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Note

Synthesis of 4-cyanophenyl and 4-nitrophenyl 2-azido-2-deoxy-1,5-dithio-β-D-arabino- and -β-D-lyxopyranosides possessing antithrombotic activity☆

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Abstract

Tri-*O*-acetyl-5-thio-D-ribopyranosyl bromide was converted into 3,4-di-*O*-benzoyl-1,5-anhydro-5-thio-D-*erythro*-pent-1-enitol (3,4-di-*O*-benzoyl-5-thio-D-ribal), the azidonitration of which afforded an unstable mixture of 2-azido-3,4-di-*O*-benzoyl-2-deoxy-1-*O*-nitro-5-thio-D-pentopyranoside isomers. This was converted without separation into the corresponding 1-*O*-acetyl derivatives from which an α,β anomeric mixture of the 1-*O*-acetyl-2-azido-3,4-di-*O*-benzoyl-2-deoxy-5-thio-D-arabinopyranose isomers could be isolated in high yield. Glycosidation of this mixture with 4-cyano- or 4-nitrobenzenethiol, using trimethylsilyl triflate or boron trifluoride etherate, respectively, as promoters gave the corresponding β anomers exclusively. Zemplén debenzoylation afforded 4-cyanophenyl as well as 4-nitrophenyl 2-azido-2-deoxy-1,5-dithio-β-D-arabinopyranoside, respectively. When 1-*O*-acetyl-2-azido-3,4-di-*O*-benzoyl-2-deoxy-5-thio-D-lyxopyranose was used as glycosyl donor only the corresponding β anomers, i.e., 4-cyanophenyl as well as 4-nitrophenyl 2-azido-2-deoxy-1,5-dithio-β-D-lyxopyranosides, could be isolated after Zemplén debenzoylation in high yield. All four 1,5-dithioglycosides possess significant oral antithrombotic activity.

Keywords: 2-Azido-2-deoxy-5-thio-D-arabinose; 2-Azido-2-deoxy-5-thio-D-lyxose; Azidonitration reaction; Glycosidation reactions; Thioglycosides; 1,5-Dithioglycosides; Oral antithrombotic activity

1. Introduction

In our previous papers [1,2], we showed that the oral antithrombotic activity of 4-cyanophenyl 1,5-dithio-β-D-xylopyranoside (beciparcil, **1**) [3] could be significantly increased by changing the chirality of the pentopyranose moiety at C-3 (D-ribopyranoside) or C-2 and C-3 (D-arabinopyranoside). A similar increase in this biological activity was achieved by substituting the HO-2 group of **1** with an azido group (**2**) [4]. For our further structure–activity studies, we decided to synthesize such beciparcil analogs in which the two aforementioned alterations are introduced simultaneously, i.e., the sugar residue differs from D-xylose in the chirality of C-2 and/or C-3 and carries an azido group at C-2 (**4** and **6**) (Scheme 1).

☆ Orally active antithrombotic thioglycosides, Part IX. For Part VIII see [1].

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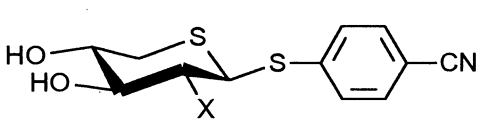
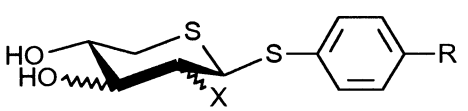
2. Results and discussion

