation of **22** and **24** according to the Zemplén procedure afforded **23** and **3**, respectively.

Synthesis of 4-cyanophenyl 3-deoxy-3-azido-1,5-dithio-β-D-xylo-pyranoside (**4**).—For the synthesis of **4**, 3-azido-3-deoxy-5-thio-D-xylopyranose triacetate **31** was needed as donor, which was synthesised starting from D-glucose. According to the literature [6], the latter was converted in a 9 steps process into the 3-azido-5-tosylate **25**. (See Scheme 3.) For introducing the sulfur atom at C-5, **25** was treated with potassium thioacetate in *N,N*-dimethylformamide at 110 °C. Besides the desired substitution reaction, reduction of the azide and simultaneous acetylation of the formed amine intermediate took place too and the corresponding crystalline 5-*S*-acetyl-3-acetamido derivative **27** was isolated in high yield (85%). Evaporation of the mother liquor afforded an inseparable mixture of **27** and the 1,3-oxazine derivative **30**. Treatment of this mixture with sodium methoxide removed **27** and let **30** unchanged. It is known from the literature [7,8] that azides can be reduced by thioacids via simultaneous conversion into the corresponding amides, but formation of **27** as the main product means that this reaction is faster in the case of **25** than the substitution of the 5-*O*-tosyl group, and **26** is probably formed as an intermediate. Formation of **30** as a by-product is in agreement with this proposal. The structure of **30** was proved by its spectra. In the ^1H NMR spectrum, besides the *O*-isopropylidene methyl groups a further methyl group appeared at 1.85 ppm as a doublet with a long range coupling ($^5J_{3,Me}$) [3] of 1.5 Hz, and in the ^{13}C NMR spectrum the signal of the quaternary carbon atom of the 1,3-oxazine ring appeared at 158.4 ppm. To avoid the unwanted reduction reaction, tosylate **25** was treated with the more bulky potassium thiobenzoate which may prefer the attack at the less hindered, primary tosyloxy group. In *N,N*-dimethylformamide at 110 °C, **25** was consumed within 30 min and the required azide **28** as well as the corresponding 3-benzamido derivative **29** were formed in a ratio of 2:1. Debenzoylation of **28** was carried out with 1.1 equivalent of sodium methoxide in methanol and the O-isopropylidene group was removed subsequently from the resulting thiol without separation by acidifying the solution with hydrochloric acid. After complete hydrolysis, the crude product was acetylated to give a mixture containing the two anomeric triacetates **31α** and **31β** as well as the α-methyl pyranoside **32** in a 6:1:1 ratio. The latter could be separated by column chromatography and was converted

[3] Numbering refers to the carbohydrate skeleton.



Scheme 3.

by treatment with sulfuric acid in acetic anhydride into the mixture of the triacetates **31**α and **31**β. In the glycosidation step, this mixture was used as donor, 4-cyanothiophenol as acceptor and trimethylsilyl triflate as promoter to give the α- (**33**) and β-anomer (**35**) in a 1:1.5 ratio. Those were deacetylated after separation to yield **34** and the target compound **4**, respectively. For checking the influence of the azido group on the biological activity, **4** was reduced with sodium borohydride in the presence of nickel chloride into the amino derivative **36**. As the basicity of the amino group in **36** might influence the activity, the less basic acetamido derivative **38** was also synthesised by converting **36** into its peracetate **37** and removing the *O*-acetyl groups by the Zemplén procedure.

Table 1
Oral antithrombotic activity of 4-cyanophenyl 1,5-dithio-D-xylopyranosides in rats

Compound	**1**	**3**	**4**	**34**	**36**	**38**
ED_{50} (mg/kg)	25	7	10	> 100	13	50

Biological results.—The oral antithrombotic activity of **3**, **4**, **34** , **36**, and **38** was determined on rats, using Pescador's model [9] and beciparcil (**1**) as reference compound. All compounds were administered orally 3 h before ligation. From the data listed in Table 1, it can be seen that the activity increased 3.5-fold and 2.5-fold, respectively, when the 2-OH or 3-OH group of beciparcil (**1**) was exchanged with azide (**3** and **4**). On the other hand, reduction of the azido group in **4** to the amine **36** was accompanied by a slight decrease of activity, while the amide **38** proved to be less active than the reference compound **1**. The α-anomer **34** was practically inactive in accordance with literature data [10].

