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# Synthesis of the 3-methyl ether and 4-deoxy derivatives of 4-cyanophenyl 1,5-dithio-β-D-xylopyranoside (Beciparcil)☆

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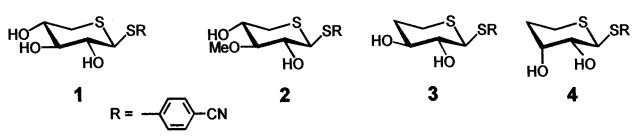
**Abstract**

Treatment of the 2,3-isopropylidene acetal of the title dithioxyloside with 2,4,5-triiodoimidazole–$PPh_3$ caused replacement of the 4-hydroxyl group by iodine to afford 82% of the 4-axial iodide **6**, converted by base into 4-cyanophenyl 2,3-*O*-isopropylidene-1,5-dithio-β-D-*glycero*-pent-3-enopyranoside (**8**). Acid treatment of **8** gave 87% of the deacetonated glycos-3-ulose, borohydride reduction of which afforded 63% of 4-cyanophenyl 4-deoxy-1,5-dithio-α-L-*threo*-pentopyranoside (**3**), together with 27% of the 3-axial epimer. The 3-methyl ether of the title dithioxyloside was satisfactorily prepared via 2,4-protection as the cyclic phenylboronate, methylation, and deprotection; alternative strategy via the 2,4-bis(triisopropylsilyl) ether was complicated because of silyl-group migration under methylation conditions. 

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

## 1. Introduction

A quest for orally active antithrombotic agents based on structural modifications of the lead compound 4-cyanophenyl 1,5-dithio-β-D-xylopyranoside (Beciparcil, **1**) has prompted the synthesis of a series of analogues for biological evaluation in vivo and as substrates for glycosyltransferases involved in glycosaminoglycan biosynthesis. Previous papers have recorded conversion of this dithioxyloside into the 2- and 4-methyl ethers and 4-deoxy-4-fluoro derivatives [2] and inversion transformations at the 4-position [1]. This report presents synthesis of the 3-methyl ether **2** and 4-deoxygenated products **3** and **4** from the parent dithioxyloside **1**.




☆ Part III of the series 'Chemistry of 4-cyanophenyl 1,5-dithio-β-D-xylopyranoside (Beciparcil)'. For Part II, see Ref. [1].

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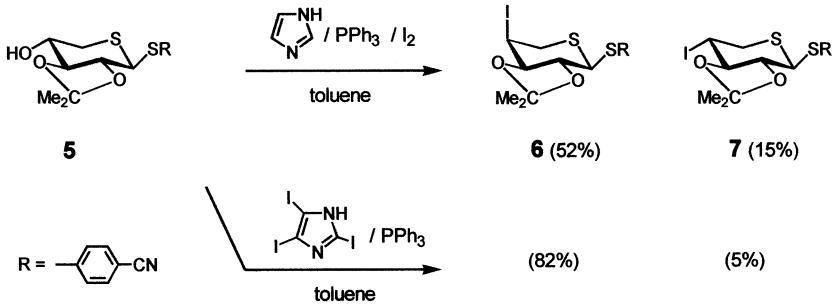
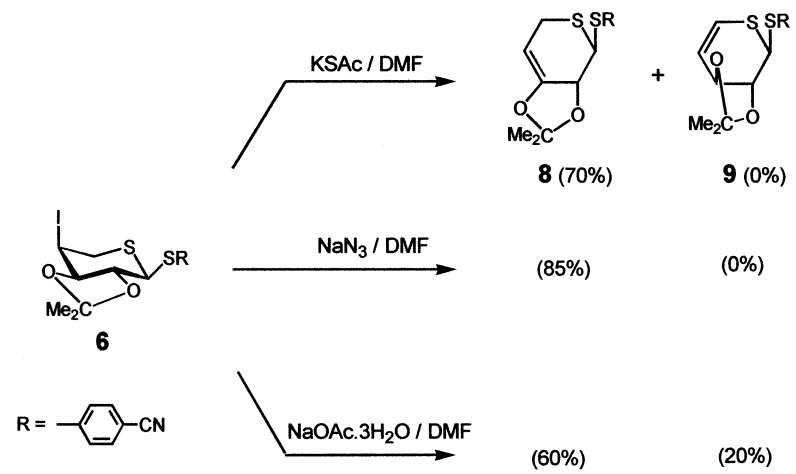



Scheme 1.

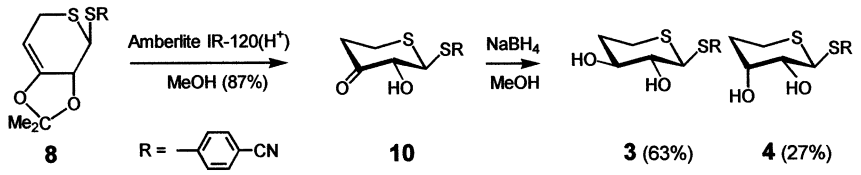



Scheme 2.