For the synthesis of **4** or **6**, a properly substituted 2-azido-2-deoxy-5-thio-pentopyranose was needed as the donor molecule. Both the corresponding 2-azido-2-deoxy-5-thio-D-*ribo* and -D-*arabino* derivatives can be theoretically obtained from 3,4-di-*O*-benzoyl-1,5-anhydro-5-thio-D-*erythro*-pent-1-enitol (3,4-di-*O*-benzoyl-5-thio-D-ribal, **10**) by applying the azidonitration reaction [4]. For this approach **10** was synthesized in a three-step process starting from 2,3,4-tri-*O*-acetyl-5-thio-D-ribopyranosyl bromide **7** [1] and converting it into a 95% yield of the 1-ene derivative **8** by using zinc in ethyl acetate in the presence of picoline [5,6]. Deacetylation and subsequent benzoylation of **8** afforded crystalline **10** in 71% yield. The azidonitration reaction of **10** was carried out in acetonitrile with sodium azide and ceric ammonium nitrate at −20 °C and afforded a mixture of the corresponding 2-azido-1-*O*-nitro derivatives **11** showing, on thin-layer chromatography (TLC), two distinct spots. This mixture could be purified by column chromatography but the components could not be separated because of their instability and their very similar R_f values. Therefore, the mixture was immediately treated with sodium acetate in acetic acid at 100 °C. The 1-*O*-acetates formed gave a single spot on TLC, and could be isolated in a yield of 72% after column chromatography. According to NMR spectroscopy, this mixture contained only two components in a 3:7 ratio, having both the D-arabino configuration and differing only in the chirality of C-1, being the α (**12**) and β anomers (**13**). This means that during the azidonitration process addition of the azido group to the double bond at C-2 of **10** occurs mainly from the upper side, i.e., trans to the 3-*O*-benzoyl group. This is in sharp contrast to the corresponding 3,4-di-*O*-benzoyl-5-thio-D-*threo*-pent-1-enitol isomer, where the same reaction afforded a 1:1 mixture of the corresponding cis (D-*lyxo*) **18** and trans (D-*xylo*) isomers [4]. This difference is probably due to the steric arrangement of the 3-*O*-benzoyl substituent, which in **10** occupies an axial position, whereas in the *threo*-pent-1-enitol isomer it is equatorially oriented. It is worthwhile mentioning that according to NMR spectroscopy, the α anomer **12** occupies predominantly a $^4C_1$ conformation, while the β anomer **13** is present in a $^1C_4$ conformation.

For the synthesis of the corresponding 4-cyanophenylthio glycoside, a 3:7 mixture of the two 1-*O*-acetate anomers (**12** and **13**) was used as donor, 4-cyanobenzenethiol as acceptor and trimethylsilyl triflate as promoter. The reaction was carried out in 1,2-dichloroethane at −10 °C, when only one isomer, the β anomer **14**, was formed. This is probably due to the presence of the bulky axial substituent at C-3 in the $^4C_1$ conformation, which, because of the unfavoured 1,3-diaxial arrangement, prohibits the formation of the corresponding α anomer, while in the $^1C_4$ conformation the axially oriented C-4 substituent and the weak anomeric effect [7], diminished further by the presence of the exogenous sulfur atom [8], makes this anomer energetically less favoured. Debenzoylation of **14** was carried out according to the Zemplén procedure, affording crystalline **15** in high yield (80%). According to the NMR data, **15** is present in dimethyl sulfoxide solution in a $^4C_1 \leftrightarrow {}^1C_4$ conformational equilibrium, which is strongly shifted towards the latter conformer (Scheme 2).