3. Experimental

General methods.—Organic solns were dried over $MgSO_4$ and concd under diminished pressure at or below 40 °C. TLC: E. Merck precoated Silica Gel 60

Table 2
Selected ^{1}H NMR data for solutions in $CDCl_3$

Compound	Chemical shifts (δ)					
	H-1	H-2	H-3	H-4	H-5ax	H-5eq
3 [a]	4.62		3.20–3.60		2.75	2.52
4 [a]	4.85	3.35	3.20	3.52	2.75	2.58
6	6.22	4.25	5.80	5.46	3.20	3.04
7	6.18	4.60	5.72	5.76	3.17	3.02
8α	6.16	4.05	5.40	5.40	3.15	3.02
8β	5.88	4.16	5.88	5.48	3.15	2.90
9α	4.72	3.83	5.95	5.35	3.05	2.87
9β	4.53	4.03	5.24–5.48		2.72	3.10
11	5.95	4.43	5.78	5.75	3.14	3.02
12	4.50	4.48	5.84	5.70	3.02	2.85
14	4.79	4.09	5.46–5.60		3.34	2.63
16	4.41	4.56	5.18	5.10	2.78	2.66
17 [a]	4.35	3.93	3.37	3.44	2.52	2.39
18	4.36	4.44	4.90	5.01	2.56	3.14
19 [a]	4.30	3.80	3.12	3.42	2.36	2.67
20	4.28	4.94	5.26	5.07	2.82	2.62
21 [a]	4.28	4.32	3.50	3.78	2.35–2.45	
22	4.74	4.53	5.80	5.42	3.35	3.05
23 [a]	5.16	4.04	3.36–3.55		2.78	2.60
24	4.16	3.90	5.44	5.39	2.92	3.05
31α	6.04	5.02	3.86	4.95	2.90	2.78
32	4.57	5.00	3.93	4.88	2.74	2.62
33	4.89	5.13	3.92	4.89	3.05	2.78
34 [a]	4.95	3.90	3.35	2.45	2.78	2.55
35	4.11	5.08	4.54	4.94	2.70	2.87
36 [a]	4.55	3.46	2.78	3.62	2.73	2.58
38 [a]	4.48		3.38–3.65		2.74	2.55

Compound	Coupling constants (Hz)						
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5ax}$	$J_{4,5eq}$	$J_{5ax,5eq}$	$J_{1,5eq}$
3 [a]	10.9	nd [b]	nd	10.9	4.4	13.3	–
4 [a]	10.0	8.5	8.5	10.8	4.5	13.2	–
6	3.4	10.0	10.0	11.1	4.5	13.4	1.2
7	3.7	3.2	10.0	10.4	4.4	13.3	1.4
8α	3.1	10.5	nd	11.0	4.6	13.2	1.0
8β	9.4	9.8	10.1	11.1	4.7	13.3	–
9α	2.7	10.5	10.1	11.2	4.6	13.8	1.2
9β	9.1	9.2	nd	10.2	3.7	13.6	–
11	4.2	2.9	9.8	9.8	4.4	13.3	1.1
12	3.8	3.1	10.0	10.5	4.5	13.0	1.3
14	2.7	3.4	nd	2.2	5.1	14.4	–
16	2.8	9.8	9.8	10.6	4.3	13.1	1.2
17 [a]	2.7	10.6	10.1	10.4	4.4	13.2	1.5
18	6.0	6.3	6.3	6.9	3.0	14.2	–
19 [a]	8.8	8.5	8.5	10.0	4.0	13.6	–
20	3.6	4.0	10.5	11.0	4.5	12.8	1.4
21 [a]	3.5	4.0	~ 9	~ 10	~ 4.5	nd	~ 1
22	4.3	10.3	9.9	11.0	4.4	13.5	1.4
23 [a]	4.3	9.9	8.7	10.7	4.4	13.5	1.2
24	10.8	9.7	9.7	9.9	4.2	13.4	–
31α	3.0	10.5	10.2	11.1	4.7	13.2	1.0
32	2.8	10.2	10.2	11.0	4.8	13.0	1.0
33	4.5	10.4	10.2	11.2	4.5	13.5	1.0
34 [a]	4.1	9.8	9.7	10.8	4.4	13.5	1.0
35	10.6	9.9	9.9	10.8	4.6	13.5	–
36 [a]	10.1	9.4	9.5	9.5	4.0	13.6	–
38 [a]	9.5	nd	nd	10.4	3.7	13.2	–

[a] Me_2SO-d_6.
[b] nd: Not determined.

Table 3
Selected ^{13}C NMR data for solutions in $CDCl_3$

Compound	Chemical shifts (δ)				
	C-1	C-2	C-3	C-4	C-5
6	81.0	64.9	71.0 [b]	72.8 [b]	26.4
7	82.5	62.3	71.3 [b]	68.6 [b]	27.1
9α	83.1	66.1	73.2 [b]	73.8 [b]	27.4
9β	85.2	68.3	71.0 [b]	72.8 [b]	25.0
11	74.0 [b]	63.8	71.5 [b]	69.2 [b]	27.2
12	84.0	65.0	71.6 [b]	69.8 [b]	25.8
14	82.8	60.3	70.9 [b]	68.8 [b]	23.5
16	82.4	56.1	71.3 [b]	72.5 [b]	24.6
18	83.4	52.2	69.3 [b]	70.3 [b]	24.6
20	84.6	51.8	69.1 [b]	69.4 [b]	24.8
22	53.8	66.2	71.7 [b]	73.3 [b]	26.7
24	51.8	68.0	72.6 [b]	74.8 [b]	31.6
31α	73.9 [b]	73.1 [b]	62.3	70.2 [b]	26.0
32	80.4	73.6 [b]	62.2	75.6 [b]	24.4
33	51.3	73.2 [b]	62.6	75.3 [b]	26.1
34 [a]	53.7	72.2 [b]	69.7	74.0 [b]	29.3
35	50.9	73.0 [b]	67.2	73.6 [b]	31.8

[a] Me_2SO-d_6.
[b] Arbitrary assignment.

