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A Facile Synthesis of 6-Aryl-5-cyano-1-(β-D-pyranosyl or β-D-furanosyl)-2-thiocytosines

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Abstract—The treatment of a piperidinium salt of 6-aryl-5-cyano-2-thiouracil with an *O*-peracetyl-α-D-pyranosyl bromide produces a mixture of *N*1-(β-D-pyranosyl)-2-thiouracil and its *N*1,*S*[2]-disubstituted analog. By contrast, the reaction of a silyl derivative of the 2-thiouracil with an *O*-peracetyl-β-D-pyranose furnishes the mononucleoside selectively. Both the mononucleoside/dinucleoside mixture and pure mononucleoside undergo ammonolysis under mild conditions to give the β-D-nucleoside of 6-aryl-5-cyano-2-thiocytosine. The silyl method also provides an easy access to β-D-ribosyl nucleosides. © 2000 Elsevier Science Ltd. All rights reserved.

Ammonolysis of 4-thiouracils is a cornerstone in the preparation of cytosines.[1] Similar selective transformations of the 4-thioxo function in 2,4-dithiouracils, 2,4-dithiobarbituric acids, and 2,4-dithiohydantoins are also well known.[2,3] On the other hand, direct conversion of uracils to cytosines are rare and, as a rule, they are conducted by using complex reagents and under extremely harsh conditions.[4] The exception is ammonolysis of 5-fluorosulfonyluracil, which takes place at room temperature and furnishes 5-fluorosulfonylcytosine in a modest yield.[5] Recently, we have also reported the first ammonolysis of 2-thiouracil nucleosides to 2-thiocytosine nucleosides.[6]

In particular, a mixture of a glycoside **2** and a bis-glycoside **2′**, obtained by treatment of a 5-cyano-2-thiouracil **7** with tetra-*O*-acetyl-1-α-D-glucopyranosyl bromide in the presence of potassium hydroxide, was subjected to ammonolysis under mild conditions to give a 2-thiocytosine glucoside **10** in a high yield (structure in Scheme 1). Since 4-pyrimidinones lacking the 5-cyano group are inert toward ammonia, this facile transformation is assisted by the cyano functionality[6] (vide infra).

In this paper we describe a more efficient synthetic route to compounds **2**–**6**/**2′**–**6′** which are precursors to 2-thiocytosine nucleosides **10**–**14**. Presented also are an independent and efficient synthesis of **2**–**6**, full experimental details of the ammonolysis reaction, and characterization of all compounds.

5-Cyano-2-thiouracils are readily available by a number of methods.[7–9] A simple route to **7**–**9** and other 6-substituted analogs (R=aryl, heteroaryl or *tert*-alkyl) involves condensation of an aldehyde with ethyl cyanoacetate and thiourea in the presence of potassium carbonate.[7,8] The product is isolated by acidification followed by crystallization of the resultant precipitate.

An improved synthesis of **7**–**9**, in which piperidine is substituted for potassium carbonate, is given in Scheme 1. The advantages of this method are that (i) a crystalline piperidinium salt **1** precipitates directly from the mixture, which facilitates workup, and (ii) following acidification of the salt the 2-thiouracil is obtained in a greater yield than that for the previously described procedure. More importantly, due to the high purity of the precipitated salt **1**, this material can be used directly in the preparation of **2**–**6**/**2′**–**6′** in the absence of any additional base. Ammonolysis of the mixtures **2**–**6**/**2′**–**6′** furnishes the corresponding cytosine β-nucleosides **10**–**14**.

The synthesis of single nucleosides **2**–**6** is given in Scheme 2. In this method, 2-thiouracils **7**–**9** are treated with 1,1,1,3,3,3-hexamethyldisilazane (HMDS) and the resultant bis(trimethylsilyl) derivatives **15**, without isolation, are allowed to react with β-D-glucose pentaacetate, β-D-galactose pentaacetate or β-D-xylose tetraacetate. After purification by a single crystallization, the corresponding products **2**–**6** are then subjected to ammonolysis to give **10**–**14**.

