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Synthesis of the 2- and 4-monomethyl ethers and the 4-deoxy-4-fluoro derivative of 4-cyanophenyl 1,5-dithio-β-D-xylopyranoside as potential antithrombotic agents

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ABSTRACT

The title glycoside undergoes acetonation with 2-methoxypropene to give a 2:1 mixture of the crystalline 2,3- and 3,4-isopropylidene acetals in 94% yield, which upon methylation under controlled conditions followed by deacetonation afforded the respective 4- and 2-monomethyl ethers. The 2,3-acetal underwent reaction with diethylaminosulfur trifluoride to introduce fluorine at C-4 with net retention of stereochemistry, but the 3,4-acetal under comparable conditions underwent migration of the arylthio group to C-2 and fluorination at C-1, with stereochemical retention at both positions.

INTRODUCTION

In a quest for orally active antithrombotic agents for mammalian systems, a range of synthetic glycopyranosides varying in the nature of the aglycon, configuration, and chain length of the sugar, and replacement by sulfur of either the ring-oxygen atom, the oxygen atom linked ot the aglycon, or both, has been evaluated in an animal model[1,2]. Among the various sugar configurations examined, significant activity is manifested only in those examples having the β-D-xylopyranosyl structure, and a particularly promising example proved to be 4-cyanophenyl 1,5-dithio-β-D-xylopyranoside (**1**)[2].

Although the exact biological mechanism responsible for this observed activity is not fully elucidated, it is well known that β-D-xylopyranosyl derivatives can act as exogeneous primers for glycosaminoglycan synthesis. The natural process[3] is

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initiated by transfer of xylose from UDP-D-xylose to an L-serine of the core protein of the proteoglycan undergoing biosynthesis. This is followed by stepwise addition of individual monosaccharides from UDP sugars by a series of glycosyltransferase reactions[4].

Considering that the dithioxyloside **1** might exert its activity by competing with the endogenous xylose-substituted core protein, it was of interest to prepare and evaluate analogues of compound **1** having functional variation at the three hydroxyl sites, O-2, O-3, and O-4, while retaining the same overall β-D-xylopyranosyl stereochemistry. As the synthesis of compound **1** is quite involved, but has been successfully optimized[2], the possibility of preparing the three possible monomethyl ethers of **1** from **1** directly was envisaged and is addressed in this report. The multifunctionality of **1** places severe limitations on the range of chemical reagents that can be utilized for functional transformations. Nevertheless, it was found possible to introduce fluorine at the 4-position of **1**, although attempts to introduce fluorine at C-2 led to a glycosyl fluoride derivative through group migration.

RESULTS AND DISCUSSION

Attempts at conducting high-yielding monofunctionalization reactions on 4-cyanophenyl 1,5-dithio-β-D-xylopyranoside (**1**) are fraught with difficulties because of the multiplicity of sensitive functional groups present: conventional oxidizing and reducing reagents are inapplicable as are hydrogenation catalysts and many electrophilic reagents, and the high nuleophilicity of sulfur in two environments creates a great propensity for internal displacement of potential leaving groups. The mutual *trans*-disposition of the three hydroxyl groups invalidates most methods for selective protection of a pair of these groups.

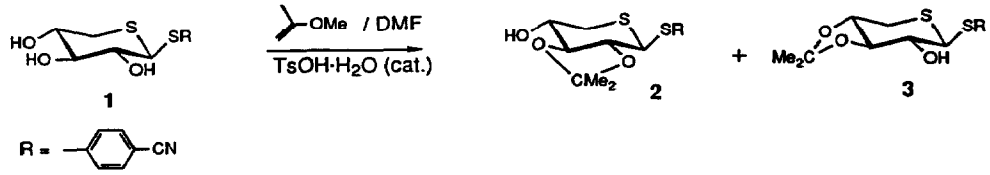
Preparation of the 2-ether (**10**) *and 4-ether* (**5**) *of glycoside* **1**.—The kinetic acetonation procedure employing 2-methoxypropene developed by Gelas and Horton[5] has the potential for forming cyclic acetals from *trans*-disposed vicinal diols in 6-membered ring-systems when no *cis*-disposed diols are available, as has been demonstrated in glucopyranoside[6] and xylopyranoside[7] systems.

The dithioxyloside **1** was subjected to acetonation with 2-methoxypropene in dry *N*,*N*-dimethylformaldehyde (DMF) with a trace of *p*-toluenesulfonic acid monohydrate as catalyst, and a detailed comparative study (Table I) was performed to establish optimum preparative conditions. Reaction for 1 h at room temperature with 2 mol of the reagent gave the best (94%) total conversion and afforded the readily separable 2,3-acetal **2** and 3,4-acetal **3**, both crystalline, in a 2:1 ratio. The 3,4-acetal **3** was preponderant under all conditions studied, especially at higher temperatures. Reaction at low temperature required more reagent to consume all of the glycoside **1**, but did not lead to a higher yield of the 2,3-acetal **2**.

