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Chemical interconversions of 4-cyanophenyl 1,5-dithio-β-D-xylopyranoside (Beciparcil®): structural modification at the C-4 position

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Abstract

The title dithioxyloside **1**, an orally active antithrombotic agent, as its 2,3-isopropylidene acetal, was converted into the corresponding glycos-4-ulose, which served as precursor via reduction to the 4-epimer of **1** and via oximation–reduction to the 4-acetamido-4-deoxy 4-epimer of **1**.

Keywords: Xylosides; Dithio sugars; 1,5-Dithioxylosides; Antithrombotic agents

1. Introduction

As a part of a program to find venous antithrombotic agents orally active in mammalian systems [1,2], we have identified 4-cyanophenyl 1,5-dithio-β-D-xylopyranoside (Beciparcil, **1**) as a particularly promising compound, and its behavior in a range of biological assays has been discussed in detail [2]. With the goal of enhancing the biological activity and evaluating structure–activity relationships, a range of synthetically modified analogues have been prepared from **1**. A previous paper [3] described the synthesis of the 2- and 4-monomethyl ethers and the 4-deoxy-4-fluoro derivative of **1**, and we now report results on the inversion of configuration at the C-4 position and amination at C-4. The high interest in structural modifications of this dithioxyloside is manifested in recent work from other laboratories [4].

The multiplicity of sensitive functional groups present in **1** limits the range of chemical reagents that can be utilized for functional transformations; most conventional oxidizing and reducing reagents cannot be utilized. Furthermore, the replacement of the ring oxygen atom of sugars by sulfur leads to significant changes in the behavior of these compounds. The high nucleophilicity of sulfur in two environments creates a great propensity for internal displacement of potential leaving-groups. Despite these limitations, carefully regulated procedures enabled the conversion of thioglycoside **1** into its corresponding 4-axial hydroxyl analogue **2** and its 4-axial 4-acetamido analogue **3**.

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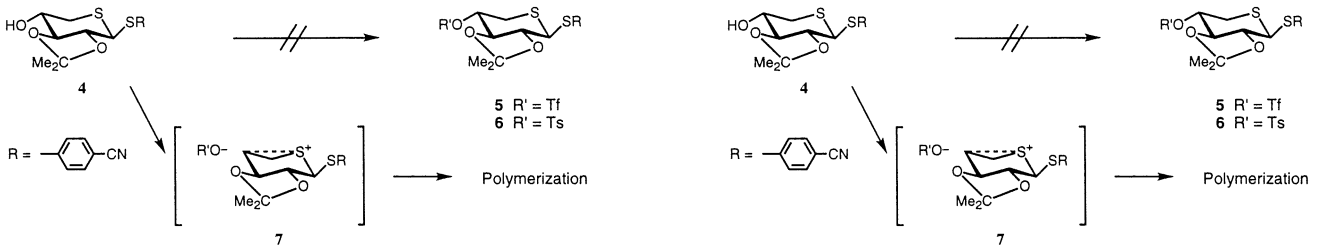


2. Results and discussion

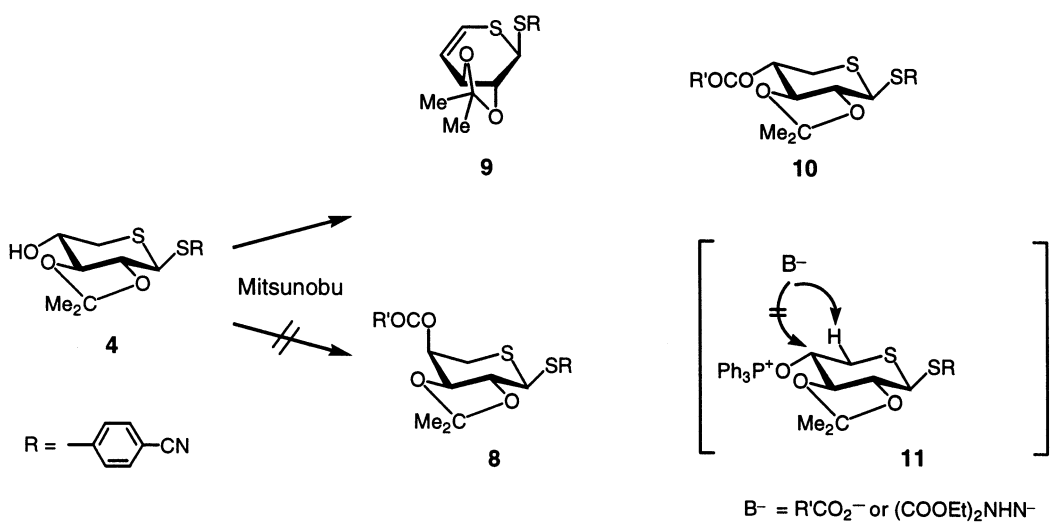
Although only a few methods for the specific protection of trans-disposed vicinal diols in six-membered ring-systems are available in the literature [5], we have shown that **1** can be readily transformed into the readily separable, crystalline 2,3- and 3,4-isopropylidene acetals in 94% total yield [3]. The present work describes functional transformations of the 2,3-acetal **4**.