The structure determination for 2-thiouracil glucosides **2**

Keywords: 6-aryl-5-cyano-2-thiouracils; ammonolysis; 1-(β-D-pyranosyl)-2-thiocytosines; 1-(β-D-furanosyl)-2-thiocytosines.

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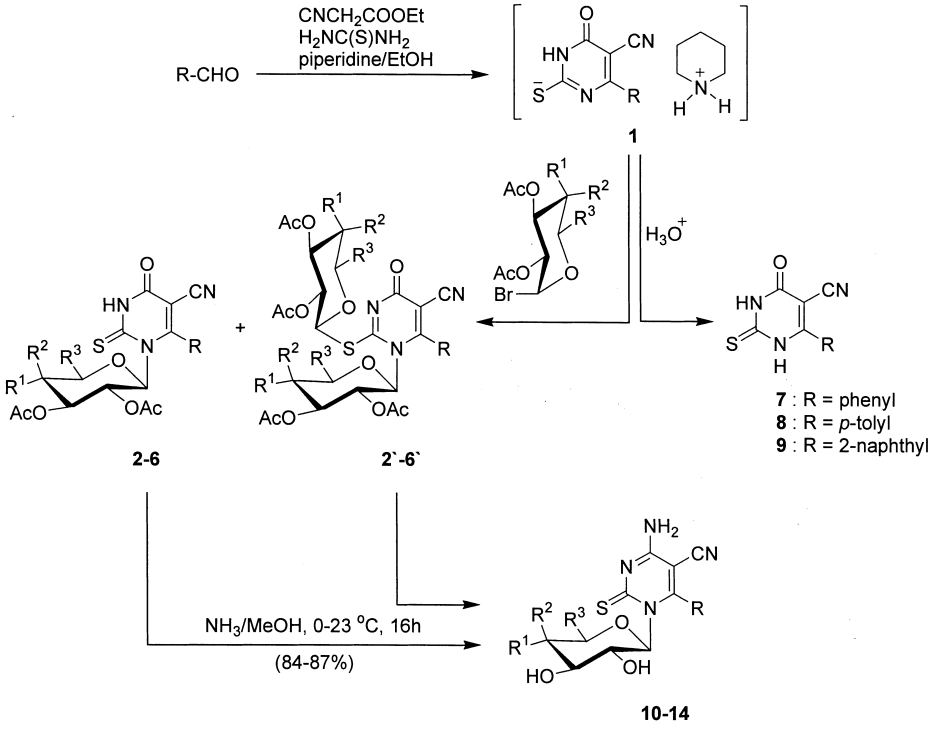


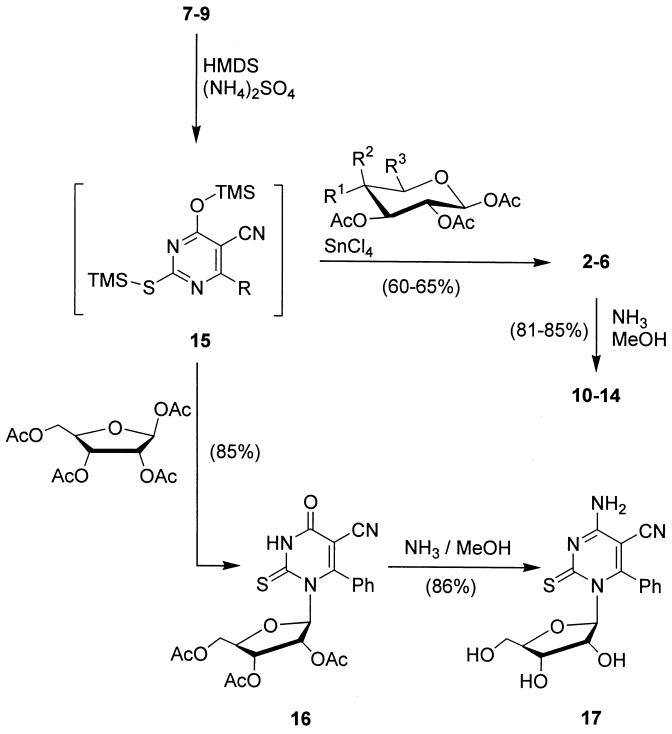
	compound	R	R^1	R^2	R^3
glucosides	**2** **2`**	phenyl	OAc	H	CH_2OAc
	10	phenyl	OH	H	CH_2OH
	3 **3`**	*p*-tolyl	OAc	H	CH_2OAc
	11	*p*-tolyl	OH	H	CH_2OH
	4 **4`**	2-naphthyl	OAc	H	CH_2OAc
	12	2-naphthyl	OH	H	CH_2OH
galactosides	**5** **5`**	phenyl	H	OAc	CH_2OAc
	13	phenyl	H	OH	CH_2OH
xylosides	**6** **6`**	2-naphthyl	OAc	H	H
	14	2-naphthyl	OH	H	H