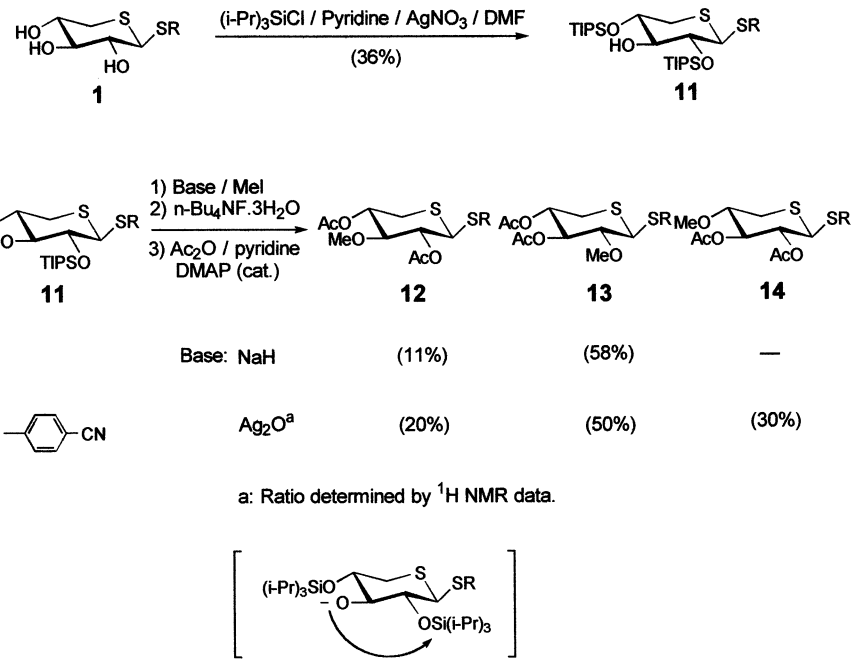
## 2. Results and discussion

*Synthesis of 4-deoxy derivatives.*—The conveniently accessible [2] 4-cyanophenyl 2,3-*O*-isopropylidene-1,5-dithio-β-D-xylopyranoside (**5**) was a logical precursor for the target 4-deoxygenated analogue **3** of the title dithioxyloside, but the presence of the 4-cyanophenylthio group in the molecule, an effective radical trap, made an established method for deoxygenation, via tributylstannane treatment of a derived 4-xanthate [3], inapplicable in this instance. An alternative approach, based on the introduction of iodide at the 4-position, was explored. Two procedures were examined for replacement of the 4-hydroxyl group by iodide, based on the reaction of **5** with 2,4,5-triiodoimidazole–$PPh_3$ or with imidazole–$I_2$–$PPh_3$ [4,5]. Both procedures effected the desired reaction, but the former gave the higher (87%) net yield as well as higher stereoselectivity, with 82% of the axial 4-iodo derivative **6** and only 5% of the equatorial 4-iodo derivative **7** (Scheme 1).

It was found that even such excellent nucleophiles as thiolacetate (1.5 equiv) or azide (1.6 equiv) in *N*,*N*-dimethylformamide (DMF) solution at room temperature failed to effect SN2 displacement of iodide from **6**; instead these reagents acted as bases to abstract H-3 and effect E2 *trans*-diaxial elimination to give the enol–ether derivative **8,** obtained in 85% yield when azide was the reagent. In neither instance was the alternative 4,5-*trans*-elimination product observed, although when sodium acetate (4 equiv) was used the 80% of elimination product formed was found by NMR spectroscopy to be a 3:1 mixture of the 3,4-elimination product **8** and the 4,5-elimination product **9**. The latter compound had been obtained earlier [1] from **5** by the Mitsunobu reaction. This convenient access to 4-cyanophenyl 4-deoxy-2,3-*O*-isopropylidene-β-D-*glycero*-pent-3-enopyranoside (**8**) provided a suitable route not involving radical chemistry to the desired 4-deoxygenated structure (Scheme 2).




Scheme 3.



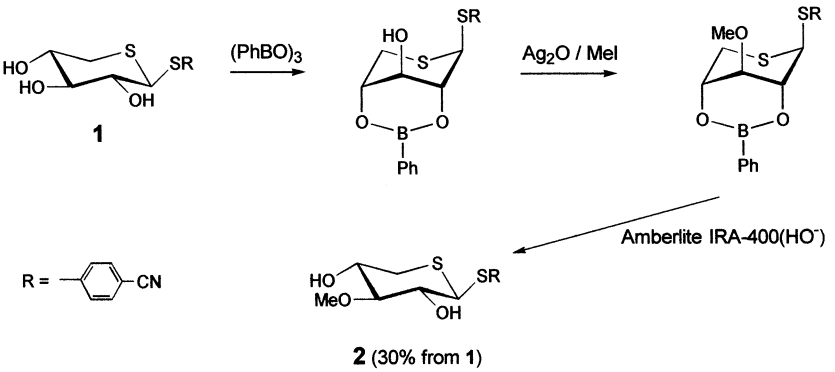

Scheme 4.

Mild acid treatment of compound **8** effected hydrolysis of the enol ether and removal of the isopropylidene group to give the crystalline glycos-3-ulose derivative **10** in 87% yield. Reduction of **10** with sodium borohydride afforded the 3-equatorial alcohol **3** as the major compound (63% yield) and its 3-axial epimer **4** as the minor product (27% yield). The structural assignments were based on $^1$H NMR spectra; compound **3** showed $J_{2,3} = 8.1$ Hz, whereas **4** showed $J_{2,3} = 2.6$ Hz, indicating that H-3 in **3** is axially disposed, and H-3 in **4** is equatorial (Scheme 3).