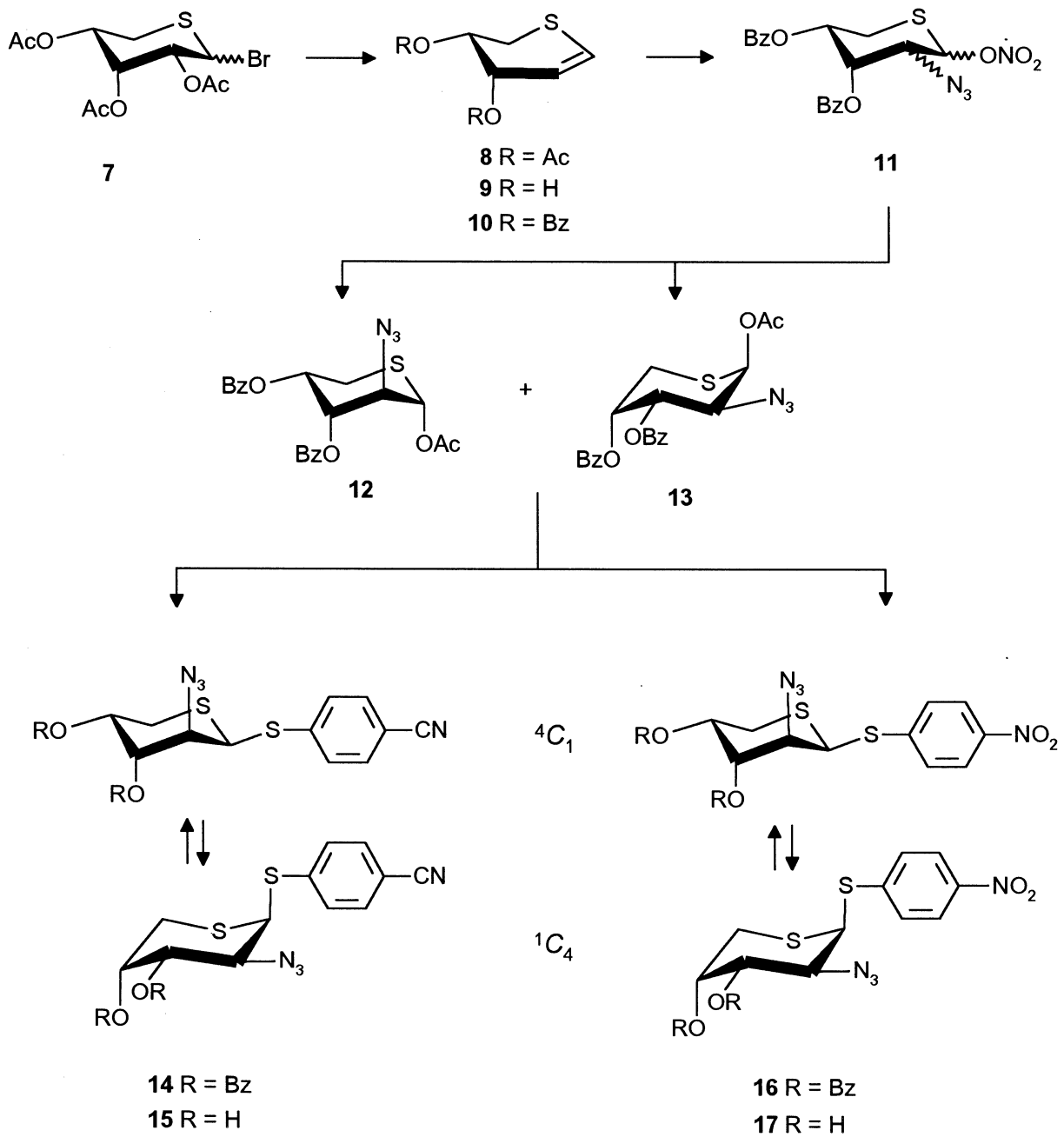


1 X = OH (beciparcil)
2 X = N_3



3 X = OH, R = CN
4 X = N_3, R = CN
5 X = OH, R = NO_2
6 X = N_3, R = NO_2

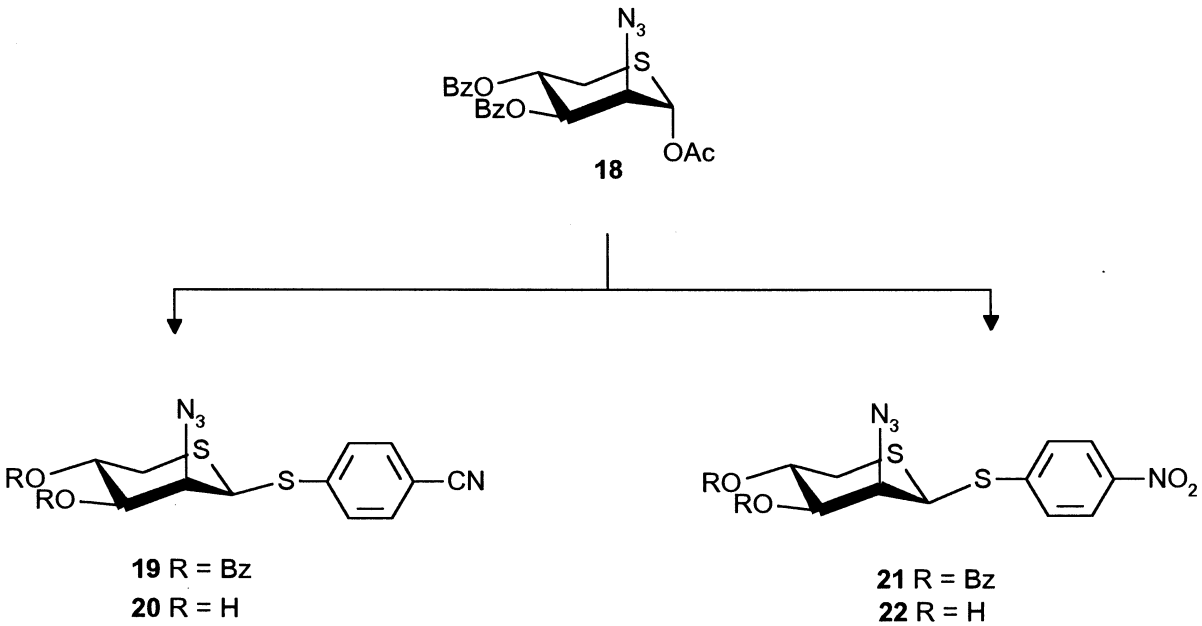
Scheme 1.