*Synthesis of 4-cyanophenyl 1,5-dithio-α-*L*-arabinopyranoside* (**2**).—Attempts to convert the 2,3-acetal **4** into the corresponding 4-triflate **5** from **4** by the action of triflic anhydride–pyridine in dichloromethane led only to a polymer-like, brown precipitate that was not soluble in either organic solvents (ether, ethyl acetate, or acetone) or water. The tosylate **6** (prepared with *p*-toluenesulfonyl chloride and pyridine in dichloromethane) darkened (decomposed) very rapidly in chloroform-*d* at room temperature (rt) to form a dark-brown, insoluble solid.

The difficulties encountered in the preparation of **5** and **6** evidently arise from participation of the sulfur ring-atom to form an intermediate episulfonium ion **7** when a good leaving group such as a triflate or a tosylate is present at C-4. Similar instances have been previously reported [6]. An intermediate such as **7** would be prone to polymerization.

Application of the Mitsunobu reaction [7] to the 2,3-acetal **4** did not afford the desired inversion product **8**. Isolated instead were mainly the β-elimination product **9**, along with a small proportion of the simple acylation product **10** (when acetic acid was utilized, R′ = Me) (Scheme 1). The formation of **9** can be accounted for by an elimination reaction rather than substitution of the intermediate **11**, because of the slightly acidic character of the proton at C-5. When no acid was added to the reaction, the formation of **9** reached 80%, and thus would constitute an efficient method for the preparation of **9** (Table 1).

Different methods were tested for selective oxidation of the hydroxyl function in **4** in the



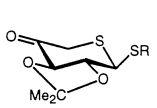
Scheme 1.

Table 1
Attempted Mitsunobu reaction of the 2,3-acetal **4**

Conditions[a]	Time (h)	Product (%)		
		4	**9**	**10**
DEAD (6 equiv)–PPh_3 (6 equiv)–$PhCO_2H$ (3.5 equiv)	50	0	31	0
DEAD (4 equiv)–PPh_3 (4 equiv)–AcOH (4 equiv)	28	70	0	25
DEAD (2 equiv)–PPh_3 (2 equiv)	15	0	80	0

[a] All reactions conducted in THF at rt.

presence of the two sulfur atoms. All attempts to oxidize alcohol **4** to ketone **12** with chromium(VI) oxidants such as pyridinium chlorochromate (PCC) or pyridinium dichlorochromate (PDC) suffered from poor yields (15–20%). However, the use of dimethyl sulfoxide as oxidant gave better results. The best yield was obtained with a Swern-type oxidation (dimethyl sulfoxide–oxalyl chloride–triethylamine [8]) conducted at low temperature (Table 2).



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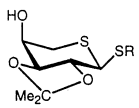

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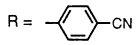


The reduction of **12** with sodium borohydride took place from the less-hindered side to give predominantly (91%) the 4-axial alcohol **13,** along with 5% of its 4-epimer **4**. The ^1H NMR spectrum of **13** showed $J_{3,4} = 2.1$ Hz, as compared with $J_{3,4} = 9.3$ Hz for **4**, indicating clearly that the proton at C-4 in **13** was equatorial. Acidic hydrolysis of **13** gave the target *arabino* analogue **2**.