No significant distortion of the pyranoside ring conformation was effected by the *trans*-fusion of the acetal ring in **2** and **3**, as the magnitudes (9–10 Hz) of the $J_{1,2}$ and $J_{2,3}$ couplings were consistent with the *trans*-diaxial disposition of H-1, -2,

TABLE I

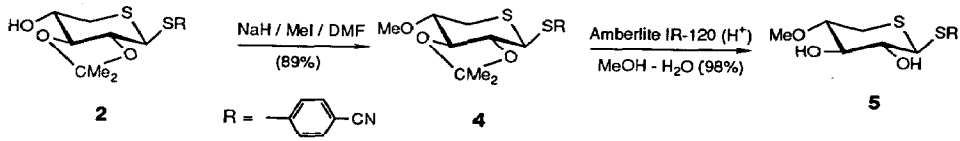
Acetonation of 4-cyanophenyl 1,5-dithio-β-D-xylopyranoside (1)



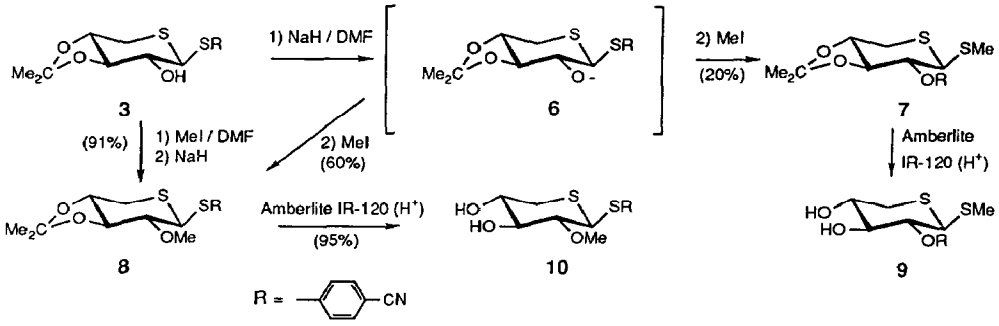
OMe (equiv)	Temperature (°C)	Time (h)	Yield (%)	
			2	3
3	−10	4	7	42
3	0	4	22	70
2	25	1	31	63
2	50	1	7	89

and -3 in both glycosides; this behavior parallels that observed[6] with 2,3-isopropylidene acetals in glucopyranoside systems. The anomeric carbon atom displays in the ^{13}C NMR spectrum a remarkably high (~ 50 ppm) field-position, attributable to the presence of the two sulfur atoms.

The 2,3-acetal **2** underwent classic methylation by deprotonation with sodium hydride in DMF followed by reaction with methyl iodide, and the 4-methyl ether **4** was obtained crystalline in 89% yield. Deactonation of this product could be effected with a cation-exchange resin (H^+) at room temperature in methanol and a controlled amount of water with careful TLC monitoring: the resultant crystalline 4-monomethyl ether **5** was obtained in practically quantitative yield.



Methylation of the 3,4-acetal **3** was less straightforword; the procedure used for **2** when applied to **3** gave a product migrating as a single zone in TLC, but this was a mixture of two components having the same R_f value, as became evident when acid-catalyzed deacetonation (under the conditions used for **4**) was performed. Chromatography on silica gel gave the desired 2-methyl ether (**10**) of **1**, crystalline and dextrorotatory in 60% yield, along with 20% of an isomeric product, also crystalline but strongly levorotatory. This isomer was determined to be methyl 2-*O*-(4-cyanophenyl)-1,5-dithio-β-D-xylopyranoside (**9**) from consideration of NMR and mass-spectral data (see Experimental), notably from the high-field (δ 14.5 in ^{13}C, 2.12 in ^{1}H) location of the signal for the methyl group, the mass-spectral fragmentation pathways, and the similarity of the $J_{1,2}$ and $J_{2,3}$ values for both **9** and **10**.



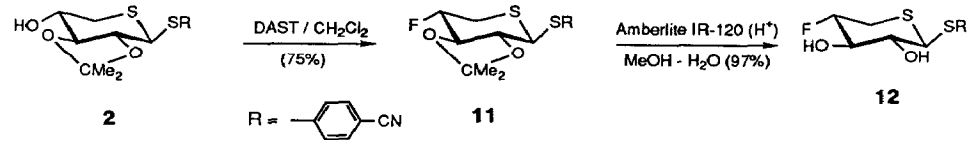
Scheme 1.

It appears (Scheme 1) that the initial alkoxide **6** resulting from deprotonation of **3** undergoes conventional methylation to the 2-methyl ether **8** as the principal reaction pathway, but concurrent S → O migration of the 4-cyanophenyl group with methylation at S-1 affords a minor proportion of the methyl thioglycoside acetal **7** that comigrates with its isomer **8**.