Scheme 2.

When 4-nitrobenzenethiol was used in the glycosylation reaction as acceptor, and boron trifluoride etherate as promoter, the corresponding β-thioglycoside **16** was isolated as a crystalline compound in a yield of 62.5%. Debenzoylation according to the Zemplén procedure afforded **17** as a syrup.

For the synthesis of the corresponding *lyxo* isomers, 1-*O*-acetyl-2-azido-3,4-di-*O*-benzoyl-2-deoxy-5-thio-α-D-lyxopyranose (**18**) [4] was used as donor and the reactions with 4-cyano- and 4-nitrobenzenethiol were carried out under the same conditions mentioned above (Scheme 3). In these reactions the β anomers **19** and **21** were formed in satisfactory yield and no α anomers could be detected. That is contrary to the results obtained with the same donor in the reaction with methanol, where the corresponding methyl α- and β-pyranosides were formed in a 5:2 ratio. This might be due to the fact that the phenylthio group is much bulkier than the methoxy group, there-



Scheme 3.

fore its equatorial arrangement prevailing in the β anomers is energetically favoured, and the anomeric effect that operates in the case of the O-glycosides is less pronounced [8] in the case of S-glycosides. Zemplén debenzoylation of crude **19** and **21** afforded the crystalline thioglycosides **20** and **22** in high yield. The β anomeric configuration of these compounds was evident from their NMR spectra; according to the large $J_{3,4}$ 8.7 Hz and $J_{4,5ax}$ 9.7 Hz couplings, both are present in the $^4C_1$ conformation and an NOE could be observed on H-3 (5%) and H-5a (2%) by irradiating H-1. On the other hand, no long-range coupling between H-5e and H-1 could be detected, excluding the equatorial arrangement of the latter.

Biological results.—The oral antithrombotic activity of **15**, **17**, **20** and **22** was determined on rats, using Pescador's model [9] and beciparcil **1** as the reference compound. For comparison, the data of the D-arabinose derivatives **3** and **5** are also given. All compounds were administered orally 3 h before ligation. From the data listed in Table 1, it can be seen that the activity of the 2-azido-derivatives **15** and **17** was much higher compared with beciparcil (**1**), and practically equalled that of the 2-hydroxy analogs (**3** and **5**). Consequently, the exchange of the 2-OH group by the azido group did not increase the activity further. A change in the configuration of C-3 (*arabino* → *lyxo*) (**15** → **20** and **17** → **22**) was accompanied by a further minor increase in the activity.

3. Experimental

General methods.—Organic solutions were dried over $MgSO_4$ and concentrated under diminished pressure at or below 40 °C. TLC: E. Merck precoated Silica Gel 60 F_{254} plates, with hexane–EtOAc mixtures (A, 4:1; B, 3:1; C, 1:1), EtOAc (D), and toluene–MeOH mixtures (E, 4:1); 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. Melting points are uncorrected. Optical rotations were determined on 1.0% solns in $CHCl_3$ at 20 °C unless stated otherwise. NMR spectra were recorded with a

Table 1
Oral antithrombotic activity of beciparcil (**1**), 4-cyanophenyl and 4-nitrophenyl 1,5-dithio-β-D-arabino- (**3** and **5**), 2-azido-2-deoxy-1,5-dithio-β-D-arabino- (**15** and **17**) as well as β-D-lyxopyranosides (**20** and **22**) in rats using Pescador's model [9]

Compound	**1**	**3**	**5**	**15**	**17**	**20**	**22**
ED_{50} (mg/kg)	25	3.5	3.5	3	5	2	2

Bruker AC 250 spectrometer at 250 MHz (^{1}H) and 62.9 MHz (^{13}C) for solns in $CDCl_3$ (internal Me_4Si) unless stated otherwise. Multiplicities of the ^{13}C NMR spectra were obtained from DEPT experiments. The assignment of the protons was 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 ^{1}H NMR.