F_{254} plates, with hexane–EtOAc mixtures (*A*, 9:1; *B*, 4:1; *C*, 2:1; *D*, 1:3) and toluene–MeOH mixtures (*E*, 9:1; *F*, 4:1; *G*, 1:1); detection by spraying the plates with a 0.02 M soln of I_2 and a 0.30 M soln of KI in 10% aq H_2SO_4 soln followed by heating at ca. 200 °C. For column chromatography, Kieselgel 60 was used. Mp are uncorrected. Optical rotations were determined on 0.5% solns in $CHCl_3$ at 20 °C unless stated otherwise. NMR spectra were recorded with a Bruker AC 250 spectrometer at 250 MHz (^1H) and 62.9 MHz (^{13}C) and a Varian XL-400 spectrometer at 400 MHz (^1H) and 100 MHz (^{13}C) for solns in $CDCl_3$ (internal Me_4Si) unless stated otherwise (Tables 2, 3). Multiplicities of the ^{13}C NMR spectra were obtained from DEPT experiments. The assignment of the protons were based on homonuclear decoupling. Connectivities between identified protons and protonated carbons were observed by means of HETCOR experiments. The ratio of α:β anomeric mixtures was determined by ^1H NMR.

*2-Azido-2-deoxy-3,4-di-*O*-benzoyl-1-*O*-nitro-5-thio-α*-D-*xylo-* (**6**) *and α-*D*-lyxopyranoses* (**7**).—Under Ar, NaN_3 (0.7 g, 10.8 mmol) was added to a stirred soln of **5** [1] (2.4 g, 7 mmol) in MeCN (40 mL). The slurry was cooled to −20 °C, $Ce(NH_4)_2(NO_3)_6$ (11.6 g, 21 mmol) was added and stirring was continued at −20 °C for 3 h. Then, the mixture diluted with ice-cold CH_2Cl_2 (170 mL) was washed with ice-water (35 mL), 6% aq $NaHCO_3$, and water. The residue obtained upon concn of the organic soln was submitted to column chromatography (solvent *A*). Concn of the first fraction yielded **7** (1.0 g, 32%) as an unstable syrup which decomposed on standing at room temperature; R_f 0.4 (solvent *A*). Anal. Calcd for $C_{19}H_{16}N_4O_7S$: C, 51.35; H, 3.63; N, 12.61; S, 7.21. Found: C, 51.47; H, 3.75; N, 12.73; S, 7.28.

Concn of the second fraction gave **6** (1.1 g, 35%); $[\alpha]_D$ +140°; R_f 0.3 (solvent *A*). Anal. Calcd for $C_{19}H_{16}N_4O_7S$: C, 51.35; H, 3.63; N, 12.61; S, 7.21. Found: C, 51.43; H, 3.80; N, 12.79; S, 7.32.

*1-*O*-Acetyl-2-azido-2-deoxy-3,4-di-*O*-benzoyl-5-thio-*D*-xylopyranose* (**8**).—To a stirred soln of **6** (1.34 g, 3 mmol) in AcOH (10 mL), NaOAc (0.5 g, 6 mmol) was added and stirring was continued at 100 °C for 1 h. After cooling to room temperature, the mixture was diluted with CH_2Cl_2, washed with water, 6% aq $NaHCO_3$, and water. The residue obtained upon concn was submitted to column chromatography (solvent *B*) to yield **8** (0.87 g, 65%) as a 1:1 mixture of its α and β anomers; R_f 0.6 (solvent *B*); ^{13}C NMR: δ 168.8, 168.5, 165.5, 165.2 (C=O), 133.5, 129.7, 128.8, 128.4 (aromatic), 73.2, 72.9, 72.6, 72.5, 72.3, 71.1 (C-1,3,4), 66.9, 65.3 (C-2), 27.9, 26.4 (C-5), 21.0, 20.6 (OAc). Anal. Calcd for $C_{21}H_{19}N_3O_6S$: C, 57.14; H, 4.34; N, 9.52; S, 7.26. Found: C, 57.25; H, 4.23; N, 9.63; S, 7.37.

*Methyl 2-azido-2-deoxy-3,4-di-*O*-benzoyl-5-thio-*D*-xylopyranoside* (**9**).—Under Ar, MeOH (0.1 mL, 2.5 mmol) was added to a stirred soln of **8** (0.5 g, 1.1 mmol) in CH_2Cl_2 (15 mL). The mixture was cooled

to −10 °C, then TMSOTf (0.2 mL, 1.2 mmol) was added. After 2 h the temperature was raised to ambient and stirring was continued for 5 h. The reaction was quenched with Et_3N, concd and the residue purified by column chromatography (solvent *B*) to yield **9** (290 mg, 62%) as a 1:1 mixture of its α and β anomers; R_f 0.5 (solvent *B*). Anal. Calcd for $C_{20}H_{19}N_3O_5S$: C, 58.10; H, 4.63; N, 10.16; S, 7.75. Found: C, 58.23; H, 4.75; N, 10.25; S, 7.91.