Scheme 1.

and **2′** and the 2-thiocytosine glucoside **10** has been discussed previously in detail.[6] The remaining compounds were analyzed in a similar fashion. Briefly, the β-configuration of the pyranosyl moieties was established by ^{1}H NMR from a large coupling constant for a diaxial interaction between H1′ and H2′.[10–12] The *N*1-substitution at the pyrimidine of **2**–**6** and **10**–**14** was shown by a strong NOE between H1′ and the adjacent protons of the 6-aryl substituent.

As a brief extension of the silyl method, the silyl derivative **15** (R=Ph) was allowed to react with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose in the presence of trimethylsilyl triflate. Following a standard workup and crystallization from 95% EtOH (again without chromatography) this reaction furnished a 1-(β-D-ribofuranosyl)-2-thiouracil **16** in an 85% yield. Ammonolysis of **16** gave a 1-(β-D-ribofuranosyl-2-thiocytosine **17** in an 86% yield after crystallization. The ^{1}H NMR spectrum of **16** is characterized by a doublet at δ 6.22 for H1′ with a coupling constant to H2′ of 2.7 Hz. In a similar way a doublet at δ 5.86 (J=3.6 Hz) is observed for H1′ of **17**. These values are typical for 1-(β-D-ribofuranosyl) derivatives of 6-substituted pyrimidines.[12,13] The structures of **16** and **17** were confirmed by proton NOE experiments which gave a strong interaction between H1′ of the ribose and ortho protons of the 6-phenyl substituent at the pyrimidine.

Removal of a sugar moiety from S-nucleosides, such as **2′**–**6′**, under nucleophilic conditions is well known. On the other hand, the observed transformation of **2**–**6**, **2′**–**6′** and **16** to the corresponding cytosine nucleosides **10**–**14**, **17** upon treatment with ammonia is an unusual result. Ammonolysis of acyl protected nucleosides is a general, widely used method for deprotection of such derivatives to free nucleosides. The treatment of **2**–**6**, **2**–**6**/**2′**–**6′**, **16** with ammonia in methanol to give **10**–**14**, **17** must be conducted under anhydrous conditions; otherwise a complicated mixture of products is obtained. In particular, the ammonolysis conducted in wet methanol produces 2-thiouracils



Scheme 2.

7–9, the yields of which increase with an increasing content of water in the solvent. A similar degradation of the N1-glycosylic bond to give **7–9** as the major products is also observed for potassium hydroxide mediated hydrolysis of **2–6**, or **2–6/2′–6′**, **16** in aqueous methanol. The products **7–9** were easily isolated as precipitates after acidification of the mixtures.

In conclusion, we have described two facile synthetic routes to mixtures of nucleosides **2–6/2′–6′** and pure nucleosides **2–6**, **16**. These compounds undergo efficient ammonolysis to the corresponding 1-(β-D-pyranosyl)-2-thiocytosines. For the ammonolysis reaction, the mixtures **2–6/2′–6′** are purified by flash chromatography that does not result in separation of individual components, and the products **2–6**, **16** obtained by the silyl method are purified by a single crystallization.