3,4-Di-O-*acetyl-1,5-anhydro-5-thio*-D-erythro-*pent-1-enitol* (**8**).—To a stirred solution of a 1:3 mixture of bromides **7a** and **7b** [1] (7.1 g, 20 mmol) in dry EtOAc (100 mL), 4-picoline (2.1 mL, 21 mmol) and Zn powder (10 g) were added and the mixture was refluxed for 20 min. The reaction was cooled to room temperature (rt) and Zn was filtered off. The filtrate was washed with M HCl, aq $NaHCO_3$, dried, concentrated and the residue was purified by column chromatography (solvent B) to yield **8** (4.1 g, 95%); $[\alpha]_D$ +393°; R_f 0.6 (solvent B); ^{1}H NMR: δ 6.36 (d, 1 H, $J_{1,2}$ 10.0 Hz, H-1), 5.75 (dd, 1 H, $J_{2,3}$ 4.4 Hz, H-2), 5.28 (dd, 1 H, $J_{3,4}$ 4.6 Hz, H-3), 5.16 (m, 1 H, H-4), 3.00–3.10 (m, 2 H, H-5a, H-5b), 2.08 (s, 3 H, OAc), 2.04 (s, 3 H, OAc); ^{13}C NMR: δ 169.9, 169.8 (C=O), 125.8 (C-1), 117.2 (C-2), 66.7, 66.4 (C-3, C-4), 26.3 (C-5), 21.0, 20.9 (OAc). Anal. Calcd for $C_9H_{12}O_4S$: C, 49.99; H, 5.59; S, 14.83. Found: C, 50.10; H, 5.81; S, 14.77.

3,4-Di-O-*benzoyl-1,5-anhydro-5-thio*-D-erythro-*pent-1-enitol* (**10**).—To a stirred solution of **8** (4.3 g, 20 mmol) in MeOH (50 mL) M NaOMe (0.1 mL) in MeOH was added and the mixture was left at rt 1 h. The reaction was neutralised with solid CO_2 and concentrated. The residue (**9**) was dissolved in a mixture of pyridine (15 mL) and CH_2Cl_2 (60 mL) and a soln of benzoyl chloride (7.0 mL, 60.3 mmol) in CH_2Cl_2 (35 mL) was added dropwise during 10 min at rt. The reaction was stirred at rt for 1 h, then poured into water and processed in the usual way to yield **10** (4.8 g, 71%) after recrystallization from EtOH; mp 93–95 °C; $[\alpha]_D$ +451°; R_f 0.7 (solvent B); ^{1}H NMR: δ 6.40 (dd, 1 H, $J_{1,2}$ 9.8 Hz, H-1), 5.96 (dd, 1 H, $J_{2,3}$ 5.6 Hz, H-2), 5.85 (m, 1 H, $J_{3,5eq}$ 1.5 Hz, H-3), 5.59 (ddd, 1 H, $J_{3,4}$ 3.2, $J_{4,5ax}$ 11.2, $J_{4,5eq}$ 3.2 Hz, H-4), 3.45 (dd, 1 H, $J_{5ax,5eq}$ 12.2 Hz, H-5ax), 3.03 (m, 1 H, $J_{1,5eq}$ 0.7 Hz, H-5eq); ^{13}C NMR: δ 165.4, 165.1 (C=O), 133.0–128.1 (aromatic), 126.4 (C-1), 117.5 (C-2), 69.4, 65.1 (C-3, C-4), 24.5 (C-5). Anal. Calcd for $C_{19}H_{16}O_4S$: C, 67.04; H, 4.74; S, 9.42. Found: C, 67.15; H, 4.88; S, 9.39.