*1-O-Acetyl-2-azido-2-deoxy-3,4-di-O-benzoyl-5-thio-α-*D-*lyxopyranose* (**11**).—To a stirred soln of freshly prepared **7** (1.4 g, 3.15 mmol) in AcOH (10 mL), NaOAc (0.5 g, 6 mmol) was added and the mixture was kept at 100 °C for 1 h. After cooling to room temperature, it was diluted with CH_2Cl_2, washed with water, 6% aq $NaHCO_3$, water, concd and purified by column chromatography (solvent *B*) to yield **11** (0.4 g, 29%). $[\alpha]_D$ +66°; R_f 0.5 (solvent *B*). Anal. Calcd for $C_{20}H_{19}N_3O_5S$: C, 58.10; H, 4.63; N, 10.16; S, 7.75. Found: C, 58.19; H, 4.71; N, 10.23; S, 7.87.

Methyl 2-azido-2-deoxy-3,4-di-O-benzoyl-5-thio-α- (**12**) *and β-*D-*lyxopyranosides* (**14**).—Treatment of **11** (0.5 g, 1.1 mmol) as described for the preparation of **9**, yielded a syrup (280 mg, 60%) containing **12** and **14** in a 5:2 ratio; R_f 0.5 (solvent *B*). Anal. Calcd for $C_{20}H_{19}N_3O_5S$: C, 58.10; H, 4.63; N, 10.16; S, 7.75. Found: C, 58.24; H, 4.71; N, 10.24; S, 7.80.

Methyl 3,4-di-O-acetyl-2-acetamido-2-deoxy-5-thio-α- (**16**) *and β-*D-*xylopyranosides* (**18**).—To a stirred soln of **9** (290 mg, 0.7 mmol) in MeOH (15 mL) M NaOMe (0.1 mL), in MeOH was added at room temperature. After 1 h the mixture was neutralized with solid CO_2 and concd. To the residue dissolved in EtOH (12 mL), $NaBH_4$ (60 mg, 1.6 mmol) and $NiCl_2 \cdot 6H_2O$ (6 mg) were added and the mixture was stirred at room temperature for 2 h. Then, further $NaBH_4$ (60 mg, 1.6 mmol) and $NiCl_2 \cdot 6H_2O$ (6 mg) were added and stirring was continued for 30 min. The mixture was then neutralized with 4% aq HCl, filtered and concd. The residue was dissolved in pyridine (5 mL) and Ac_2O (2.5 mL) was added. After 20 h, the mixture was processed the usual way and the residue was submitted to column chromatography (solvent *D*). Concn of the first fraction gave crystalline **16** (70 mg, 33%); mp 199–204 °C (hexane–EtOAc); $[\alpha]_D$ +144° (*c* 0.6, $CHCl_3$); R_f 0.3 (solvent *D*). Anal. Calcd for $C_{12}H_{19}NO_6S$: C, 47.20; H, 6.27; N, 4.59; S, 10.50. Found: C, 47.33; H, 6.35; N, 4.72; S, 10.68.

Concn of the second fraction gave **18** (50 mg, 23%); mp 199–201 °C (hexane–EtOAc); $[\alpha]_D$ −158° (*c* 0.9, $CHCl_3$); R_f 0.2 (solvent *D*). Anal. Calcd for $C_{12}H_{19}NO_6S$: C, 47.20; H, 6.27; N, 4.59; S, 10.50. Found: C, 47.35; H, 6.38; N, 4.72; S, 10.69.

*Methyl 2-acetamido-2-deoxy-5-thio-α-*D-*xylo-pyranoside* (**17**).—To a stirred soln of **16** (60 mg, 0.2 mmol) in MeOH (10 mL) M NaOMe (0.1 mL), in MeOH was added and the mixture was kept at room temperature for 1 h. The soln was concd after neutralization with Dowex 50WX resin to yield **17** (40 mg, 92%); mp 207–211 °C (ether); $[\alpha]_D$ +161° (*c* 0.37, H_2O); R_f 0.3 (solvent *F*). Anal. Calcd for $C_8H_{15}NO_4S$: C, 43.43; H, 6.83; N, 6.33; S, 14.49. Found: C, 43.57; H, 6.96; N, 6.25; S, 14.38.

*Methyl 2-acetamido-2-deoxy-5-thio-β-*D-*xylo-pyranoside* (**19**).—Deacetylation of **18** (50 mg, 0.16 mmol), as described for **17**, afforded **19** (35 mg, 97%); mp 205–208 °C (ether); $[\alpha]_D$ −59° (*c* 0.25, H_2O); R_f 0.3 (solvent *F*). Anal. Calcd for $C_8H_{15}NO_4S$: C, 43.43; H, 6.83; N, 6.33; S, 14.49. Found: C, 43.35; H, 6.73; N, 6.38; S, 14.59.