*Synthesis of 4-cyanophenyl 3-*O*-methyl-1,5-dithio-β-*D*-xylopyranoside* (**2**).—In order to prepare the target 3-methyl ether **2** from the starting triol **1**, a suitable strategy for protecting the 2- and 4-hydroxyl groups was required. It was expected that the bulky triisopropylsilyl (TIPS) group would provide good selectivity at the C-2 and C-4 positions because the C-3 position is sterically unfavored. Accordingly, the triol **1** was treated with chlorotriisopropylsilane (TIPSCl)–pyridine in anhydrous DMF, under promotion by silver nitrate [7], and the 2,4-disilylated product **11** was obtained as a colorless crystalline solid in 36% yield.

It was envisaged that methylation of **11** followed by desilylation would provide a straightforward route to the desired 3-methyl ether. However, attempts to methylate **11** led to migration of the TIPS group under the alkaline conditions of the methylation (Scheme 4).

Compound **11** was first methylated with sodium hydride–iodomethane in anhydrous DMF, and the crude product was then desilylated ($Bu_4NF{\cdot}3H_2O$ in THF). At this stage, TLC (4:1 EtOAc–hexane) showed only one single spot, but the $^1$H NMR spectrum showed a mixture of two products. In order to assign the structures, the mixture was fully acetylated [acetic anhydride–pyridine–4-




Scheme 5.

dimethylaminopyridine (cat.) in $CH_2Cl_2$]. Purification by chromatography over silica gel (3:2 $Et_2O$–hexane) afforded the 2,4-diacetate **12** of the desired 3-methyl ether, but in only low yield (11%), together with the diacetylated 2-methyl ether **13** as the major product (58% yield).

Methylation of **11** by using silver oxide–iodomethane in anhydrous DMF afforded a mixture of three compounds **12, 13,** and the 4-methyl analogue **14** in the ratio of 2:5:3 (as determined by $^1H$ NMR data). An authentic sample of compound **14** was prepared by acetylating the known 4-cyanophenyl 4-*O*-methyl-1,5-dithio-β-D-xylopyranoside [2].

These results showed that the TIPS group was less than satisfactory for the intended purpose. Evidently an initially produced 3-oxyanion displaces the protecting group at O-2 and the resultant 2-oxyanion directs etherification at this position as the major reaction outcome. Attempts to utilize the benzoyl group for 2,4-protection were even less satisfactory; subsequent methylation under the aforementioned conditions led to almost exclusive 2-methylation.

An effective preparative route to the target 3-methyl ether **2** was accomplished by using phenylboronic anhydride [$(PhBO)_3$] [6] as a reagent to introduce into compound **1** the 2,4-cyclic phenylboronate protecting group, which affords the requisite alkali stability for the conditions of methylation. Thus the dithioxyloside **1** was treated with 0.35 equiv of $(PhBO)_3$ in toluene in the presence of crushed 4 Å molecular sieve, and the crude product obtained was directly methylated with silver oxide–iodomethane in anhydrous DMF, followed by saponification of the protecting group with Amberlite IRA-400 ($HO^-$) resin. The crystalline product isolated was the desired 3-methyl ether **2**, obtained in a net yield of 30% from **1** (Scheme 5).

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

*Iodination of 4-cyanophenyl 2,3-O-isopropylidene-1,5-dithio-β-D-xylopyranoside* (**5**).—To a solution of **5** [2] (345 mg, 1.07 mmol) in anhydrous toluene (22 mL) was added $PPh_3$ (1.12 g, 4 equiv) and 2,4,5-triiodoimidazole [5] (0.953 g, 2 equiv). The mixture was heated under argon at 120 °C (bath) for 1.5 h. After cooling to room temperature (rt), saturated aq $NaHCO_3$ (3 mL) was added. Iodine was then added to the mixture until the organic layer

remained red–brown in color for 10 min. After extraction with ether (3 × 50 mL), the ether layer was washed with 5% aq $Na_2S_2O_3$ (to remove the excess of $I_2$), and then water (15 mL), dried ($MgSO_4$), and evaporated. The crude product was purified by chromatography on silica gel (1:4 to 2:3 $Et_2O$–hexane) to afford first the equatorial 4-iodo product **7** (23 mg, 5%) as a colorless solid, and later the axial 4-iodo product **6** as a colorless solid (378 mg, 82%).

*4-Cyanophenyl 4-deoxy-4-iodo-2,3-*O*-isopropylidene-1,5-dithio-α-*L*-arabinopyranoside* (**6**) had mp (from EtOH) 153–155 °C (dec), $[\alpha]_D^{20}$ +121.5° (*c* 0.67, $CHCl_3$), $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 7.63 (m, 4 H, Ar), 4.87 (m, 1 H, H-4), 4.45 (d, 1 H, $J_{1,2}$ 10.4 Hz, H-1), 4.03 (dd, 1 H, $J_{2,3}$ 8.4 Hz, H-2), 3.40 (dd, 1 H, $J_{4,5a}$ 2.9, $J_{5a,5b}$ 15.2 Hz, H-5a), 2.82 (dd, 1 H, $J_{4,5b}$ 3.0 Hz, H-5b), 2.52 (dd, 1 H, $J_{3,4}$ 3.2 Hz, H-3), 1.49 (s, 3 H, Me), 1.48 (s, 3 H, Me); $^{13}$C NMR (63 MHz, $CDCl_3$): $\delta$ 139.3 (Ar-C), 132.3 (Ar-CH), 131.4 (Ar-CH), 118.4 (Ar-C), 111.1 ($Me_2CO_2$), 109.4 (*C*N), 79.8 (C-3), 77.3 (C-2), 51.4 (C-1), 39.2 (C-5), 29.6 (C-4), 27.0 (Me), 26.9 (Me); MS (EI): 433 (2.9, $M^+$), 299 (19.8, $M - SC_6H_4CN$), 241 (62.2, $M - SC_6H_4CN - Me_2CO$), 171 (36.3, $M - SC_6H_4CN - HI$), 128 (9.1, HI), 116 (100). Anal. Calcd for $C_{15}H_{16}INO_2S_2$ (433.31): C, 41.58; H, 3.72. Found: C, 41.60; H, 3.67.