1-O-*Acetyl-2-azido-2-deoxy-3,4-di*-O-*benzoyl-5-thio-α-* (**12**) *and β*-D-*arabinopyranose* (**13**).—Under argon, NaN_3 (1.0 g, 15.4 mmol) was added to a stirred solution of **10** (3.5 g, 10.28 mmol) in MeCN (60 mL). The slurry was cooled to −20 °C, $Ce(NH_4)_2(NO_3)_6$ (16.9 g, 30.8 mmol) was added and stirring was continued at −20 °C for 3 h. Then, the mixture diluted with ice-cold CH_2Cl_2 (250 mL) and washed with ice-water (50 mL), 6% aq $NaHCO_3$ and water. The residue obtained upon concentration of the organic solution was submitted to column chromatography (solvent A) to yield a mixture of the 1-*O*-nitro-isomers **11** (4.2 g, 92%) as an unstable syrup. R_f 0.50 and 0.55 (solvent A). To a stirred solution of crude **11** (4.2 g, 9.4 mmol) in AcOH (25 mL), NaOAc (1.5 g, 18 mmol) was added and stirring was continued at 100 °C for 1 h. After cooling to rt, the mixture was diluted with CH_2Cl_2, washed with water, 6% aq $NaHCO_3$, and water to yield **12** and **13** (3.0 g, 72%) as a 3:7 mixture; R_f 0.4 (solvent A); ^{1}H NMR: **12** δ 5.87 (d, 1 H, $J_{1,2}$ 5.8, H-1), 5.74 (ddd, 1 H, $J_{3,4}$ 2.3, $J_{4,5ax}$ 8.2, $J_{4,5eq}$ 2.9 Hz, H-4), 5.38 (dd, 1 H, $J_{2,3}$ 6.7 Hz, H-3), 4.42 (dd, 1 H, H-2), 3.37 (dd, 1 H, $J_{5ax,5eq}$ 13.8 Hz, H-5ax), 2.95 (dd, 1 H, H-5eq), 2.03 (s, 3 H, OAc); **13** δ 6.21 (dd, 1 H, $J_{1,2}$ 2.0 Hz, $J_{1,5eq}$ 1.2 Hz, H-1), 5.92 (m, 1 H, H-4), 5.63 (dd, 1 H, $J_{2,3}$ 10.8, $J_{3,4}$ 2.8, Hz, H-3), 4.42 (dd, 1 H, H-2), 3.45 (dd, 1 H, $J_{4,5ax}$ 1.5, $J_{5ax,5eq}$ 14.5 Hz, H-5ax), 2.98 (ddd, 1 H, $J_{4,5eq}$ 4.3 Hz, H-5eq), 2.22 (s, 3 H, OAc); ^{13}C NMR: **12** δ 168.6, 165.3, 165.0 (C=O), 133.5–128.4 (aromatic), 72.0, 70.8, 67.7, 62.4 (C-1,2,3,4), 31.1 (C-5), 20.6 (OAc); **13** δ 168.9, 165.3, 165.1 (C=O), 133.5–128.4 (aromatic), 73.0, 70.3, 68.7, 61.2 (C-1,2,3,4), 27.9 (C-5), 20.9 (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, 57.18; H, 4.48; N, 9.60; S, 7.22.

4-Cyanophenyl 2-azido-2-deoxy-3,4-di-O-*benzoyl-1,5-dithio-β-*D-*arabinopyranoside* (**14**).—Under argon, 4-cyanobenzenethiol (0.9

g, 6.6 mmol) was added to a stirred solution of **12** and **13** (1.45 g, 3.28 mmol) in dry 1,2-dichloroethane (30 mL). The mixture was cooled to −10 °C, then Me_3SiOTf (0.6 mL, 3.2 mmol) was added and the temperature was slowly raised to ambient temperature. After stirring at rt for 1 h, the reaction was quenched with Et_3N, concentrated, and the residue was submitted to column chromatography (solvent A) to yield **14** (1.35 g, 79%); $[\alpha]_D$ −315° (*c* 0.5, $CHCl_3$); R_f 0.35 (solvent A); ^1H NMR: δ 7.98–7.30 (m, 14 H, aromatic), 5.78 (ddd, 1 H, $J_{3,4}$ 2.8, $J_{4,5ax}$ 2.0, $J_{4,5eq}$ 6.6 Hz, H-4), 5.53 (dd, 1 H, $J_{2,3}$ 8.0 Hz, H-3), 4.69 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 4.66 (dd, 1 H, H-2), 3.28 (dd, 1 H, $J_{5ax,5eq}$ 13.3 Hz, H-5ax), 3.05 (dd, 1 H, H-5eq); ^{13}C NMR: δ 165.2, 165.0 (C=O), 140.3–128.5 (aromatic), 118.2 (CN), 111.0 (C-4′), 71.0, 68.3 (C-3,4), 63.4 (C-2), 52.7 (C-1), 28.8 (C-5). 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, 60.52; H, 3.88; N, 10.81; S, 12.37.