The difficulty in methylating the 3,4-acetal **3** could be circumvented by reversing the order of addition of the reagents. Thus, portionwise addition of sodium hydride to the mixture of **3** and methyl iodide in DMF afforded uniquely the desired acetal **8** in 91% yield; the isomer **7** arising through group migration was not detectable by ^{1}H NMR spectroscopy. The deacetonation conditions used as before converted **8** into the diol **10** in essentially quantitative yield.

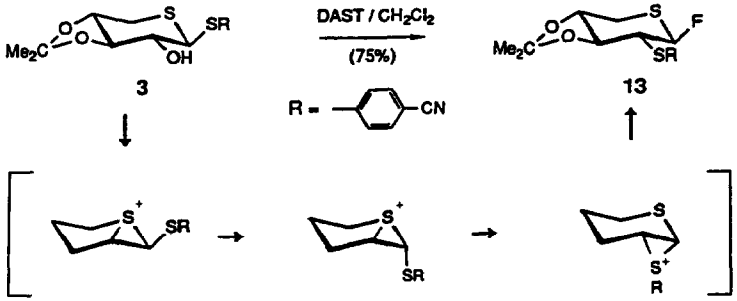
Fluorination of the 2,3-acetal (2) and 3,4-acetal (3).—Fluorination of **2** with diethylaminosulfur trifluoride (DAST)[8] in dichloromethane at −20°C gave a crystalline product in 75% yield whose analysis indicated replacement of the hydroxyl group by fluorine and whose NMR spectral data (see Experimental) were consistent with introduction of fluorine at C-4 with net retention of configuration to give 4-cyanophenyl 4-deoxy-4-fluoro-2,3-*O*-isopropylidene-1,5-dithio-β-D-xylopyranoside (**11**). The ^{1}H NMR proton–proton couplings of 9–10 Hz between H-1, -2, -3, and -4 affirmed the mutually diaxial orientations of these protons. Further support for equatorial fluorine at C-4 was provided by the observed four- and five-bond proton–fluorine couplings, and the ^{13}C signal for C-4 at δ 89.8 showed the anticipated large (187.3 Hz) C–F coupling.

Deacetonation of **11** by the general procedure used with the monoether derivatives afforded in 97% yield the crystalline 4-fluoro glycoside **12**, whose NMR parameters (see Experimenal) again left no doubt as to the structure and stereochemistry of the product.



It might have been expected[9] from precedent in reaction of DAST with conventional protected glycosides having a single equatorial alcohol group that fluorine would have been introduced with stereochemical inversion at C-4 to afford a product having the L-*arabino* configuration. In the present instance, where the ring heteroatom is the highly nucleophilic sulfur rather than oxygen, it is reasonable to postulate that, subsequent to the reagent's introducing leaving-group character by reaction at O-4, participation by S-5 generates an episulfonium-ion intermediate which is then attacked by fluorine at C-4, effecting a net double inversion.

When the fluorination conditions succesfully used for converting the 4-alcohol **2** into the 4-fluoro analogue **11** were applied to the 2-alcohol **3**, the product obtained, in 75% yield, was a chromatographically homogeneous oil that was quite unstable and elemental analysis was not feasible. Nevertheless, the ^{1}H and ^{13}C NMR spectra verified that the product was a pure compound and allowed its structural attribution as 2-*S*-(4-cyanophenyl)-3,4-*O*-isopropylidene-2,5-dithio-β-D-xylopyranosyl fluoride (**13**), a product of net migration of the arylthio group from C-1 to C-2 with retention of configuration and introduction of fluorine at C-1. Large proton–proton couplings indicated the mutually axial dispositions of H-1, -2, -3, and -4. The chemical shift of C-1 (δ 102.1) and H-1 (δ 5.87) and the C–F and H–C–F couplings left no doubt that fluorine was attached to C-1, and the high-field (δ 43.4) location of the C-2 signal was consistent with attachment of sulfur at C-2; additional spin-coupling data (see Experimental) were all again in full accord with the assigned structure.



The net 1 → 2 migration of an arylthio group observed in the conversion of **3** into **13** has precedent in an example reported by Nicolaou et al.[10], except that their reaction (with a conventional "oxygen-in-the-ring" glycoside) led to a product having the 1,2-diaxial orientation. In their example, the *trans*-disposed S-1 atom presumably attacks at C-2 with inversion to displace the DAST-generated leaving group. In the present instance, the alternative availability of S-5 to participate in displacement of the leaving group could generate an episulfonium ion susceptible to *trans*-attack at C-2 by the 1-arylthio group to lead to a net product of double inversion at C-2. A possible synchronous attack by fluorine at C-1 could account

for the equatorial entry of fluorine. Such double inversions in dithio sugar derivatives have precedent in early work from this laboratory[11].