*4-Cyanophenyl 4-deoxy-4-iodo-2,3-*O*-isopropylidene-1,5-dithio-β-*D*-xylopyranoside* (**7**) had mp (from EtOH) 163–164 °C, $[\alpha]_D^{25}$ −106.3° (*c* 0.80, $CHCl_3$); $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 7.61 (m, 4 H, Ar), 4.42 (d, 1 H, $J_{1,2}$ 10.3 Hz, H-1), 4.18 (ddd, 1 H, $J_{3,4}$ 10.7, $J_{4,5a}$ 11.7, $J_{4,5b}$ 4.2 Hz, H-4), 3.64 (dd, 1 H, $J_{2,3}$ 8.3 Hz, H-2), 3.47 (dd, 1 H, H-3), 3.33 (dd, 1 H, $J_{5a,5b}$ 13.8 Hz, H-5a), 3.08 (dd, 1 H, H-5b), 1.50 (s, 3 H, Me), 1.48 (s, 3 H, Me); $^{13}$C NMR (63 MHz, $CDCl_3$): $\delta$ 138.8 (Ar-C), 132.3 (Ar-CH), 131.6 (Ar-CH), 118.2 (Ar-C), 111.2 ($Me_2CO_2$), 108.1 (*C*N), 84.4, 79.1 (C-2, 3), 51.2 (C-1), 38.7 (C-5), 26.7 (Me), 26.5 (Me), 21.7 (C-4); MS (EI): 433 (1.2, $M^+$), 299 (3.0, $M - SC_6H_4CN$), 241 (65.3, $M - SC_6H_4CN - Me_2CO$), 114 (19.4, $M - SC_6H_4CN - Me_2CO - I$), 113 (21.2, $M - SC_6H_4CN - Me_2CO - HI$), 65 (100). HRMS Calcd for $C_{15}H_{16}INO_2S_2$: 432.967. Found: 432.964.

Treatment of **5** (217 mg, 0.67 mmol) by the same procedure with $PPh_3$ (2.5 equiv), imidazole (2.2 equiv), and iodine (1.1 equiv) in toluene (5 mL) for 35 min afforded, after column chromatography on silica gel, the 4-axial product **6** (151 mg, 52%) and the 4-equatorial product **7** (44 mg, 15%).

*4-Cyanophenyl 2,3-*O*-isopropylidene-1,5-dithio-β-*D*-glycero-pent-3-enopyranoside* (**8**). —To a solution of the 4-axial iodide **6** (877 mg, 2.03 mmol) in anhydrous DMF (20 mL) was added $NaN_3$ (216 mg, 1.6 equiv). After 48 h at rt, $Et_2O$ (250 mL) was added. The organic solution was washed with water (5 × 10 mL), dried ($MgSO_4$), and evaporated to afford **8** as a pure (NMR), colorless solid (500 mg, 80%) that was used directly for the next step (a decrease in yield resulted if the crude product was purified by chromatography on silica gel with 1:4 $Et_2O$–hexane as eluent), mp (from EtOH) 64.5–65 °C, $[\alpha]_D^{19}$ +84.0° (*c* 0.47, $CHCl_3$); $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 7.61 (m, 4 H, Ar), 4.96 (dt, 1 H, $J_{2,4}$ 1.9, $J_{4,5a} = J_{4,5b} = 3.7$ Hz, H-4), 4.59 (dddd, 1 H, $J_{1,2}$ 9.6, $J_{2,5a}$ 2.6 Hz, $J_{2,5b}$ 2.1 Hz, H-2), 4.21 (d, 1 H, H-1), 3.57 (ddd, 1 H, $J_{5a,5b}$ 16.0 Hz, H-5a), 3.09 (ddd, 1 H, H-5b), 1.51 (s, 3 H, Me), 1.49 (s, 3 H, Me); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 150.8 (C-3), 140.1 (Ar-C), 132.2 (Ar-CH), 130.4 (Ar-CH), 118.3 (Ar-C), 110.5 ($Me_2CO_2$), 110.2 (*C*N), 89.9 (C-4), 74.6 (C-2), 49.1 (C-1), 26.8 (C-5), 26.6 (Me), 24.8 (Me); MS (EI): 305 (0.3, $M^+$), 171 (7.0, $M - SC_6H_4CN$), 135 (12.7, $HSC_6H_4CN$), 126 (15.6, $M - SC_6H_4CN - SCH_2 + 1$), 113 (13.8, $M - SC_6H_4CN - Me_2CO$), 55 (100).

This product was unstable and decomposed before an elemental analysis could be obtained.