*Synthesis of 4-cyanophenyl 4-acetamido-4-deoxy-1,5-dithio-α-*L*-arabinopyranoside* (**3**).—The glycos-4-ulose **12** was converted into its oxime **14** with hydroxylamine hydrochloride–pyridine in excellent yield (Scheme 2). It is noteworthy that only one isomeric oxime was formed, as shown by the ^1H NMR spectrum of the crude product. The possibility of hydrogen bonding between the hydroxyl group of the oxime and the O-3 atom suggests that the configuration of the oxime is *syn*. Acetylation of **14** [acetic anhydride–triethylamine–*N*,*N*-dimethylaminopyridine (cat.)] gave the acetoxime **15** in 82% yield.

Several reducing agents were tested for their ability to selectively reduce the oxime **14** and its acetate **15** to an amine in the presence of the cyano group. For practical reasons, the crude reduction product was acetylated directly (Ac_2O–pyridine) and the acetamido compound **16** was isolated by chromatography on silica gel. The best result obtained involved reduction of the free oxime **14** with sodium borohydride–molybdenum trioxide [9], which afforded 38% of the axial acetamide **16** along with 23% of the acetylated oxime **15** (resulting from the acetylation of the unreacted starting oxime **14**). Other procedures, for example sodium borohydride–nickel chloride hexahydrate [9], diborane–tetrahydrofuran, sodium cyanoborohydride–$TiCl_3$ [10], and hydrogen–Raney nickel [11] gave less satisfactory results. There was no detectable production of the equatorial acetamide. Deacetonation of **16** under acidic conditions gave the target acetamido product **3** in excellent yield.

Compounds **2** and **3** were examined for their ability to act as acceptors of D-galactose using a partially purified galactosyltransferase I from chick embryo [12]. Both were essentially inactive at 5×10^{-3} M.

3. Experimental

General methods.—TLC was performed on precoated plates of Silica Gel 60F-254 (E. Merck); components were detected by UV light and by spraying the plates with 10% H_2SO_4 and subsequent heating. Melting points were determined with a Thomas–Hoover apparatus and are uncorrected. Evaporation were performed under diminished pressure. Specific rotations were recorded with a

Table 2
Selective oxidation of the hydroxyl group of **4**

Conditions[a]	Temp. (°C)	Time (h)	Yield (%)	
			12	**4**
PCC (5 equiv)	rt	20	15	47
PDC (4 equiv)	rt	72	18	53
Me_2SO (2 equiv)–TFAA (1.5 equiv)–Et_3N (3 equiv)	−60 to −50	0.5	33	25
Me_2SO (3 equiv)–$(COCl)_2$ (1.5 equiv)–Et_3N (7 equiv)	−60 to −45	0.5	65–75	0

[a] CH_2Cl_2 was the solvent in each experiment.

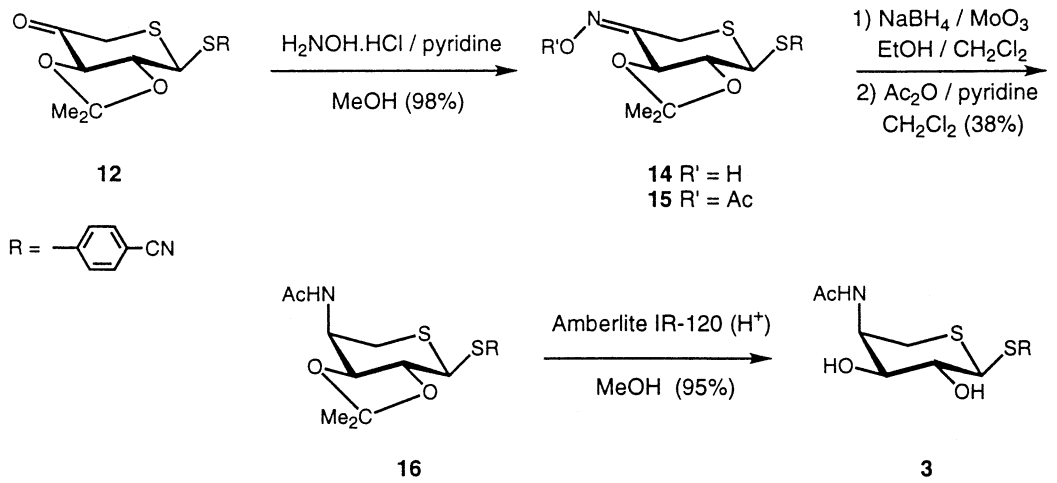
Perkin–Elmer 141 polarimeter. ^1H and ^{13}C NMR spectra were recorded with a Bruker AM-250 or AM-300 spectrometer, and chemical shifts refer to an internal standard of Me_4Si ($\delta = 0.00$). Chemical-ionization (CI) mass spectra were recorded at The Ohio State University Chemical Instrument Center with Kratos MS-30 and VG 70-250S mass spectrometers. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA.