*4-Cyanophenyl 2-azido-2-deoxy-1,5-dithio-β-*D*-arabinopyranoside* (**15**).—To a stirred solution of **14** (1.25 g, 2.4 mmol) in MeOH (30 mL) and 1,2-dichloroethane (10 mL), M NaOMe (0.1 mL) in MeOH was added and the mixture was kept at rt for 1 h. After neutralization with solid CO_2, the mixture was concentrated and the residue was submitted to column chromatography (solvent C, then D) to yield **15** (0.6 g, 80%); mp 78–83 °C (water); $[\alpha]_D$ −322° (*c* 0.5, MeOH); R_f 0.3 (solvent C); ^1H NMR (Me_2SO-d_6): δ 7.80–7.55 (m, 4 H, aromatic), 5.52 (d, 1 H, $J_{3,OH}$ 5.9 Hz, 3-OH), 5.14 (d, 1 H, $J_{4,OH}$ 4.6 Hz, 4-OH), 5.08 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 4.30 (dd, 1 H, $J_{2,3}$ 8.3 Hz, H-2), 4.00 (m, 1 H, H-4), 3.76 (ddd, 1 H, $J_{3,4}$ 2.4 Hz, H-3), 2.78 (m, 2 H, H-5ax,5eq). 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, 46.82; H, 3.85; N, 18.20; S, 20.85.

*4-Nitrophenyl 2-azido-2-deoxy-3,4-di-*O*-benzoyl-1,5-dithio-β-*D*-arabinopyranoside* (**16**).—To a stirred solution of **12** and **13** (1.45 g, 3.28 mmol) in dry 1,2-dichloroethane (30 mL) 4-nitrobenzenethiol (0.56 g, 3.6 mmol) was added. After addition of $BF_3{\cdot}Et_2O$ (0.4 mL, 3.23 mmol), the mixture was stirred at rt for 24 h, then poured into ice-cold 6% aq $NaHCO_3$. The organic layer was separated, washed with 6% aq $NaHCO_3$, water and concentrated. The residue was submitted to column chromatography (solvent A then B) to yield **16** (1.1 g, 62.5%); mp 155–160 °C (ether); $[\alpha]_D$ −293° (*c* 0.5, $CHCl_3$); R_f 0.35 (solvent A); ^1H NMR: δ 8.15–7.40 (m, 14 H, aromatic), 5.79 (ddd, 1 H, $J_{3,4}$ 2.7, $J_{4,5ax}$ 1.5, $J_{4,5eq}$ 6.6 Hz, H-4), 5.55 (dd, 1 H, $J_{2,3}$ 8.5 Hz, H-3), 4.74 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.68 (dd, 1 H, H-2), 3.28 (dd, 1 H, $J_{5ax,5eq}$ 14.1 Hz, H-5ax), 3.06 (dd, 1 H, H-5eq); ^{13}C NMR: δ 165.2, 165.0 (C=O), 146.7-124.1 (aromatic), 71.1, 68.3 (C-3,4), 63.4 (C-2), 52.5 (C-1), 28.3 (C-5). Anal. Calcd for $C_{25}H_{20}N_4O_6S_2$: C, 55.96; H, 3.76; N, 10.44; S, 11.95. Found: C, 55.93; H, 3.78; N, 10.51; S, 11.90.

*4-Nitrophenyl 2-azido-2-deoxy-1,5-dithio-β-*D*-arabinopyranoside* (**17**).—To a stirred solution of **16** (1.0 g, 1.86 mmol) in MeOH (30 mL) and 1,2-dichloroethane (10 mL), M NaOMe (0.1 mL) in MeOH was added and the mixture was kept at rt for 1 h. After neutralization with solid CO_2, the mixture was concentrated and the residue was submitted to column chromatography (solvent A, then D) to yield **17** (0.54 g, 88.5%); $[\alpha]_D$ −307° (*c* 0.5, MeOH); R_f 0.3 (solvent C); ^1H NMR (Me_2SO-d_6): δ 8.20–7.62 (m, 4 H, aromatic), 5.56 (d, 1 H, $J_{3,OH}$ 5.9 Hz, 3-OH), 5.15 (d, 1 H, $J_{4,OH}$ 4.9 Hz, 4-OH), 5.12 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 4.32 (dd, 1 H, $J_{2,3}$ 8.3 Hz, H-2), 4.01 (m, 1 H, H-4), 3.78 (ddd, 1 H, $J_{3,4}$ 2.7 Hz, H-3), 2.80 (m, 2 H, H-5ax,5eq). Anal. Calcd for $C_{11}H_{12}N_4O_4S_2$: C, 40.24; H, 3.68; N, 17.06; S, 19.53. Found: C, 40.30; H, 3.75; N, 17.11; S, 19.59.