*Methyl 3,4-di-O-acetyl-2-acetamido-2-deoxy-5-thio-α-*D-*lyxopyranoside* (**20**).—Deacylation, reduction and subsequent acetylation of the syrup (280 mg) containing **12** and **14** in a 5:2 ratio was carried out, as described for the conversion of **9** into **16**, to yield after column chromatography **20** (78 mg, 38%) as an oil; $[\alpha]_D$ +139° (*c* 0.8, $CHCl_3$); R_f 0.3 (solvent *D*). Anal. Calcd for $C_{12}H_{19}NO_6S$: C, 47.20; H, 6.27; N, 4.59; S, 10.50. Found: C, 47.31; H, 6.38; N, 4.67; S, 10.57.

*Methyl 2-acetamido-2-deoxy-5-thio-α-*D-*lyxopyranoside* (**21**).—Deacetylation of **20** (80 mg, 0.26 mmol) as described for **17** afforded **21** (55 mg, 96%); mp 170–173 °C (ether); $[\alpha]_D$ +103° (*c* 0.25, H_2O); R_f 0.3 (solvent *F*). Anal. Calcd for $C_8H_{15}NO_4S$: C, 43.43; H, 6.83; N, 6.33; S, 14.49. Found: C, 43.51; H, 6.95; N, 6.40; S, 14.39.

4-Cyanophenyl 2-azido-3,4-di-O-benzoyl-2-deoxy-1,5-dithio-α- (**22**) *and β-*D-*xylopyranosides* (**24**).—Under Ar, 4-cyanothiophenol (0.8 g, 5.9 mmol) was added to a stirred soln of **8** (1.3 g, 2.9 mmol) in CH_2Cl_2 (35 mL). The mixture was cooled to −10 °C, then TMSOTf (0.6 mL, 3.3 mmol) was added and the temperature was slowly raised to ambient temperature. After stirring at room temperature for 1 h, the reaction was quenched with Et_3N. Concn led to a residue which was submitted to column chromatography (solvent *B*) to afford, as the first fraction, crys-

talline **24** (0.35 g, 23%); mp 151–154 °C (hexane–EtOAc); $[\alpha]_D$ +59°; R_f 0.5 (solvent *B*). Anal. Calcd for $C_{26}H_{20}N_4O_4S_2$: C, 60.45; H, 3.90; N, 10.85; S, 12.41. Found: C, 60.47; H, 4.03; N, 10.92; S, 12.33.

Concn of the second fraction gave **22** (0.35 g, 23%) as a syrup; $[\alpha]_D$ +245°; R_f 0.4 (solvent *B*). Anal. Calcd for $C_{26}H_{20}N_4O_4S_2$: C, 60.45; H, 3.90; N, 10.85; S, 12.41. Found: C, 60.35; H, 3.93; N, 10.75; S, 12.38.

*4-Cyanophenyl 2-azido-2-deoxy-1,5-dithio-β-*D*-xylopyranoside* (**3**).—To a stirred soln of **24** (350 mg, 0.68 mmol) in MeOH (15 mL), M NaOMe (0.1 mL) in MeOH was added and the mixture was kept at room temperature for 1 h. After neutralization with solid CO_2, the mixture was concd and the residue submitted to column chromatography (solvent *E*) to yield **3** (160 mg, 77%) as an oil; $[\alpha]_D$ +91° (*c* 0.5, MeOH); R_f 0.3 (solvent *E*). Anal. Calcd for $C_{12}H_{12}N_4O_2S_2$: C, 46.74; H, 3.92; N, 18.17; S, 20.79. Found: C, 46.88; H, 4.03; N, 18.25; S, 20.90.

*4-Cyanophenyl 2-azido-2-deoxy-1,5-dithio-α-*D*-xylopyranoside* (**23**).—To a stirred soln of **22** (0.35 g, 0.68 mmol) in MeOH (15 mL), M NaOMe (0.1 mL) in MeOH was added. After 1 h at room temperature, the mixture was neutralized with CO_2 to yield, after concn and column chromatography (solvent *E*), **23** (170 mg, 83%) as a syrup; $[\alpha]_D$ +371° (*c* 0.5, MeOH); R_f 0.3 (solvent *E*). Anal. Calcd for $C_{12}H_{12}N_4O_2S_2$: C, 46.74; H, 3.92; N, 18.17; S, 20.79. Found: C, 46.78; H, 4.01; N, 18.14; S, 20.81.