*4-Cyanophenyl 4-deoxy-2,3-*O*-isopropylidene-1,5-dithio-α-*L*-threo-pent-4-eno-pyranoside* (**9**).—To a solution of 4-cyanophenyl 2,3-*O*-isopropylidene-1,5-dithio-β-D-xylopyranoside [3] (**4**, 60 mg, 0.19 mmol) and PPh_3 (97 mg, 2 equiv) in anhyd THF (2 mL) cooled to 0 °C was added dropwise 59 mL (2 equiv) of diethyl azodicarboxylate (DEAD, Aldrich) via a syringe under argon. The cold bath was removed and the mixture was stirred under argon for 15 h at rt. The solvent was evaporated off and the crude product purified by chromatography over silica gel (1:4 Et_2O–hexane) to afford **9** as a colorless solid (45 mg, 80%), mp (from EtOH) 97–99.5 °C, $[\alpha]_D^{19}$ −135° (*c* 1.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 7.62 (m, 4 H, Ar), 5.97 (dd, 1 H, $J_{3,5}$ 1.5, $J_{4,5}$ 9.6 Hz, H-5), 5.88 (dd, 1 H, $J_{3,4}$ 2.4 Hz, H-4), 4.97 (d, 1 H, $J_{1,2}$ 10.9 Hz, H-1), 4.33 (ddd, 1 H, $J_{2,3}$ 8.4 Hz, H-3), 3.78 (dd, 1 H, H-2), 1.50 (s, 3 H, Me), 1.48 (s, 3 H, Me); ^{13}C NMR (63 MHz, $CDCl_3$): d 138.8 (Ar-C), 132.3 (Ar-CH), 132.2 (Ar-CH), 121.4, 119.9 (C-4, 5), 118.3 (Ar-C), 111.5 (Me_2CO_2), 111.4 (*C*N), 78.0, 77.2 (C-2, 3), 50.0 (C-1), 26.9 (Me), 26.7 (Me); MS (EI): 305 (1.0, M^+), 230 [6.9, $M - Me_2C(OH)O$], 113 (100, $M - SC_6H_4CN - Me_2CO$). Anal. Calcd for $C_{15}H_{15}NO_2S_2$ (305.40): C, 58.99; H, 4.95. Found: C, 58.98; H, 4.97.

When **4** (69 mg, 0.21 mmol) was treated by the same procedure with PPh_3 (224 mg, 4 equiv), AcOH (38 mL, 4 equiv), and DEAD (134 mL, 4 equiv) in THF (2 mL) for 28 h at rt, only the starting 2,3-acetal **4** (48 mg, 70%) and its 4-acetate **10** (19 mg, 25%) were obtained.

*4-Cyanophenyl 4-*O*-acetyl-2,3-*O*-isopropylidene-1,5-dithio-β-*D*-xylopyranoside* (**10**).—This was obtained as a colorless oil; $[\alpha]_D^{32}$ −39° (*c* 2.6, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 7.61 (m, 4 H, Ar), 5.04 (m, 1 H, H-4), 4.32 (d, 1 H, $J_{1,2}$ 10.3 Hz, H-1), 3.70 (dd, 1 H, $J_{2,3}$ 8.7 Hz, H-2), 3.49 (dd, 1 H, $J_{3,4}$ 9.8 Hz, H-3), 2.92 (dd, 1 H, $J_{4,5a}$ 4.7, $J_{5a,5b}$ 13.3 Hz, H-5a), 2.69 (dd, 1 H, $J_{4,5b}$ 10.7 Hz, H-5b), 2.10 (s, 3 H, OAc), 1.48 (s, 3 H, Me), 1.45 (s, 3 H, Me); ^{13}C NMR (63 MHz, $CDCl_3$): δ 169.9 ($COCH_3$), 138.9 (Ar-C), 132.2 (Ar-CH), 131.6 (Ar-CH), 118.2 (Ar-C), 111.2 (*C*N), 109.0 (Me_2CO_2), 80.1, 78.7, 72.4 (C-2, 3, 4), 50.0 (C-1), 32.4 (C-5), 26.7 (Me), 26.6 (Me), 21.0 ($COCH_3$). High-resolution MS: calcd for $C_{17}H_{19}NO_4S_2$: *m*/*z* 365.0755; found: 365.0760.