Currently we are studying the interesting possibility that the described ammonolysis of 2-thiouracil nucleosides to 2-thiocytosine nucleosides is a particular case of a general nucleophile-mediated reaction under non-hydrolytic conditions. It also appears that, at least, the ammonolysis reaction is not limited to the 5-cyanouracil nucleosides and can be extended on uracil derivatives that contain other electron withdrawing groups at C5. According to our PM3-AQ calculations of HOMO electron densities the atom C4 in the anions derived from such pyrimidin-4(3*H*)-ones is an electrophilic site. Thus, the uracil-to-cytosine transformation may involve a direct nucleophilic addition of ammonia to C4 followed by elimination of hydroxide ion from the resultant aminal derivative of the anionic pyrimidine. A rather complex mechanistic pathway that is consistent with the computational work albeit limited to 5-cyanouracils has been suggested by us previously.[6]

Experimental

General

All reactions were conducted under an atmosphere of dry nitrogen. Melting points (pyrex capillary) are not corrected. Unless stated otherwise, the ^{1}H NMR and selected ^{13}C NMR spectra were obtained at 400 MHz and 100 MHz, respectively, by using a solution in $CDCl_3$ and TMS as an internal reference. As shown by elemental analysis, compounds **2–6**, **2′–6′**, **10–14**, **16**, and **17** crystallize with water. This was confirmed by comparing their ^{1}H NMR spectra with that of the solvent. In the spectra of **2–6** and **16** taken in $CDCl_3$ the H_2O singlet at δ 1.5–1.6 includes also a signal for NH. The complete assignments for sugar moieties of **10–14** and **16** were obtained by using COSY. Specific optical rotations (c=0.2 g/100 mL in all cases, sodium D line, 25°C) were obtained for solutions in $CDCl_3$ (**2–6**, **2′–6′**, and **16**) and MeOH (**10–14** and **17**).

2-Thiouracils 7–9. A solution of an aldehyde (RCHO, 10 mmol), ethyl cyanoacetate (1.0 mL, 10 mmol), thiourea (0.76 g, 10 mmol) and piperidine (2.0 mL, 20 mmol) in absolute ethanol (50 mL) was heated under reflux for 6 h and then cooled. The resultant precipitate (**1**, R=Ph): ^{1}H NMR (DMSO-d_6) δ 1.57 (m, 6H), 2.97 (m, 4H), 7.48 (m, 3H), 7.72 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 21.5, 22.1, 43.6, 85.4, 118.6, 127.9, 128.0, 130.0, 137.5, 162.3, 167.4, 182.8. Anal. Calcd for $C_{16}H_{18}N_4OS$: C, 61.12; H, 5.77; N, 17.82. Found: C, 61.02; H, 5.67; N, 17.76. The salt **1** was dissolved in water (6 mL) and the solution was neutralized by slow addition of 2N HCl that caused crystallization of **7–9**.

5-Cyano-6-phenyl-2-thiouracil (7). Yield 67%; mp 297–299°C (reported[9,14] mp 298–300°C); ^{1}H NMR (DMSO-d_6) δ

7.63 (m, 5H), 13.14 (bs, exchangeable with D_2O, 2H); ^{13}C NMR (DMSO-d_6) δ 90.8, 114.7, 128.3, 128.8, 129.3, 132.2, 158.5, 161.0, 176.2.

5-Cyano-6-(4-tolyl)-2-thiouracil (8). Yield 65%; mp 245–47°C (reported[14] mp 245°C); ^1H NMR (DMSO-d_6) δ 2.40 (s, 3H), 7.37 (d, J=8.1 Hz, 2H), 7.57 (d, J=8.1 Hz, 2H), 13.11 (bs, exchangeable with D_2O, 2H).

5-Cyano-6-(2-naphthyl)-2-thiouracil (9). Yield 63%; mp 276–78°C; ^1H NMR (DMSO-d_6) δ 7.72 (m, 3H), 8.03 (s, 1H), 8.09 (m, 3H), 13.20 (bs, exchangeable with D_2O, 1H), 13.22 (bs, exchangeable with D_2O, 1H); ^{13}C NMR (DMSO-d_6) δ 90.8, 114.4, 124.7, 126.5, 127.0, 127.6, 127.9, 128.2, 128.6, 129.3, 131.6, 134.0, 158.2, 160.7,176.1. Anal. Calcd for $C_{15}H_9N_3OS$: C, 64.50; H, 3.25; N, 15.04. Found: C, 64.61; H, 3.19; N, 14.95.