*3-Acetamido-5-*S*-acetyl-3-deoxy-1,2-*O*-isopropylidene-α-*D*-xylofuranose* (**27**).—Under N_2, a soln of **25** (3.7 g, 10 mmol) and KSAc (2.3 g, 20 mmol) in DMF (40 mL) was stirred at 110 °C for 1.5 h. The residue obtained upon concn was dissolved in $CHCl_3$, washed with water and brine to give after column chromatography (solvent *D*) crystalline **27** (2.45 g, 85%); mp 148–149 °C (hexane–EtOAc); $[\alpha]_D$ −3°; R_f 0.3 (solvent *D*). Anal. Calcd for $C_{12}H_{19}NO_5S$: C, 49.81; H, 6.62; N, 4.84; S, 11.08. Found: C, 49.78; H, 6.55; N, 4.73; S, 11.17.

*3-Azido-3-deoxy-5-*S*-benzoyl-1,2-*O*-isopropylidene-α-*D*-xylofuranose* (**28**) *and 3-*N*-benzoyl-3-deoxy-5-*S*-benzoyl-1,2-*O*-isopropylidene-α-*D*-xylofuranose* (**29**).—A stirred soln of **25** [6] (5.2 g. 14 mmol) and KSBz (2.7 g, 15 mmol) in DMF (35 mL) was stirred at 110 °C for 30 min. The residue obtained on concn was dissolved in $CHCl_3$, washed with water and brine and then submitted to column chromatography (solvent *B*). Concn of the first fraction gave **28** (2.03 g, 43%); mp 72–74 °C (hexane–EtOAc); $[\alpha]_D$ −118°; R_f 0.6 (solvent *B*); ^{1}H NMR: δ 7.97–7.45 (m, 5 H, aromatic), 5.92 (d, 1 H, H-1), 4.70 (d, 1 H, H-2), 4.38 (ddd, 1 H, H-4), 4.02 (d, 1 H, H-3), 3.42 (dd, 1 H, H-5a), 3.32 (dd, 1 H, H-5b), 1.45 (s, 3 H, CMe_2), 1.30 (s, 3 H, CMe_2); $J_{1,2}$ 3.7, $J_{2,3}$ 0, $J_{3,4}$ 3.2, $J_{4,5a}$ 7.0, $J_{4,5b}$ 7.0, $J_{5a,5b}$ 13.6 Hz; ^{13}C NMR: δ 190.7 (C=O), 136.5, 136.5, 128.6, 127.3 (aromatic), 112.3 (CMe_2), 104.7 (C-1), 83.4, 78.4 (C-2,4), 66.8 (C-3), 27.3 (C-5), 26.5, 26.2 (CMe_2). Anal. Calcd for $C_{15}H_{17}N_3O_4S$: C, 53.72; H, 5.11; N, 12.53; S, 9.56. Found: C, 53.88; H, 5.03; N, 12.45; S, 9.67.

Concn of the second fraction gave **29** (1.05 g, 18%); mp 157–162 °C (hexane–EtOAc); $[\alpha]_D$ −66°; R_f 0.1 (solvent *B*). ^{1}H NMR: δ 7.92–7.35 (m, 10 H, aromatic), 6.55 (d, 1 H, NH), 5.92 (d, 1 H, H-1), 4.75 (d, 1 H, H-3), 4.65 (d, 1 H, H-2), 4.52 (ddd, 1 H, H-4), 3.44 (dd, 1 H, H-5a), 3.37 (dd, 1 H, H-5b), 1.50 (s, 3 H, CMe_2), 1.25 (s, 3 H, CMe_2); $J_{1,2}$ 3.7, $J_{2,3}$ 0, $J_{3,4}$ 3.4, $J_{4,5a}$ 7.3, $J_{4,5b}$ 6.9, $J_{5a,5b}$ 14.0 Hz; ^{13}C NMR: δ 190.6, 167.3 (C=O), 136.4, 133.6, 133.6, 131.8, 128.6, 128.5, 127.3, 127.0 (aromatic), 112.1 (CMe_2), 104.3 (C-1), 84.6, 77.3 (C-2,4), 56.7 (C-3), 26.8 (C-5), 26.4, 26.0 (CMe_2). Anal. Calcd for $C_{22}H_{23}NO_5S$: C, 63.91; H, 5.61; N, 3.39; S, 7.75. Found: C, 63.85; H, 5.75; N, 3.33; S, 7.87.

(1R,3S,8S,9R)-2,5,10,12-Tetraoxa-7-aza-6,11,11-trimethyl-tricyclo [7, 3, $0^{1,9}$, $0^{3,8}$]dodeca-6-ene (**30**).—The residue (0.3 g), obtained from concn of the mother liquor of **27**, was dissolved in MeOH (5 mL) and M NaOMe (0.3 mL) in MeOH was added. After 2 h at room temperature, the mixture was neutralized with CO_2 to yield after concn and column chromatography (*D*) **30** (0.16 g, 8%), mp 47–50 °C (hexane–EtOAc); $[\alpha]_D$ −19°; R_f 0.45 (solvent *D*). ^{1}H NMR: δ 5.74 (d, 1 H, H-1), 4.54 (d, 1 H, H-9), 4.37 (ddd, 1 H, H-3), 4.27 (dd, 1 H, H-4a), 4.05 (dd, 1 H, H-4b), 3.73 (m, 1 H, H-8), 1.85 (d, 3 H, Me-13), 1.42 (s, 3 H, CMe_2), 1.24 (s, 3 H, CMe_2); $J_{3,4a}$ ~ 2, $J_{3,4b}$ ~ 2, $J_{3,8}$ 3.6, $J_{4a,4b}$ 12.7, $J_{8,9}$ ~ 0, $J_{8,13}$ 1.5, $J_{1,9}$ 3.5 Hz; ^{13}C NMR: δ 158.4 (C-6), 111.7 (C-11), 105.1 (C-1), 85.6, 70.5 (C-3,9), 63.1 (C-4), 57.7 (C-8), 26.8, 26.0 (CMe_2), 21.7 (C-13). Anal Calc. for $C_{10}H_{15}O_4N$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.30; H, 7.17; N, 6.34.