When compound **6** (100 mg, 0.23 mmol) was treated by the same procedure with $NaOAc{\cdot}3H_2O$ (4 equiv) in DMF (3 mL) for 48 h, a chromatographically homogeneous pro-duct (56 mg, 80%) was isolated, but its NMR spectrum showed it to be a 3:1 mixture of **8** and an isomeric product determined to be 4-cyanophenyl 2,3-*O*-isopropylidene-1,5-dithio-α-L-*threo*-pent-4-enopyranoside (**9**). Compound **9** has already been reported [1].

*4-Cyanophenyl 1,5-dithio-β-*D-glycero-*pentopyranosid-3-ulose* (**10**).—To a mixture of **8** (77 mg, 0.25 mmol) in MeOH (4 mL) and $H_2O$ (1 mL) was added Amberlite IR-120 ($H^+$) resin ($\sim$15 mg). After 19 h at rt[1], the mixture was heated for 16 h at 50 °C (bath). After removal of resin over Celite, the solvents were removed by evaporation under diminished pressure. The crude product crystallized from EtOAc–hexane to give **10** as colorless crystals (43 mg, 64%). The mother liquor was purified by chromatography on silica gel (2:3 EtOAc–hexane) to furnish an additional 15 mg (22%) of **10** (total yield: 87%), mp (from EtOAc–hexane) 148 °C, $[\alpha]_D^{19}$ +21.0° (*c* 0.21, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.61 (m, 4 H, Ar), 4.21 (m, 2 H, H-2, OH, $D_2O$ exchangeable), 4.16 (d, 1 H, $J_{1,2}$ 10.5, H-1), 3.02–2.80 (m, 4 H, H-4,5); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 205.8 (C-3), 139.1 (Ar-C), 132.2 (Ar-CH), 131.9 (Ar-CH), 118.2 (Ar-C), 111.2 (*C*N), 78.1 (C-2), 56.5 (C-1), 42.3 (C-4), 29.3 (C-5); MS (EI): 265 (1.6, $M^+$), 135 (100, $HSC_6H_4CN$), 131 (25.5, $M-SC_6H_4CN$), 113 (2.7, $M-SC_6H_4CN-H_2O$). Anal. Calcd for $C_{12}H_{11}NO_2S_2$ (265.34): C, 54.32; H, 4.18. Found: C, 54.14; H, 4.21.

*Reduction of 4-cyanophenyl 1,5-dithio-β-*D-glycero-*3-pentopyranosid-3-ulose* (**10**).—To a suspension of compound **10** (422 mg, 1.59 mmol) in MeOH (6 mL) cooled to 0 °C was added $NaBH_4$ (61 mg, 1 equiv) during 10 min. After 30 min at 0 °C, 25% aq AcOH (1 mL) was added and the solvents were evaporated off under diminished pressure. Water (20 mL) was added and the mixture extracted with EtOAc (3 × 70 mL). The organic layer was washed with satd aq $NaHCO_3$ (2 × 20 mL), and then satd aq NaCl (2 × 20 mL), dried ($MgSO_4$), and evaporated. The crude solid was carefully crystallized from EtOAc–hexane to furnish 65 mg (15%) of **3** as colorless crystals. The mother liquor was purified by chromatography over silica gel (1:1 EtOAc–hexane) to afford the solid epimer **4** (114 mg, 27%) and **3** (203 mg, 48%).

*4-Cyanophenyl 4-deoxy-1,5-dithio-α-*L-threo-*pentopyranoside* (**3**) was obtained in a total yield of 63%, mp (from EtOAc–hexane) 141–141.5 °C, $[\alpha]_D^{19}$ +23.3° (*c* 0.46, MeOH); $^1$H NMR (250 MHz, $Me_2SO$-$d_6$/$D_2O$): $\delta$ 7.74 (m, 2 H, Ar), 7.60 (m, 2 H, Ar), 4.43 (d, 1 H, $J_{1,2}$ 9.0 Hz, H-1), 3.37 (ddd, 1 H, $J_{2,3}$ 8.1, $J_{3,4a}$ 10.4, $J_{3,4e}$ 3.7 Hz, H-3), 3.31 (dd, 1 H, H-2), 2.78 (ddd, 1 H, $J_{4e,5a}$ 2.5, $J_{4a,5a}$ 11.8, $J_{5a,5e}$ 14.1 Hz, H-5a), 2.51 (m, 1 H, H-5e), 2.20 (m, 1 H, H-4e), 1.68 (m, 1 H, H-4a); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 140.1 (Ar-C), 132.5 (Ar-CH), 130.9 (Ar-CH), 118.3 (Ar-C), 111.1 (*C*N), 76.8, 74.1 (C-2, 3), 53.9 (C-1), 34.7 (C-5), 28.2 (C-4); MS (EI): 249 (0.1, $M-H_2O$), 135 (100, $HSC_6H_4CN$), 133 (4.0, $M-SC_6H_4CN$), 115 (19.2, $M-SC_6H_4CN-H_2O$). Anal. Calcd for $C_{12}H_{13}NO_2S_2$ (267.35): C, 53.90; H, 4.90; N, 5.26. Found: C, 53.73; H, 4.88; N, 5.14.