In summary, this work provides practical methods for the preparation of monoethers **5** and **10**, and the monofluoro derivative **12** from the dithioglycoside precursor **1**, demonstrates the feasibility of synthetic transformations on this highly functionalized glycoside, and affords insight into the possibilities for structural and stereochemical rearrangements in transformations effected with sugar derivatives having sulfur as the ring heteroatom. The 3-monomethyl ether of **1** is not accessible by the routes described here, and its synthesis by alternative strategy will be detailed elsewhere, as will biological test-data on these and related compounds.

EXPERIMENTAL

General methods.—TLC was performed on precoated plates of Silica Gel 60-254-F (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 NMR 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 ($\delta = 0.00$). Chemical-ionization (Cl) 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, Georgia.

*Acetonation of 4-cyanophenyl 1,5-dithio-β-*D*-xylopyranoside* (**1**).—To a solution of compound **1** (10.1 g, 35.7 mmol) in anhyd DMF (50 mL) was added $TsOH \cdot H_2O$ (50 mg). The solution was cooled to 0°C and 6.8 mL (2 equiv) of 2-methoxypropene was then added dropwise via a syringe. After 1 h at 25°C, Na_2CO_3 (0.2 g) was added and the mixture was stirred for 0.5 h at room temperature. The DMF was evaporated off under diminished pressure, the residue was saturated with EtOAc, and the mixture was filtered through Celite. Evaporation of the filtrate afforded and oil which was carefully crystallized from EtOAc–hexane to furnish 1.45 g (12.6%) of the 2,3-acetal **2**. Further crystallization of the mother liquor from EtOAc–hexane gave 2.34 g (20.3%) of the 3,4-acetal **3**. The mother liquor was purified by chromatography on silica gel (2:3 EtOAc–hexane) to furnish an additional 2.14 g (18.6%) of **2** and 4.95 g (42.9%) of **3**.

*4-Cyanophenyl 2,3-*O*-isopropylidene-1,5-dithio-β-*D*-xylopyranoside* (**2**). Net yield 31%; mp (from EtOAc–hexane) 178–178.5°C; $[\alpha]_D^{20}$ −46.7° (*c* 0.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 7.61 (m, 4 H, Ar), 4.32 (d, 1 H, $J_{1,2}$ 10.4 Hz, H-1), 4.05 (m, 1 H, H-4), 3.66 (dd, 1 H, $J_{2,3}$ 8.7 Hz, H-2), 3.31 (dd, 1 H, $J_{3,4}$ 9.3 Hz, H-3), 2.76 (m, 2 H, H-5), 2.44 (d, 1 H, $J_{4,OH}$ 3.1 Hz, OH, D_2O exchangeable), 1.48 (s, 3 H, Me), 1.47 (s, 3 H, Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.4 (Ar-C), 132.3 (Ar-CH), 131.2 (Ar-CH), 118.3 (Ar-C), 111.0 (Me_2CO_2), 110.0 (*C*N), 83.3, 78.3, 71.4 (C-2, 3, 4), 50.2 (C-1), 35.1 (C-5), 26.8 (Me), 26.6 (Me); MS (EI): 323 (4.4, M^+),

248 [7.1, M – $Me_2(OH)O$], 189 (13.4, M – SC_6H_4CN), 131 (100, M – SC_6H_4CN – Me_2CO). Anal. Calcd for $C_{15}H_{17}NO_3S_2$ (323.42): C 55.70, H 5.30, N 4.33, S 19.83. Found: C 55.64, H 5.28, N 4.37, S 19.91.

*4-Cyanophenyl 3,4-O-isopropylidene-1,5-dithio-β-*D*-xylopyranoside* (**3**). Net yield 63%; mp (from EtOAc–hexane) 128–128.5°C; $[\alpha]_D^{25}$ −25.4° (*c*0.35, $CHCl_3$); ^1H NMR (500 MHz, Me_2SO-d_6): δ 7.75 (m, 2 H, Ar), 7.60 (m 2 H, Ar), 6.05 (d, 1 H, $J_{2,OH}$ 6.4 Hz, OH, D_2O exchangeable), 4.43 (d, 1 H, $J_{1,2}$ 9.5 Hz, H-1), 3.73 (ddd, 1 H, $J_{3,4}$ 8.9, $J_{4,5a}$ 11.0, $J_{4,5b}$ 3.9 Hz, H-4), 3.60 (dt, 1 H, $J_{2,3}$ 9.4 Hz, H-2), 3.32 (dd, 1 H, H-3), 2.89 (dd, 1 H, $J_{5a,5b}$ 11.8 Hz, H-5a), 2.77 (dd, 1 H, H-5b), 1.33 (s, 3 H, Me), 1.31 (s, 3 H, Me); ^{13}C NMR (125 MHz, Me_2SO-d_6): δ 142.1 (Ar-C), 132.4 (Ar-CH), 128.6 (Ar-CH), 118.6 (Ar-C), 108.5 (Me_2CO_2), 108.3 (*C*N), 82.5 (C-3), 76.2 (C-4), 73.7 (C-2), 51.5 (C-1), 31.5 (C-5), 26.8 (Me), 26.7 (Me); MS (EI): 323 (1.6, M^+), 189 (13.4, M – SC_6H_4CN), 131 (50.8, M – SC_6H_4CN – Me_2CO), 43 (100). Anal. Calcd for $C_{15}H_{17}NO_3S_2$ (323.42): C 55.70, H 5.30, N 4.33, S 19.83. Found: C 55.63, H 5.35, N 4.35, S 19.80.