*1,2,4-Tri-*O*-acetyl-3-azido-3-deoxy-5-thio-*D*-xylopyranose* (**31**) *and methyl 2,4-di-*O*-acetyl-3-azido-3-deoxy-5-thio-α-*D*-xylopyranoside* (**32**).—To a stirred soln of **28** (2.9 g, 8.65 mmol) in MeOH (40 mL), 3 M NaOMe (4.4 mL) in MeOH was added. After 1 h at room temperature, 4% aq HCl (20 mL) was added and the mixture was refluxed for 2 h. After cooling to room temperature, Et_3N (2 mL) was added and the

residue obtained on concn was dissolved in pyridine (20 mL), cooled to 0 °C and treated with Ac_2O (10 mL). The mixture was kept at room temperature overnight, before processing in the usual way. The residue obtained on concn of the organic soln was purified by column chromatography (solvent *B*). Concn of the first fraction gave **32** (0.3 g, 12%); mp 64–67 °C (hexane–EtOAc); $[\alpha]_D$ +241°; R_f 0.5 (solvent *B*). Anal. Calcd for $C_{10}H_{15}N_3O_5S$: C, 41.52; H, 5.23; N, 14.52; S, 11.08. Found: C, 41.65; H, 5.19; N, 14.67; S, 11.20.

Concn of the second fraction yielded **31** (2.0 g, 73%) as an anomeric mixture ($\alpha:\beta = 85:15$); R_f 0.4 (solvent *B*). ^{1}H NMR: α anomer, for data see Table 2; β anomer, δ 5.79 (d, 1 H, H-1), $J_{1,2} = 9.1$ Hz, the other signals overlapped with those of the α anomer; Anal. Calcd for $C_{11}H_{15}N_3O_6S$: C, 41.64; H, 4.76; N, 13.24; S, 10.10. Found: C, 41.58; H, 4.63; N, 13.25; S, 10.23.

*1,2,4-Tri-*O*-acetyl-3-azido-3-deoxy-5-thio-*D*-xylopyranose* (**31**).—To a stirred soln of **32** (0.9 g, 3.1 mmol) in Ac_2O (9 mL), concd H_2SO_4 (0.1 mL) was added at 0 °C and stirring was continued at 0 °C for 15 min. Then NaOAc (0.5 g) was added, and the mixture was diluted with ice-water (10 mL), extracted with $CHCl_3$. The organic layer was washed with 6% aq $NaHCO_3$, water and concd to yield **31** (0.9 g, 91%, $\alpha:\beta$ ratio 95:5).

*4-Cyanophenyl 2,4-di-*O*-acetyl 3-azido-3-deoxy-1,5-dithio-α-* (**33**) *and β-*D*-xylopyranosides* (**35**).—4-Cyanothiophenol (0.8 g, 5.9 mmol) was added under Ar to a stirred soln of **31** (1.0 g, 3.15 mmol) in CH_2Cl_2 (30 mL) and the mixture was cooled to −10 °C. After addition of TMSOTf (0.6 mL, 3.3 mmol), the temperature was allowed to raise and the mixture was stirred at room temperature for 2 h, then quenched with Et_3N. The residue obtained on concn was submitted to column chromatography (solvent *C*). Concn of the first fraction gave **33** (310 mg, 25%); $[\alpha]_D$ +320°; R_f 0.7 (solvent *C*). Anal. Calcd for $C_{16}H_{16}N_4O_4S_2$: C, 48.97; H, 4.11; N, 14.28; S, 16.34. Found: C, 49.05; H, 4.03; N, 14.33; S, 16.51.

Concn of the second fraction yielded **35** (0.43 g, 35%); mp 163–166 °C (hexane–EtOAc); $[\alpha]_D$ +44°; R_f 0.6 (solvent *C*). Calcd for $C_{16}H_{16}N_4O_4S_2$: C, 48.97; H, 4.11; N, 14.28; S, 16.34. Found: C, 48.88; H, 4.14; N, 14.25; S, 16.44.