*4-Cyanophenyl 4-deoxy-1,5-dithio-β-*D-erythro-*pentopyranoside* (**4**), 27% had mp (from EtOAc–hexane) 97–98 °C, $[\alpha]_D^{18}$ −159.7° (*c* 0.58, $CHCl_3$); $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 7.59 (m, 4 H, Ar), 4.52 (d, 1 H, $J_{1,2}$ 8.4 Hz, H-1), 4.12 (m, 1 H, H-3), 3.80 (ddd, 1 H, $J_{2,OH}$ 5.0, $J_{2,3}$ 2.6 Hz, H-2), 3.03 (ddd, 1 H, $J_{4e,5a}$ 2.7, $J_{4a,5a}$ 10.1, $J_{5a,5e}$ 13.8 Hz, H-5a), 2.95 (d, 1 H, OH-2, $D_2O$ exchangeable), 2.51 (ddd, 1 H, $J_{4e,5e}$ 6.0, $J_{4a,5e}$ 3.7 Hz, H-5e), 2.32 (d, 1 H, $J_{3,OH}$ 4.0 Hz, OH-3, $D_2O$ exchangeable), 2.18 (m, 1 H, H-4e), 2.04 (m, 1 H, H-4a); $^{13}$C NMR (63 MHz, $CDCl_3$): $\delta$ 140.2 (Ar-C), 132.5 (Ar-CH), 131.1 (Ar-CH), 118.3 (Ar-C), 110.8 (*C*N), 71.9, 68.0 (C-2, 3), 51.7 (C-1), 32.6 (C-5), 24.6 (C-4); MS (EI): 267 (0.1, $M^+$), 135 (72.0, $HSC_6H_4CN$), 133 (12.8, $M-SC_6H_4CN$), 115 (39.8, $M-SC_6H_4CN-H_2O$), 97 (4.5, $M-SC_6H_4CN-2\times H_2O$). Anal. Calcd for $C_{12}H_{13}NO_2S_2$ (267.35): C, 53.90; H, 4.90; N, 5.26. Found: C, 53.58; H, 4.85; N, 5.16.

*4-Cyanophenyl 2,4-di-*O*-(triisopropyl)silyl-1,5-dithio-β-*D-*xylopyranoside* (**11**).—To a solution of the triol **1** (1 g, 3.53 mmol), chlorotriisopropylsilane (TIPSCl) (3.03 mL, 4 equiv) and pyridine (2.86 mL, 10 equiv) in anhydrous DMF (10 mL) was added 2.025 g (3.4 equiv) of $AgNO_3$ under argon. The mixture was stirred under argon for 20 h at rt and then MeOH (2 mL) was added. After 5 min, $CH_2Cl_2$ (50 mL) was then added and the mixture was filtered through Celite. The solvent was evaporated off under diminished

[1] It is important to leave the reaction at room temperature at first. The starting material may be totally decomposed if heating is initiated directly.

pressure and the crude product purified by chromatography over silica gel (1:9 $Et_2O$–hexane) to afford **11** as a colorless solid (756 mg, 36%), mp (from hexane) 144–144.5 °C, $[\alpha]_D^{20}$ + 13° (*c* 0.45, $CHCl_3$); $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$ 7.54 (m, 4 H, Ar), 4.09 (d, 1 H, $J_{1,2}$ 9.9 Hz, H-1), 3.92 (m, 1 H, H-4), 3.88 (dd, 1 H, $J_{2,3}$ 8.4 Hz, H-2), 3.25 (dt, 1 H, $J_{3,OH}$ 1.6, $J_{3,4}$ 8.4 Hz, H-3), 2.67 (dd, 1 H, $J_{4,5a}$ 10.6, $J_{5a,5b}$ 13.3 Hz, H-5a), 2.65 (d, 1 H, OH, $D_2O$ exchangeable), 2.57 (dd, 1 H, $J_{4,5b}$ 4.5 Hz, H-5b), 1.34–1.23 (m, 6 H, 3 × CHSi), 1.12–1.06 (m, 36 H, 12 × Me); $^{13}C$ NMR (63 MHz, $CDCl_3$): $\delta$ 142.4 (Ar-C), 132.2 (Ar-CH), 129.2 (Ar-CH), 118.6 (Ar-C), 109.7 (*C*N), 80.9 (C-3), 77.0 (C-2), 75.0 (C-4), 54.0 (C-1), 34.4 (C-5), 18.4 (Me), 18.0 (Me), 13.3 (*C*HSi), 12.5 (*C*HSi); MS (EI): 534 (0.5, M − i-Pr − $H_2O$), 417 (12.1, M − i-Pr − $HSC_6H_4CN$), 378 [3.9, M − i-Pr − $HOSi(i\text{-}Pr)_3$], 59 (100). Anal. Calcd for $C_{30}H_{53}NO_3S_2Si_2$ (596.03): C, 60.45; H, 8.96. Found: C, 60.55; H, 9.02.

*Methylation of 4-cyanophenyl 2,4-di*-O-*(trisisopropyl)silyl-1,5-dithio-β*-D-*xylopyranoside* (**11**)

*Method A*. To a solution of the 2,4-disilylated product **11** (100 mg, 0.17 mmol) and MeI (52 μL, 5 equiv) in anhydrous DMF (1 mL) under argon and cooled to − 15 °C was added 13 mg of NaH (80% in mineral oil, 2.5 equiv). After 30 min at − 15 °C, satd aq $NH_4Cl$ (5 mL) and $Et_2O$ (50 mL) were added. The ether layer was washed with $H_2O$ (3 × 10 mL), 5% aq $Na_2S_2O_3$ (5 mL), $H_2O$ (10 mL), and dried ($MgSO_4$). The solvent was evaporated off under diminished pressure, and the crude product was used for the next step without purification.