*4-Cyanophenyl 2,3-*O*-isopropylidene-1,5-dithio-α-*L*-threo-pentopyranosid-4-ulose* (**12**).—To a solution of $(COCl)_2$ (0.46 mL, 1.5 equiv) in anhyd CH_2Cl_2 (10 mL) cooled to −60 °C was added dropwise 0.745 mL (3 equiv) of anhyd Me_2SO via a syringe under argon. After 5 min at −60 °C, a solution of 1.132 g (3.5 mmol) of 4-cyanophenyl 2,3-*O*-isopropylidene-1,5-dithio-β-D-xylopyranoside [3] (**4**) in anhyd CH_2Cl_2 (20 mL) was added dropwise via a cannula needle. The temperature was allowed to rise slowly to −45 °C (40 min) and



Scheme 2.

3.4 mL (7 equiv) of Et_3N was then added at −50 °C. The temperature was allowed to rise to −25 °C (~30 min) and then water (30 mL) was added and the cold bath removed. The mixture was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic layer was washed with 10% aq AcOH (2 × 20 mL), saturated aq $NaHCO_3$ (to pH 8), and water (2 × 30 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by chromatography on silica gel (2:3 EtOAc–hexane) to afford **12** as a colorless solid (730 mg, 65%), mp (from EtOAc–hexane) 161–162 °C, $[\alpha]_D^{18}$ +134.6° (*c* 0.5, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.65 (m, 4 H, Ar), 4.65 (d, 1 H, $J_{1,2}$ 10.1 Hz, H-1), 4.23 (dd, 1 H, $J_{2,3}$ 9.6, $J_{3,5a}$ 1.0 Hz, H-3), 3.91 (dd, 1 H, H-2), 3.64 (dd, 1 H, $J_{5a,5b}$ 14.2 Hz, H-5a), 3.05 (d, 1 H, H-5b), 1.50 (s, 6 H, 2 × Me); ^{13}C NMR (63 MHz, $CDCl_3$): δ 195.0 (C-4), 138.0 (Ar-C), 132.4 (Ar-CH), 132.3 (Ar-CH), 118.1 (Ar-C), 111.8 (Me_2CO_2), 111.3 (*C*N), 82.0, 81.1 (C-2, 3), 51.2 (C-1), 38.4 (C-5), 26.7 (Me), 26.3 (Me); EIMS: 321 (1.0, M^+), 246 [4.3, M − $Me_2C(OH)O$], 187 (26.2, M − SC_6H_4CN), 129 (100, M − SC_6H_4-CN − Me_2CO). Anal. Calcd for $C_{15}H_{15}NO_3S_2$ (321.40): C, 56.05; H, 4.70. Found: C, 55.91; H, 4.67.

Table 2 details the outcome of other procedures for oxidation of compound **4**.