*4-Cyanophenyl 2-azido-2-deoxy-1,5-dithio-β-*D*-lyxopyranoside* (**20**).—Under argon, 4-cyanobenzenethiol (0.6 g, 4.44 mmol) was added to a stirred solution of **18** [4] (0.95 g, 2.15 mmol) in dry 1,2-dichloroethane (30 mL). The mixture was cooled to −10 °C, then Me_3SiOTf (0.45 mL, 2.5 mmol) was added and the temperature was slowly raised to ambient temperature. After stirring at rt for 1 h, the reaction was quenched with Et_3N, concentrated, and the residue was submitted to column chromatography (solvent A) to yield **19** (0.54 g, 49%); R_f 0.4 (solvent A). To a stirred solution of crude **19** (0.54 g) in MeOH

(30 mL), M NaOMe (0.1 mL) in MeOH was added and the mixture was kept at rt for 1 h. After neutralization with solid CO_2, the mixture was concentrated and the residue was submitted to column chromatography (solvent E) to yield **20** (0.24 g, 75%); mp 154–157 °C (ether); $[\alpha]_D$ −80.5° (*c* 0.5, pyridine); R_f 0.3 (solvent E); ^{1}H NMR (Me_2SO-d_6): δ 7.80–7.60 (m, 4 H, aromatic), 5.71 (d, 1 H, $J_{3,OH}$ 4.2 Hz, 3-OH), 5.26 (d, 1 H, $J_{4,OH}$ 4.5 Hz, 4-OH), 5.01 (d, 1 H, $J_{1,2}$ 2.3 Hz, H-1), 4.32 (dd, 1 H, $J_{2,3}$ 3.0 Hz, H-2), 3.72 (m, 1 H, H-4), 3.62 (ddd, 1 H, $J_{3,4}$ 8.7 Hz, H-3), 2.64 (dd, 1 H, $J_{4,5ax}$ 9.7, $J_{5ax,5eq}$ 13.2 Hz, H-5ax), 2.58 (dd, 1 H, $J_{4,5eq}$ 4.7 Hz, H-5eq). 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, 46.80; H, 3.88; N, 18.21; S, 20.83.

*4-Nitrophenyl 2-azido-2-deoxy-1,5-dithio-β-*D*-lyxopyranoside* (**22**).—To a stirred solution of **18** [4] (0.65 g, 1.47 mmol) in dry 1,2-dichloroethane (10 mL) 4-nitrobenzenethiol (0.25 g, 1.6 mmol) was added. After addition of $BF_3{\cdot}Et_2O$ (0.2 mL, 1.6 mmol), the mixture was stirred at rt for 24 h, then poured into ice-cold 6% aq $NaHCO_3$. The organic layer was separated, washed with 6% aq $NaHCO_3$, water and concentrated. The residue was submitted to column chromatography (solvent A) to yield **21** (0.43 g, 54%); R_f 0.4 (solvent A). To a stirred solution of crude **21** (0.43 g) in MeOH (20 mL) and 1,2-dichloroethane (10 mL), M NaOMe (0.1 mL) in MeOH was added and the mixture was kept at rt for 1 h. After neutralization with solid CO_2, the mixture was concentrated and the residue was submitted to column chromatography (solvent E) to yield **22** (0.2 g, 76%); mp 174–176 °C (ether); $[\alpha]_D$ −17° (*c* 0.5, MeOH); R_f 0.3 (solvent E); ^{1}H NMR (Me_2SO-d_6): δ 8.20–7.65 (m, 4 H, aromatic), 5.74 (d, 1 H, $J_{3,OH}$ 3.9 Hz, 3-OH), 5.29 (d, 1 H, $J_{4,OH}$ 4.4 Hz, 4-OH), 5.06 (d, 1 H, $J_{1,2}$ 2.2 Hz, H-1), 4.35 (dd, 1 H, $J_{2,3}$ 2.6 Hz, H-2), 3.75 (m, 1 H, H-4), 3.64 (ddd, 1 H, $J_{3,4}$ 8.7 Hz, H-3), 2.65 (m, 2 H, H-5ax,5eq). Anal. Calcd for $C_{11}H_{12}N_4O_4S_2$: C, 40.24; H, 3.68; N, 17.06; S, 19.53. Found: C, 40.28; H, 3.72; N, 17.09; S, 19.60.

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