*4-Cyanophenyl 3-azido-3-deoxy-1,5-dithio-β-*D*-xylopyranoside* (**4**).—Deacetylation of diacetate **35** (470 mg, 1.2 mmol) with methanolic M NaOMe (0.1 mL) in MeOH (30 mL) yielded, after deionization with Dowex 50WX resin and concn, **4** (340 mg, 92%); mp 192–194 °C (ether); $[\alpha]_D$ +81° (*c* 0.5, MeOH); R_f 0.3 (solvent *E*). Anal. Calcd for $C_{12}H_{12}N_4O_2S_2$: C, 46.74; H, 3.92; N, 18.17; S, 20.79. Found: C, 46.79; H, 4.01; N, 18.22; S, 20.92.

*4-Cyanophenyl 3-azido-3-deoxy-1,5-dithio-α-*D*-xylopyranoside* (**34**).—To a stirred soln of **33** (0.3 g, 0.76 mmol) in MeOH (10 mL), M NaOMe (0.1 mL) in MeOH was added. After 1 h at room temperature, it was neutralized with Dowex 50WX resin and concd to yield **34** (205 mg, 87%) as white crystals; mp 185–188 °C (ether); $[\alpha]_D$ +586° (*c* 0.5, MeOH); R_f 0.3 (solvent *E*). Anal. Calcd for $C_{12}H_{12}N_4O_2S_2$: C, 46.74; H, 3.92; N, 18.17; S, 20.79. Found: C, 46.78; H, 4.01; N, 18.27; S, 20.89.

*4-Cyanophenyl 3-amino-3-deoxy-1,5-dithio-β-*D*-xylopyranoside* (**36**).—To a stirred soln of **4** (230 mg, 0.75 mmol) in EtOH (25 mL), $NaBH_4$ (80 mg, 2.1 mmol) and $NiCl_2 \cdot 6H_2O$ (10 mg) were added and stirring was continued at room temperature for 30 min. Then, it was neutralized with 4% HCl, filtered, concd and submitted to column chromatography (solvent *G*) to yield **36** (200 mg, 95%) as white crystals; mp 195–200 °C (ether); $[\alpha]_D$ +45° (*c* 0.5, MeOH); R_f 0.1 (solvent *F*). Anal. Calcd for $C_{12}H_{14}N_2O_2S_2$: C, 51.04; H, 5.00; N, 9.92; S, 22.71. Found: C, 51.23; H, 5.03; N, 9.87; S, 22.90.

*4-Cyanophenyl 3-acetamido-3-deoxy-1,5-dithio-β-*D*-xylopyranoside* (**38**).—A soln of **36** (200 mg, 0.71 mmol) in pyridine (5 mL) and Ac_2O (2.5 mL) was stirred at room temperature overnight. After usual processing, the residue was dissolved in MeOH (10 mL), and M NaOMe (0.1 mL) in MeOH was added. After 1 h at room temperature, it was neutralized with Dowex 50WX resin and concd to yield **38** (180 mg, 78%); mp 245–248 °C (ether); $[\alpha]_D$ +50° (*c* 0.5, MeOH); R_f 0.4 (solvent *F*). Anal. Calcd for $C_{14}H_{16}N_2O_3S_2$: C, 51.83; H, 4.97; N, 8.64; S, 19.76. Found: C, 51.88; H, 4.93; N, 8.71; S, 19.83.

Acknowledgements

The authors are very much indebted to Dr Gabriella Szabó for the biological results.

References

[1] É. Bozó, S. Boros, and J. Kuszmann, *Carbohydr. Res.*, 299 (1997) 59–67.

[2] F. Bellamy, V. Barberousse, N. Martin, P. Masson, J. Millet, S. Samreth, Ch. Sepulchre, J. Théveniaux, and D. Horton, *Eur. J. Med. Chem.*, 30 (1995) 101–115.
[3] J.P. Horwitz, J. Chua, and M. Noel, *J. Org. Chem.*, 29 (1964) 2076–2078.
[4] H. Mitsuya, K.J. Weinhold, P.A. Furman, M.H. St. Clair, S. Nusinoff-Lehrman, R.C. Gallo, D. Bolognesi, D.W. Barry, and S. Broder, *Proc. Natl. Acad. Sci. USA*, 82 (1985) 7096–7100.
[5] R.U. Lemieux and R.M. Ratcliffe, *Can. J. Chem.*, 57 (1979) 1244–1251.
[6] H. Ohrui, H. Kuzuhara, and S. Emoto, *Agric. Biol. Chem.*, 34 (1970) 375–380.
[7] T. Rosen, I.M. Lico, and D.T.W. Chu, *J. Org. Chem.*, 53 (1988) 1580–1582.
[8] N. Rakotomanomana, J.-M. Lacombe, and A.A. Pavia, *Carbohydr. Res.*, 197 (1990) 318–323.
[9] D. Bagdy, G. Szabó, É. Barabás, and S. Bajusz, *Thrombosis and Haemostasis*, 68 (1992) 125–129.
[10] F. Bellamy, D. Horton, J. Millet, F. Picart, S. Samreth, and J.B. Chazan, *J. Med. Chem.*, 36 (1993) 898–903.