4-Cyanophenyl 2,3-O-isopropylidene-1,5-dithio-α-L-arabinopyranoside (**13**).—To a solution of the glycosidulose **12** (600 mg, 1.87 mmol) in MeOH (30 mL) and CH_2Cl_2 (15 mL) cooled to 0 °C was added $NaBH_4$ (71 mg, 1 equiv) during 10 min. After 1 h at 0 °C, 25% aq AcOH (1 mL) was added and the solvents were evaporated. Water (30 mL) was added to the mixture, which was then extracted with EtOAc (3 × 100 mL). The organic layer was washed with saturated aq $NaHCO_3$ (2 × 30 mL) and then saturated aq NaCl (2 × 30 mL), dried ($MgSO_4$), and evaporated. The crude solid was purified by chromatography over silica gel (1:1 EtOAc–hexane) to afford the known **4** (30 mg, 5%) and its 4-epimer **13** as a colorless solid (549 mg, 91%), mp (from EtOAc–hexane) 131–132 °C, $[\alpha]_D^{19}$ +17.0° (*c* 0.9, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 7.62 (m, 4 H, Ar), 4.55 (m, 1 H, H-4), 4.40 (d, 1 H, $J_{1,2}$ 10.5 Hz, H-1), 4.12 (dd, 1 H, $J_{2,3}$ 8.8 Hz, H-2), 3.43 (dd, 1 H, $J_{3,4}$ 2.1 Hz, H-3), 3.11 (dd, 1 H, $J_{4,5a}$ 1.9, $J_{5a,5b}$ 14.5 Hz, H-5a), 2.75 (dd, 1 H, $J_{4,5b}$ 3.4 Hz, H-5b), 2.30 (d, 1 H, $J_{4,OH}$ 4.0 Hz, OH, D_2O exchangeable), 1.47 (s, 6 H, 2 × Me); ^{13}C NMR (63 MHz, $CDCl_3$): δ 139.9 (Ar-C), 132.3 (Ar-CH), 130.8 (Ar-CH), 118.5 (Ar-C), 110.7 (Me_2CO_2), 108.7 (*C*N), 81.5, 73.3, 66.1 (C-2, 3, 4), 51.3 (C-1), 36.1 (C-5), 26.8 (Me), 26.6 (Me); EIMS: 323 (0.6, M^+), 248 [3.6, M − $Me_2C(OH)O$], 189 (2.6, M − SC_6H_4CN), 131 (70.6, M − SC_6H_4CN − Me_2CO), 59 (100). Anal. Calcd for $C_{15}H_{17}NO_3S_2$ (323.41): C, 55.70; H, 5.30. Found: C, 55.72; H, 5.35.

4-Cyanophenyl 1,5-dithio-α-L-arabinopyranoside[1] (**2**).—To a solution of the 2,3-acetal

[1] While this article was in press, a synthesis of this compound by a different route was reported [E. Bozó, S. Boros, J. Kuszmann, *Carbohydr. Res.*, 311 (1998) 191–202], giving NMR data essentially identical to those reported here.

13 (107 mg, 0.33 mmol) in MeOH (5 mL) was added Amberlite IR-120 (H^+) resin ($\sim$20 mg), and the mixture was vigorously stirred for 17 h at rt. Removal of the resin by filtration through Celite and evaporation of MeOH gave a pale-yellow solid that was washed with ether (2 × 3 mL) to afford **2** as a colorless solid (86 mg, 92%); mp (from EtOAc) 215–217 °C, $[\alpha]_D^{20}$ −52° (*c* 0.2, MeOH); ^{1}H NMR (250 MHz, Me_2SO-d_6/D_2O): δ 7.76 (d, 2 H, *J* 8.5 Hz, Ar), 7.55 (d, 2 H, Ar), 4.41 (d, 1 H, $J_{1,2}$ 7.1 Hz, H-1), 4.01 (m, 1 H, H-4), 3.89 (t, 1 H, $J_{2,3}$ 7.0 Hz, H-2), 3.43 (m, 1 H, H-3), 2.71 (d, 2 H, $J_{4,5}$ 4.6 Hz, H-5); EIMS: 283 (0.9, M^+), 149 (23.6, $M - SC_6H_4CN$), 135 (69.6, HSC_6H_4CN), 131 (100, $M - SC_6H_4CN - H_2O$). Anal. Calcd for $C_{12}H_{13}NO_3S_2$ (283.35): C, 50.86; H, 4.62. Found: C, 50.68; H, 4.47.