*4-Cyanophenyl 2,3-O-isopropylidene-4-O-methyl-1,5-dithio-β-*D*-xylopyranoside* (**4**). —To a suspension of NaH (80% in mineral oil, 48 mg, 2.4 equiv) in anhyd DMF (4 mL) cooled to −10°C (ice–NaCl bath) was added dropwise via a cannula needle a solution of **2** (212 mg, 0.66 mmol) in anhyd DMF (3 mL). After 5 min at −10°C and 20 min at room temperature under Ar, the yellow solution was cooled to −10°C and 204 μL (5 equiv) of MeI was added dropwise. After 1.5 h at −10°C, the solution was poured into a mixture of ether (150 mL) and ice–water (10 mL). The organic layer was washed with water (4 × 10 mL) and dried ($MgSO_4$). Evaporation of the solvent gave a colorless solid (230 mg) which was washed with hexane (3 × 5 mL) to afford **4** as pure (NMR) solid (196 mg, 89%); mp (from EtOH) 145–146°C; $[\alpha]_D^{27}$ −41.0° (*c*0.4, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 7.61 (m, 4 H, Ar), 4.29 (d, 1 H, $J_{1,2}$ 10.3 Hz, H-1), 3.65 (dd, 1 H, $J_{2,3}$ 8.4 Hz, H-2); 3.62 (m, 1 H, H-4), 3.49 (s, 3 H, OMe), 3.36 (dd, 1 H, $J_{3,4}$ 9.5 Hz, H-3), 2.87 (dd, 1 H, $J_{4,5a}$ 4.5, $J_{5a,5b}$ 13.5 Hz, H-5a), 2.63 (dd, 1 H, $J_{4,5b}$ 10.1 Hz, H-5b), 1.48 (s, 6 H, 2Me); ^{13}C NMR (63 MHz, $CDCl_3$): δ 139.4 (Ar-C), 132.3 (Ar-CH), 131.2 (Ar-CH), 118.4 (Ar-C), 110.9 (Me_2CO_2), 109.8 (*C*N), 82.2, 80.0, 78.6 (C-2, 3, 4), 57.4 (OMe), 50.1 (C-1), 32.5 (C-5), 26.9 (Me), 26.6 (Me); MS (EI): 337 (5.5, M^+), 262 [4.5, M – $Me_2(OH)O$], 203 (41.9, M – SC_6H_4CN), 145 (97.7, M – SC_6H_4CN – Me_2CO), 71 (100). Anal. Calcd for $C_{16}H_{19}NO_3S_2$ (337.44): C 56.95, H 5.68, N 4.15, S 19.00. Found: C 56.86, H 5.70, N 4.21, S 19.00.

*4-Cyanophenyl 3,4-O-isopropylidene-2-O-methyl-1,5-dithio-β-*D*-xylopyranoside* (**8**). —To a mixture of **3** (248 mg, 0.77 mmol) and 240 μL (5 eq) of MeI in anhyd DMF (4 mL) cooled to −10°C (ice–NaCl bath) was added NaH (80% in mineral oil, 44 mg, 1.9 equiv) in small portions during 30 min. After 1 h at −10°C, ether (150 mL) and ice–water (10 mL) were added and the organic layer was washed with water (4 × 10 mL) and dried ($MgSO_4$). The crude oil was purified by chromatography on silica gel (1:3 ether–hexane) to give **8** as a viscous oil; $[\alpha]_D^{27}$ +22.9° (*c*1.3, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 7.57 (m, 4 H, Ar), 4.11 (d, 1 H, $J_{1,2}$ 9.4 Hz, H-1),

3.86 (ddd, 1 H, $J_{4,5a}$ 10.0, $J_{4,5b}$ 4.9 Hz, $J_{3,4}$ 8.8 Hz, H-4), 3.61 (s, 3 H, OMe), 3.43 (t, 1 H, $J_{2,3}$ 9.4 Hz, H-2), 3.28 (dd, 1 H, H-3), 2.82 (dd, 1 H, $J_{5a,5b}$ 12.2 Hz, H-5a), 2.75 (dd, 1 H, H-5b), 1.44 (s, 3 H, Me), 1.42 (s, 3 H, Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.3 (Ar-C), 132.3 (Ar-CH), 130.2 (Ar-CH), 118.4 (Ar-C), 110.4 (Me_2CO_2), 110.0 (*C*N), 83.7, 83.5, 76.5 (C-2, 3, 4), 60.4 (OMe), 52.0 (C-1), 32.5 (C-5), 26.9 (Me), 26.7 (Me); MS (EI): 337 (11.1, M^+), 203 (30.2, $M - SC_6H_4CN$), 145 (100, $M - SC_6H_4CN - Me_2CO$). Anal. Calcd for $C_{16}H_{19}NO_3S_2$ (337.44): C 56.95, H 5.68, N 4.15, S 19.00. Found: C 56.94, H 5.69, N 4.22, S 18.91.