The crude product was dissolved in THF (4 mL) and $Bu_4NF{\cdot}3H_2O$ (160 mg, 3 equiv) was added. After 20 min at rt, EtOAc (50 mL) was added. The organic layer was washed with $H_2O$ (2 × 8 mL), dried ($MgSO_4$), and evaporated under diminished pressure. At this stage, the TLC (4:1 EtOAc–hexane) showed one single spot, but the $^1H$ NMR spectrum showed two products.

To a solution of the crude product in $CH_2Cl_2$ (2 mL) was added pyridine (110 μL, 8 equiv), $Ac_2O$ (80 μL, 5 equiv), and 4-dimethylaminopyridine (cat.). After 16 h at rt, water (5 mL) was added, and the mixture was extracted with $CH_2Cl_2$ (3 × 15 mL), dried ($MgSO_4$), and evaporated to dryness. Purification by chromatography over silica gel (3:2 $Et_2O$–hexane) gave the desired 2,4-diacetate **12** (7 mg, 11% from **11**) and the 3,4-diacetate **13** (37 mg, 58% from **11**).

*Method B*. To a solution of the 2,4-disilylated derivative **11** (100 mg, 0.17 mmol) and MeI (104 μL, 10 equiv) in anhydrous DMF (1 mL) cooled to 0 °C was added under argon 195 mg (5 equiv) of $Ag_2O$ in small portions during 1 h. After stirring for 20 h at rt, EtOAc (20 mL) was added, and the mixture was filtered through Celite. The solvent was evaporated off under diminished pressure, and the crude product was used for the next step without purification.

The desilylation and diacetylation steps were effected in the same way as in Method A. The crude product after acetylation was evaluated by comparison of its $^1H$ NMR spectrum with those of the known 2,4-diacetate **12**, 3,4-diacetate **13**, and 2,3-diacetate **14**. Compound **14** was prepared from the known 4-cyanophenyl 4-*O*-methyl-1,5-dithio-β-D-xylopyranoside [2] by the foregoing diacetylation procedure. In this case, the proportions (NMR) of **12**, **13**, and **14** were 2:5:3.

*4-Cyanophenyl 2,4-di*-O-*acetyl-3*-O-*methyl-1,5-dithio-β*-D-*xylopyranoside* (**12**): mp (from EtOH) 147.5–148.5 °C, $[\alpha]_D^{21}$ + 11.3° (*c* 0.88, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.56 (m, 4 H, Ar), 5.14 (dd, 1 H, $J_{1,2}$ 10.4, $J_{2,3}$ 9.0 Hz, H-2), 4.99 (ddd, 1 H, $J_{4,5a}$ 4.5, $J_{4,5b}$ 10.7, $J_{3,4}$ 9.3 Hz, H-4), 4.10 (d, 1 H, H-1), 3.47 (s, 3 H, OMe), 3.24 (dd, 1 H, H-3), 2.84 (dd, 1 H, $J_{5a,5b}$ 13.5 Hz, H-5a), 2.63 (dd, 1 H, H-5b), 2.11 (s, 3 H, $CH_3CO$), 2.08 (s, 3 H, $CH_3CO$); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 169.6 ($CH_3CO$), 169.3 ($CH_3CO$), 139.9 (Ar-C), 132.3 (Ar-CH), 130.8 (Ar-CH), 118.2 (Ar-C), 110.9 (*C*N), 83.6, 74.3, 73.5 (C-2, 3, 4), 60.5 (OMe), 50.8 (C-1), 31.1 (C-5), 20.8 ($CH_3CO$), 20.7 ($CH_3CO$); MS (EI): 381 (0.1, $M^+$), 215 (12.1, M − $SC_6H_4CN$ − MeOH), 155 (9.8, M − $SC_6H_4CN$ − MeOH − AcOH), 145 (14.4, M − $SC_6H_4CN$ − AcO − Ac), 113 (60.4, M − $SC_6H_4CN$ − AcO − Ac − MeOH), 43 (100, Ac). HRMS Calcd for $C_{17}H_{19}NO_5S_2$: 381.0705. Found: 381.0731.

*4-Cyanophenyl 3,4-di-*O*-acetyl-2-*O*-methyl-1,5-dithio-β-*D*-xylopyranoside* (**13**): mp (from $Et_2O$) 144.5–145 °C, $[\alpha]_D^{18}$ +64° (*c* 0.58, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.59 (m, 4 H, Ar), 5.04 (m, 2 H, H-2, 4), 4.14 (d, 1 H, $J_{1,2}$ 10.2, H-1), 3.57 (s, 3 H, OMe), 3.45 (dd, 1 H, $J_{2,3}$ 8.9 Hz, H-2), 2.81–2.66 (m, 2 H, H-5), 2.11 (s, 3 H, $CH_3CO$), 2.02 (s, 3 H, $CH_3CO$); $^{13}C$ NMR (63 MHz, $CDCl_3$): δ 169.8 ($CH_3CO$), 169.5 ($CH_3CO$), 140.8 (Ar-C), 132.4 (Ar-CH), 130.3 (Ar-CH), 118.2 (Ar-C), 110.7 (*C*N), 84.4, 75.5, 72.2 (C-2, 3, 4), 61.4 (OMe), 52.0 (C-1), 31.3 (C-5), 20.7 ($CH_3CO$); MS (EI): 381 (0.1, $M^+$), 187 (3.5, $M - SC_6H_4CN - AcOH$), 127 (59.3, $M - SC_6H_4CN - 2AcOH$), 113 (15.7, $M - SC_6H_4CN - AcO - Ac - MeOH$), 43 (100, Ac). Anal. Calcd for $C_{17}H_{19}NO_5S_2$ (381.45): C, 53.52; H, 5.02. Found: C, 53.44; H, 5.03.