Nucleosides 2–6 and dinucleosides 2′–6′. The salt **1** obtained from aldehyde RCHO (10 mmol, R=phenyl, 4-tolyl, 2-naphthyl) as described above was dissolved in water (6 mL). After addition of tetra-*O*-acetyl-1-α-D-glucopyranosyl bromide, tetra-*O*-acetyl-1-α-D-galactopyranosyl bromide or tri-*O*-acetyl-1-α-D-xylopyranosyl bromide (15 mmol) in acetone (20 mL) the mixture was stirred at 23°C for 6 h. Concentration under reduced pressure followed by addition of $CHCl_3$ (100 mL) to the residue, then washing of the organic solution with water (3×25 mL), drying (Na_2SO_4), and concentration gave a crude mixture **2**–**6**/**2′**–**6′**. For the subsequent ammonolysis reaction this mixture was pre-purified by flash chromatography (20 g of silica gel; hexanes/ether/$CHCl_3$, 1:2:2) that did not result in separation of **2**–**6** and **2′**–**6′**. For characterization of individual compounds a sample of the mixture (1 g) was separated by chromatography under the same conditions. The separated compounds were crystallized from 95% EtOH. The yields given below are based on the starting aldehyde RCHO.

1-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-glucopyranosyl)-5-cyano-6-phenyl-2-thiouracil (2). Yield 25%; mp 214–216°C; [α]=38.3; ^1H NMR δ 1.90–2.14 (4s, 12H), 4.03 (m, 2H), 4.43 (m, 1H), 5.15 (m, 1H), 5.35 (m, 1H), 5.54 (m, 1H), 5.99 (d, J=10.9 Hz, 1H, H1′), 7.64 (m, 3H), 8.08 (m, 2H); ^{13}C NMR δ 20.4, 20.5, 20.6, 20.8, 61.5, 66.5, 67.4, 71.7, 74.6, 82.2, 90.1, 118.7, 128.3, 128.4, 131.1, 136.0, 167.8, 169.8, 169.9, 170.0, 170.5, 170.7, 173.5. Anal. Calcd for $C_{25}H_{25}N_3O_{10}S{\cdot}2H_2O$: C, 50.42; H, 4.91; N, 7.05. Found: C, 50.37; H, 4.92; N, 6.99.

1-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-glucopyranosyl)-2-(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosylthio)-5-cyano-6-phenyl pyrimidin-4(1*H*)-one (2′). Yield 35%; mp 114–16°C; [α]=45.0; ^1H NMR δ 1.83–2.01 (m, 24H), 4.25 (m, 6H), 5.11 (m, 4H), 5.55 (m, 2H), 5.98 (d, J=10.4 Hz, 1H, H1′), 6.50 (d, J=8.0 Hz, 1H, H1″), 7.62 (m, 3H), 8.08 (m, 2H). Anal. Calcd for $C_{39}H_{43}N_3O_{19}S{\cdot}0.5H_2O$: C, 52.07; H, 4.89; N, 4.78. Found: C, 52.15; H, 4.78; N, 4.68.

1-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-glucopyranosyl)-5-cyano-6-(*p*-tolyl)-2-thiouracil (3). Yield 30%; mp 189–92°C; [α]=23.0; ^1H NMR δ 1.98–2.18 (4 s, 12H), 2.46 (s, 3H), 3.91 (m, 1H), 4.11 (m, 2H), 5.13 (d, J=10.0 Hz, 1H), 5.23 (t, J=9.2 Hz), 5.34 (t, J=9.2 Hz), 5.76 (d, J=10.0 Hz, 1H, H1′), 7.35 (d, J=6.0 Hz, 2H), 7.95 (d, J=6.0 Hz, 2H). Anal. Calcd for $C_{26}H_{27}N_3O_{10}S{\cdot}2H_2O$: C, 51.23; H, 5.13; N, 6.89; Found: C, 51.36; H, 4.89; N, 7.03.