When the procedure used for methylation of compound **2** was used with **3**, the product was chromatographically homogeneous, but its NMR spectrum showed it to be a 3:1 mixture of **8** and an isomeric product determined to be methyl 2-*O*-(4-cyanophenyl)-3,4-*O*-isopropylidene-1,5-dithio-β-D-xylopyranoside (**7**) by deacetonation of the mixture and separation of the products **10** and **9** (see later).

4-Cyanophenyl 4-deoxy-4-fluoro-2,3-O-isopropylidene-1,5-dithio-β-D-xylopyranoside (**11**).—To a solution of the 2,3-acetal **2** (87 mg, 0.27 mmol) in anhyd CH_2Cl_2 (3 mL) cooled to −20°C was added dropwise 65 μL (2 equiv) of DAST (Aldrich) via a syringe under Ar. The temperature was allowed to rise slowly to room temperature (2.5 h) and then maintained during 1 h at room temperature with TLC monitoring. The mixture was cooled to −20°C, shaken with satd aq Na_2CO_3 (3 mL) and the product extracted with ether (3 × 20 mL). The ether layer was washed with water (5 mL), dried ($MgSO_4$), and evaporated. The crude oil was purified by chromatography on silica gel (1:3 Et_2O–hexane) to afford **11** as a colorless solid (66 mg, 75%); mp (from EtOH) 120–121.5°C; $[\alpha]_D^{20}$ −60.6° (*c*0.5, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.62 (m, 4 H, Ar), 4.80 (ddt, 1 H, $J_{4,F}$ 51.9, $J_{3,4} = J_{4,5a} = 8.9$, $J_{4,5b}$ 6.4 Hz, H-4), 4.31 (d, 1 H, $J_{1,2}$ 10.1 Hz, H-1), 3.66 (ddd, 1 H, $J_{2,3}$ 8.8, $J_{2,F}$ 1.2 Hz, H-2), 3.52 (q, 1 H, $J_{3,F}$ 8.7 Hz, H-3), 2.91 (m, 2 H, H-5), 1.49 (s, 3 H, Me), 1.48 (s, 3 H, Me); ^{13}C NMR (63 MHz, $CDCl_3$): δ 138.8 (Ar-C), 132.3 (Ar-CH), 131.6 (Ar-CH), 118.3 (Ar-C), 111.3 (Me_2CO_2), 110.6 (*C*N), 89.8 ($J_{4,F}$ 187.3 Hz, C-4), 81.0 ($J_{3,F}$ 17.3 Hz, C-3), 78.2 ($J_{2,F}$ 7.4 Hz, C-2), 50.0 (C-1), 32.7 ($J_{5,F}$ 22.5 Hz, C-5), 26.7 (Me), 26.6 (Me); MS(EI): 325 (5.4, M^+), 250 [4,4, $M - Me_2(OH)O$], 191 (35.9, $M - SC_6H_4CN$), 133 (100, $M - SC_6H_4CN - Me_2CO$). Anal. Calcd for $C_{15}H_{16}FNO_2S_2$ (325.41): C 55.36, H 4.96, N 4.30, S 19.70. Found: C 55.32, H 4.99, N 4.33, S 19.79.

2-S-(4-Cyanophenyl)-3,4-O-isopropylidene-2,5-dithio-β-D-xylopyranosyl fluoride (**13**).—To a solution of compound **3** (92 mg, 0.29 mmol) in anhyd CH_2Cl_2 (3 mL) cooled to −25°C was added dropwise 64 μL (1.7 equiv) of DAST (Aldrich) via a syringe under Ar. After 10 min at −25 to −22°C, the reaction was quenched by addion of 1 mL of MeOH at −20°C and then satd aq Na_2CO_3 (5 mL) at room temperature, and the product was extracted with ether (3 × 50 mL). The ether layer was washed with water (5 mL), dried ($MgSO_4$), and evaporated. The crude oil was purified by chromatography on silica gel (1:3 Et_2O–hexane) to afford **13** as a colorless oil (69 mg, 75%); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.60 (m, 4 H, Ar), 5.87 (dd, 1 H, $J_{1,F}$ 53.5, $J_{1,2}$ 7.4 Hz, H-1), 4.29 (ddd, 1 H, $J_{3,4}$ 9.1, $J_{4,5a}$ 10.8, $J_{4,5b}$ 6.1 Hz,