*4-Cyanophenyl 2,3-*O*-isopropylidene-1,5-dithio-α-*L*-threo-pentopyranosid-4-ulose oxime* (**14**).—To a suspension of the glycos-4-ulose **12** (102 mg, 0.32 mmol) and $NH_2OH{\cdot}HCl$ (45 mg, 2 equiv) in MeOH (5 mL) cooled to 0 °C was added dropwise 54 μL (2.1 equiv) of pyridine. The cold bath was removed and the solution was stirred for 1.5 h at rt. Ethyl acetate (50 mL) was added and the mixture was washed with water (3 × 15 mL). The organic layer was dried ($MgSO_4$), and evaporated to afford **14** as a pure (NMR), colorless solid (105 mg, 98%), mp (from EtOAc–hexane) 192–190 °C (dec.), $[\alpha]_D^{19}$ +121° (*c* 0.4, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.75 (b, 1H, OH), 7.63 (m, 4 H, Ar), 4.52 (d, 1 H, $J_{1,2}$ 10.1 Hz, H-1), 4.07 (d, 1 H, $J_{2,3}$ 9.1 Hz, H-3), 4.05 (d, 1 H, $J_{5a,5b}$ 14.8 Hz, H-5a), 3.81 (dd, 1 H, H-2), 3.18 (d, 1 H, H-5b), 1.51 (s, 6 H, 2 × Me); ^{13}C NMR (63 MHz, $CDCl_3$): δ 149.5 (C-4), 138.7 (Ar-C), 132.2 (Ar-CH), 131.8 (Ar-CH), 118.2 (Ar-C), 111.2 (*C*N), 111.1 (Me_2CO_2), 81.4, 78.2 (C-2, 3), 50.6 (C-1), 26.7 (Me), 26.5 (Me), 25.0 (C-5); MS (EI): 336 (0.1, M^+), 261 [2.8, $M - Me_2C(OH)O$], 202 (6.6, $M - SC_6H_4CN$), 135 (77.8, HSC_6H_4CN), 43 (100). Anal. Calcd for $C_{15}H_{16}N_2O_3S_2$ (336.41): C, 53.55; H, 4.79. Found: C, 53.48; H, 4.85.

*4-Cyanophenyl 4-acetoximino-2,3-*O*-isopropylidene-1,5-dithio-α-*L*-threo-pentopyranosid-4-ulose* (**15**).—To a solution of the 4-oxime **14** (65 mg, 0.19 mmol) in CH_2Cl_2 (2 mL) cooled to 0 °C was added 108 μL (4 equiv) of Et_3N, 37 μL (2 equiv) of Ac_2O, and 4-dimethylaminopyridine (DMAP, catalytic amount). The cold bath was removed, the solution was stirred for 15 h at rt, CH_2Cl_2 (30 mL) was added, and the mixture was washed with water (3 × 5 mL). The organic layer was dried ($MgSO_4$), and evaporated. The crude product was purified by chromatography over silica gel (1:1 EtOAc–hexane) to afford **15** as a colorless oil (60 mg, 82%); $[\alpha]_D^{20}$ +62° (*c* 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (m, 4 H, Ar), 4.54 (d, 1 H, $J_{1,2}$ 10.2 Hz, H-1), 4.17 (d, 1 H, $J_{2,3}$ 9.1 Hz, H-3), 3.96 (d, 1 H, $J_{5a,5b}$ 14.9 Hz, H-5a), 3.86 (dd, 1 H, H-2), 3.29 (d, 1 H, H-5b), 2.20 (s, 3H, CH_3CO), 1.53 (s, 3 H, Me), 1.52 (s, 3 H, Me); ^{13}C NMR (63 MHz, $CDCl_3$): δ 167.6 (CH_3CO), 157.2 (C-4), 138.1 (Ar-C), 132.3 (Ar-CH), 132.2 (Ar-CH), 118.1 (Ar-C), 111.6 (*C*N, Me_2CO_2), 81.3, 78.1 (C-2, 3), 50.7 (C-1), 26.6 (C-5, 2 × Me), 19.4 (CH_3CO); MS (EI): 378 (0.1, M^+), 202 (6.2, $M - SC_6H_4CN - Ac + 1$), 126 [3.6, $M - SC_6H_4CN - Ac - Me_2C(OH)O$], 43 (100, Ac). High-resolution MS: calcd for $C_{17}H_{18}N_2O_4S_2$: *m*/*z* 378.0708; found: 378.0699.

*4-Cyanophenyl 4-acetamido-4-deoxy-2,3-*O*-isopropylidene-1,5-dithio-α-*L*-arabinopyranoside* (**16**).—To a suspension of the oxime **14** (130 mg, 0.39 mmol) in MeOH (4 mL) cooled to 0 °C was added 78 mg (1.4 equiv) of MoO_3 [9] and 206 mg (14 equiv) of $NaBH_4$. The cold bath was removed and the mixture was stirred for 2 h at rt. Then added at 0 °C were 56 mg (1 equiv) of MoO_3 and 147 mg (10 equiv) of $NaBH_4$. After 2 h at rt, 10% aq AcOH (1 mL) was added to decompose the excess of $NaBH_4$, concd NH_4OH (1 mL) was then added, and the solvents were evaporated off under diminished pressure. Water (5 mL) was added to the mixture, which was then extracted with CH_2Cl_2 (3 × 40 mL). The organic layer was dried ($MgSO_4$), and evaporated.