*4-Cyanophenyl 2,3-di-*O*-acetyl-4-*O*-methyl-1,5-dithio-β-*D*-xylopyranoside* (**14**): mp (from EtOH) 135–136 °C, $[\alpha]_D^{20}$ +31° (*c* 0.17, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.58 (m, 4 H, Ar), 5.16 (dd, 1 H, $J_{1,2}$ 10.6, $J_{2,3}$ 9.4 Hz, H-2), 4.95 (t, 1 H, $J_{3,4}$ 9.4 Hz, H-4), 4.16 (d, 1 H, H-1), 3.52 (m, 1 H, H-4), 3.40 (s, 3 H, OMe), 2.86 (dd, 1 H, $J_{4,5a}$ 4.4, $J_{5a,5b}$ 13.6 Hz, H-5a), 2.63 (dd, 1 H, $J_{4,5b}$ 10.9, H-5b), 2.06 (s, 3 H, $CH_3CO$), 2.03 (s, 3 H, $CH_3CO$); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 169.7 ($CH_3CO$), 169.5 ($CH_3CO$), 139.5 (Ar-C), 132.3 (Ar-CH), 131.0 (Ar-CH), 118.1 (Ar-C), 111.1 (*C*N), 80.5, 75.4, 73.4 (C-2, 3, 4), 57.9 (OMe), 50.5 (C-1), 31.0 (C-5), 20.6 ($CH_3CO$), 20.4 ($CH_3CO$); MS (EI): 381 (0.1, $M^+$), 289 (1.0, $M - MeOH - AcOH$), 187 (15.9, $M - SC_6H_4CN - AcOH$), 145 (68.0, $M - SC_6H_4CN - AcO - Ac$), 43 (100, Ac). HRMS Calcd for $C_{17}H_{19}NO_5S_2$: 381.0705. Found: 381.0690.

*4-Cyanophenyl 3-*O*-methyl-1,5-dithio-β-*D*-xylopyranoside* (**2**).—To a suspension of the triol **1** (820 mg, 2.9 mmol), and $(PhBO)_3$ (317 mg, 0.35 equiv) in anhydrous toluene (40 mL) was added 2 g of crushed 4 Å molecular sieves, and the mixture was boiled under reflux under argon for 20 h. Toluene was evaporated off under diminished pressure, and the crude product was used for next step without purification.

To the crude product was added anhydrous DMF (8 mL) and MeI (1.1 mL, 6 equiv). $Ag_2O$ (2.7 g, 4 equiv) was then added in small portions during 2 h. After stirring for 20 h at rt, EtOAc (20 mL) was added and the mixture was filtered through Celite. The solvent was evaporated off under diminished pressure, and the crude product was used for the next step without purification. To a solution of the crude product in MeOH (25 mL) was added 3 g of Amberlite IRA-400 ($HO^-$) resin. After vigorous stirring for 20 h at rt, MeOH was evaporated off, and the crude solid was applied to a column of neutral alumina (activity I) using 1:4 MeOH–EtOAc as eluant. The product obtained was then purified over silica gel (EtOAc) to afford the 3-methyl ether **2** as a colorless solid (257 mg, 30% from **1**), mp (EtOAc–hexane) 156–157 °C, $[\alpha]_D^{21}$ −75° (*c* 0.23, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.60 (m, 4 H, Ar), 4.05 (d, 1 H, $J_{1,2}$ 9.5 Hz, H-1), 3.83 (m, 1 H, H-4), 3.70 (ddd, 1 H, $J_{2,3}$ 8.4, $J_{2,OH}$ 3.0 Hz, H-2), 3.677 (s, 3 H, OMe), 3.11 (d, 1 H, OH-2, $D_2O$ exchangeable), 2.97 (t, 1 H, $J_{3,4}$ 8.4 Hz, H-3), 2.80 (dd, 1 H, $J_{4,5a}$ 4.3, $J_{5a,5b}$ 13.5 Hz, H-5a), 2.68 (d, 1 H, $J_{4,OH}$ 3.3 Hz, OH-4, $D_2O$ exchangeable), 2.68 (dd, 1 H, $J_{4,5b}$ 10.2 Hz, H-5b); $^{13}C$ NMR (50 MHz, $CDCl_3$): δ 140.1 (Ar-C), 132.5 (Ar-CH), 131.0 (Ar-CH), 118.4 (Ar-C), 111.0 (*C*N), 87.6, 74.9, 71.7 (C-2, 3, 4), 61.3 (OMe), 53.7 (C-1), 33.1 (C-5); MS (CI, $CH_4$): 298 (M + 1), 280 ($M - H_2O$), 163 ($M - SC_6H_4CN$), 145 ($M - SC_6H_4CN - H_2O$), 131 ($M - SC_6H_4CN - MeOH$). Anal. Calcd for $C_{13}H_{15}NO_3S_2$ (297.38): C, 52.50; H, 5.08. Found: C, 52.77; H, 5.12.

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