H-4), 4.08 (dd, 1 H, $J_{2,3}$ 9.7 Hz, H-3), 3.44 (ddd, 1 H, $J_{2,F}$ 6.8 Hz, H-2), 2.91 (dd, 1 H, $J_{5a,5b}$ 8.3 Hz, H-5a), 2.82 (ddd, 1 H, $J_{5b,F}$ 2.2 Hz, H-5b), 1.50 (s, 6 H, 2 Me); ^{13}C NMR (63 MHz, $CDCl_3$): δ 138.6 (Ar-C), 132.6 (Ar-CH), 131.7 (Ar-CH), 121.7 (Ar-C), 118.1 (Me_2CO_2), 111.8 (*C*N), 102.1 ($J_{1,F}$ 226.8 Hz, C-1), 86.1, 82.8 (C-3, 4), 43.4 ($J_{2,F}$ 26.0 Hz, C-2), 27.3 (Me), 27.2 (C-5), 27.1 (Me). The product was unstable and decomposed before an elemental analysis could be obtained.

General procedure for deacetonation.—To a solution of the isopropylidene acetal (0.5 mmol) in MeOH (5 mL) was added Amberlite IR-120 (H^+) resin (~ 20 mg), and the mixture was vigorously stirred at room temperature. After 24 h, 1 drop of water was added, and stirring was continued until no more starting material was detectable by TLC. Removal of the resin by filtration over Celite and evaporation of the solvent gave in each instance a colorless solid that was chromatographically homogeneous. Thus were each of the following products prepared.

*4-Cyanophenyl 4-O-methyl-1,5-dithio-β-*D*-xylopyranoside* (**5**).—From **4** (155 mg, 0.46 mmol); yield 133 mg (97%); mp (from EtOAc–hexane) 163.5–164.5°C; $[\alpha]_D^{26}$ +17.4° (*c*1.0, MeOH); ^{1}H NMR (250 MHz, Me_2CO-d_6): δ 7.67 (m, 4 H, Ar), 4.39 (d, 1 H, $J_{1,2}$ 10.0 Hz, H-1), 3.55 (dd, 1 H, $J_{2,3}$ 8.2 Hz, H-2), 3.43 (s, 3 H, OMe), 3.34 (m, 2 H, H-3,4), 2.85 (m, 3 H, H-5a, 2 OH, D_2O exchangeable), 2.66 (dd, 1 H, $J_{4,5b}$ 10.2, $J_{5a,5b}$ 13.3 Hz, H-5b); ^{13}C NMR (63 MHz, $CDCl_3$): δ 139.9 (Ar-C), 132.4 (Ar-CH), 131.2 (Ar-CH), 118.4 (Ar-C), 111.0 (*C*N), 81.5, 77.7, 75.0 (C-2, 3, 4), 57.4 (OMe), 52.2 (C-1), 30.4 (C-5); MS (EI): 298 (2.2, M + 1), 297 (1.6, M^+), 163 (45.1, M – SC_6H_4CN), 131 (100, M – SC_6H_4CN – MeOH). Anal. Calcd for $C_{13}H_{15}HO_3S_2$ (297.38): C 52.50, H 5.08, N 4.71, S 21.56. Found: C 52.51, H 5.12, N 4.74, S 21.66.

*4-Cyanophenyl 2-O-methyl-1,5-dithio-β-*D*-xylopyranoside* (**10**).—From **8** (139 mg, 0.46 mmol); yield 120 mg (98%); mp (from EtOAc–hexane) 139–140°C; $[\alpha]_D^{20}$ +61.5° (*c*0.13, MeOH); ^{1}H NMR (250 MHz, Me_2SO-d_6): δ 7.78 (m, 2 H, Ar), 7.63 (m, 2 H, Ar), 5.21 (d, 1 H, $J_{3,OH}$ 4.9 Hz, OH-3, D_2O exchangeable), 5.20 (d, 1 H, $J_{4,OH}$ 4.3 Hz, OH-4, D_2O exchangeable), 4.62 (d, 1 H, $J_{1,2}$ 10.1 Hz, H-1), 3.50 (m, 1 H, H-4), 3.49 (s, 3 H, OMe), 3.25 (dt, 1 H, $J_{2,3} = J_{3,4} = 8.6$ Hz, H-3), 3.13 (dd, 1 H, H-2), 2.69 (dd, 1 H, $J_{4,5a}$ 10.8, $J_{5a,5b}$ 13.2 Hz, H-5a), 2.51 (dd, 1 H, $J_{4,5b}$ 4.6 Hz, H-5b); ^{13}C NMR (63 MHz, CD_3CN): δ 142.9 (Ar-C), 133.5 (Ar-CH), 130.0 (Ar-CH), 119.5 (Ar-C), 110.3 (*C*N), 86.5, 79.6, 74.1 (C-2, 3, 4), 61.4 (OMe), 51.1 (C-1), 34.0 (C-5); MS (EI): 297 (0.8, M^+), 163 (17.9, M – SC_6H_4CN), 135 (17.6, HSC_6H_4CN), 131 (44.1, M – SC_6H_4CN – MeOH), 87 (100). Anal. Calcd for $C_{13}H_{15}NO_3S_2$ (297.38): C 52.50, H 5.08, N 4.71, S 21.56. Found: C 52.47, H 5.09, N 4.74, S 21.63.