The crude oil was dissolved in CH_2Cl_2 (5 mL), and then were added 188 μL (6 equiv) of pyridine and 110 μL (3 equiv) of Ac_2O. After 16 h at rt, all solvents were evaporated off and the crude product was purified by chromatography over silica gel (2:3–4:1 EtOAc–hexane) to afford the known **15** (33 mg, 23%) and the 4-acetamido derivative **16** as a colorless solid (53 mg, 38%), mp (from EtOAc–hexane)

152.5–153.5 °C, $[\alpha]_D^{18}$ +48° (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.61 (m, 4 H, Ar), 6.05 (bd, 1H, $J_{4,NH}$ 7.4 Hz, NH), 4.92 (m, 1 H, H-4), 4.39 (d, 1 H, $J_{1,2}$ 10.4 Hz, H-1), 3.82 (dd, 1 H, $J_{2,3}$ 9.1 Hz, H-2), 3.52 (dd, 1 H, $J_{3,4}$ 3.4 Hz, H-3), 3.12 (dd, 1 H, $J_{4,5a}$ 2.7, $J_{5a,5b}$ 14.5 Hz, H-5a), 2.78 (dd, 1 H, $J_{4,5b}$ 3.1 Hz, H-5b), 2.08 (s, 3H, Ac), 1.46 (s, 3H, Me), 1.45 (s, 3 H, Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1 (CH_3CO), 139.8 (Ar-C), 132.3 (Ar-CH), 130.2 (Ar-CH), 118.3 (Ar-C), 110.6 (*C*N), 108.8 (Me_2CO_2), 79.5, 74.6 (C-2, 3), 51.2 (C-1), 46.8 (C-4), 34.8 (C-5), 26.6 (Me), 26.5 (Me), 23.4 (CH_3CO); EIMS: 364 (0.6, M^+), 305 (1.1, M – AcNH), 247 (3.8, M – AcNH – Me_2CO), 230 (4.0, M – SC_6H_4CN), 172 (41.5, M – SC_6H_4CN – Me_2CO), 135 (23.0, HSC_6H_4CN), 43 (100, Ac). Anal. Calcd for $C_{17}H_{20}N_2O_3S_2$ (364.46): C, 56.02; H, 5.53. Found: C, 55.76; H, 5.45.

*4-Cyanophenyl 4-acetamido-4-deoxy-1,5-dithio-α-*L*-arabinopyranoside* (**17**).—To a solution of the 2,3-acetal **16** (208 mg, 0.57 mmol) in MeOH (15 mL) was added Amberlite IR-120 (H^+) resin (~20 mg), and the mixture was vigorously stirred for 17 h at rt, then 3 h at reflux. Removal of the resin by filtration through Celite and evaporation of MeOH gave a pure (NMR), colorless solid (178 mg, 96%), mp (from MeOH–Et_2O) 199–200 °C, $[\alpha]_D^{20}$ −158° (*c* 0.1, MeOH); ^1H NMR (250 MHz, CD_3OD): δ 7.61 (m, 4 H, Ar), 4.51 (m, 1 H, H-4), 4.34 (d, 1 H, $J_{1,2}$ 7.2 Hz, H-1), 4.02 (t, 1 H, $J_{2,3}$ 7.2 Hz, H-2), 3.68 (dd, 1 H, $J_{3,4}$ 3.6 Hz, H-3), 2.88 (dd, 1 H, $J_{4,5a}$ 6.7, $J_{5a,5b}$ 13.8 Hz, H-5a), 2.75 (dd, 1 H, $J_{4,5b}$ 2.7 Hz, H-5b), 2.01 (s, 3H, Ac); MS (EI): 307 (0.1, M – OH), 173 (12.3, M – OH – SC_6H_4CN), 132 (14.8, M – AcNH – SC_6H_4CN), 43 (100, Ac). Anal. Calcd for $C_{14}H_{16}N_2O_3S_2$ (324.40): C, 51.83; H, 4.97; N, 8.63. Found: C, 51.90; H, 5.05; N, 8.23.

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