*Methyl-2-O-(4-cyanophenyl)-1,5-dithio-β-*D*-xylopyranoside* (**9**).—This product was obtained by deacetonation of the 3:1 mixture of **8** and **7** (125 mg, 0.37 mmol) earlier described and resolving the resultant mixture of **10** and **9** on a column of silica gel; yield 25 mg of **9** (23%); mp (from EtOAc–hexane) 150–151°C; $[\alpha]_D^{23}$ −112° (*c*0.52, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.58 (m, 2 H, Ar), 7.15 (m, 2 H, Ar), 4.36 (dd, 1 H, $J_{1,2}$ 10.0, $J_{2,3}$ 8.8 Hz, H-2), 3.93 (m, 1 H, H-4), 3.84 (d, 1 H,

H-1), 3.53 (dt, 1 H, $J_{3,OH}$ 2.5, $J_{3,4}$ 8.8 Hz, H-3), 2.90 (m, 2 H, 2 OH, D_2O exchangeable), 2.77 (dd, 1 H, $J_{4,5a}$ 4.4, $J_{5a,5b}$ 13.5 Hz, H-5a), 2.71 (dd, 1 H, $J_{4,5b}$ 9.6 Hz, H-5b), 2.12 (s, 3 H, SMe); ^{13}C NMR (63 MHz, $CDCl_3$): 162.8 (Ar-C), 134.0 (Ar-CH), 118.9 (Ar-C), 117.1 (Ar-CH), 105.1 (*C*N), 82.5 (C-2), 78.7 (C-3), 73.1 (C-4), 50.6 (C-1), 33.0 (C-5), 14.5 (SMe); MS (EI): 297 (0.3, M^+), 179 (24.3, $M - OC_6H_4CN$), 131 (28.6, $M - OC_6H_4CN - MeSH$), 119 (100, HOC_6H_4CN). Anal. Calcd for $C_{13}H_{15}NO_3S_2$ (297.38): C 52.50, H 5.08, N 4.71. Found: C 52.43, H 4.98, N 4.57.

*4-Cyanophenyl 4-deoxy-4-fluoro-1,5-dithio-β-*D*-xylopyranoside* (**12**).—From **11** (138 mg, 0.43 mmol); yield 120 mg (98%); mp (from EtOAc–hexane) 151–151.5°C; $[\alpha]_D^{23}$ +141.1° (*c*0.6, MeOH); ^1H NMR (250 MHz, CD_3CN): δ 7.61 (m, 4 H, Ar), 4.55 (dddd, 1 H, $J_{4,F}$ 50.0, $J_{3,4}$ 8.7, $J_{4,5a}$ 10.8, $J_{4,5b}$ 5.1 Hz, H-4), 4.26 (d, 1 H, $J_{1,2}$ 9.9 Hz, H-1), 4.04 (d, 1 H, *J*4.6 Hz, OH, D_2O exchangeable), 3.85 (d, 1 H, *J*3.5 Hz, OH, D_2O exchangeable), 3.46 (m, 2 H, H-2, 3), 2.92 (ddd, 1 H, $J_{5a,F}$ 4.8, $J_{5a,5b}$ 13.1 Hz, H-5a), 2.79 (ddd, 1 H, $J_{5b,F}$ 6.2 Hz, H-5b); ^{13}C NMR (63 MHz, CD_3CN): 142.1 (Ar-C), 133.5 (Ar-CH), 130.6 (Ar-CH), 119.5 (Ar-C), 110.7 (*C*N), 92.8 ($J_{4,F}$ 183.1 Hz, C-4), 77.9 ($J_{3,F}$ 17.7 Hz, C-3), 76.6 ($J_{2,F}$ 7.1 Hz, C-2), 51.8 (C-1), 31.9 ($J_{5,F}$ 23.0 Hz, C-5); MS (EI): 286 (34.8, M + 1), 285 (20.1, M^+), 151 (42.0, $M - SC_6H_4CN$), 135 (100, HSC_6H_4CN), 133 (74.4, $M - SC_6H_4CN - H_2O$). Anal. Calcd for $C_{12}H_{12}FNO_2S_2$ (285.35): C 50.51, H 4.24, N 4.91, S 22.47. Found: C 50.45, H 4.28, N 4.84, S 22.53.

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