1-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-glucopyranosyl)-2-(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosylthio)-5-cyano-6-(*p*-tolyl)-pyrimidin-4(1*H*)-one (3′). Yield 36%; mp 118–20°C; [α]=38.0; ^1H NMR δ 1.98–2.01 (m, 24H), 2.44 (s, 3H), 4.25 (m, 6H), 5.16 (m, 3H), 5.34 (m, 3H), 5.73 (d, J=10.3 Hz, 1H, H1′), 6.15 (d, J=7.5 Hz, 1H, H1″), 7.42 (d, J=11.0 Hz, 2H), 7.97 (d, J=11.0 Hz, 2H). Anal. Calcd for $C_{40}H_{45}N_3O_{19}S{\cdot}0.5\ H_2O$: C, 52.63; H, 5.04; N, 4.60; Found: C, 52.54; H, 5.00; N, 4.39.

1-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-glucopyranosyl)-5-cyano-6-(2-naphthyl)-2-thiouracil (4). Yield 23%; mp 189–92°C; [α]=32.0; ^1H NMR δ 1.96–2.12 (4 s, 12H), 4.04 (m, 1H), 4.10 (m, 1H), 4.16 (m 1H), 4.97 (m, 1H), 5.04 (m, 1H), 5.45 (m, 1H), 5.91 (d, J=10.8 Hz, 1H, H1′), 7.61 (m, 2H), 7.98 (m, 4H), 8.45 (s, 1H). Anal. Calcd for $C_{29}H_{27}N_3O_{10}S{\cdot}0.5H_2O$: C, 56.25; H, 4.52; N, 6.78; Found: C, 56.28; H, 4.30; N, 7.02.

1-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-glucopyranosyl)-2-(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosylthio)-5-cyano-6-(2-naphthyl)-pyrimidin-4(1*H*)-one (4′). Yield 32%; mp 131–33°C; [α]=29.0; ^1H NMR δ 1.88–2.12 (m, 24H), 4.45 (m, 6H), 5.22 (m, 3H), 5.48 (m, 3H), 6.21 (d, J=10.3 Hz, 1H, H1′), 6.60 (d, J=7.5 Hz, 1H, H1″), 7.58 (m, 2H), 7.93 (m, 4H), 8.41 (s, 1H). Anal. Calcd for $C_{43}H_{45}N_3O_{19}S{\cdot}1.5\ H_2O$: C, 53.36; H, 4.96; N, 4.34; Found: C, 53.27; H, 5.12; N, 4.28.

1-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-galactopyranosyl)-5-cyano-6-phenyl-2-thiouracil (5). Yield 30%; mp 232–34°C; [α]=36.4; ^1H NMR δ 1.99,2.02 (2 s, 12H), 4.03 (m, 2H), 4.33 (m, 1H), 5.15 (m, 1H), 5.36 (t, J=10.8 Hz, 1H), 5.54 (m, 1H), 5.99 (d, J=10.8 Hz, 1H, H1′), 7.60 (m, 3H), 8.07 (m, 2H). Anal. Calcd for $C_{25}H_{25}N_3O_{10}S{\cdot}2.5H_2O$: C, 49.62; H, 4.96; N, 6.95; Found: C, 49.38; H, 4.69; N, 6.78.

1-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-galactopyranosyl)-2-(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-galactopyranosylthio)-5-cyano-6-phenyl pyrimidin-4(1*H*)-one (5′). Yield 35%, mp 128–30°C; [α]=23.0; ^1H NMR δ 1.89–2.12 (m, 24H), 4.23 (m, 6H), 5.23 (t, J=5.7 Hz, 1H), 5.32 (t, J=5.7 Hz, 1H), 5.45 (t, J=5.4 Hz, 1H), 5.55 (t, J=5.4 Hz, 1H), 6.15 (d, J=8.0 Hz, 1H, H1′), 6.81 (d, J=10.8 Hz, 1H, H1″), 7.52 (m, 3H), 7.82 (m, 2H). Anal. Calcd for $C_{39}H_{43}N_3O_{19}S{\cdot}H_2O$: C, 51.60; H, 5.00; N, 4.63; Found: C, 52.00; H, 4.85; N, 4.47.

1-(2′,3′,5′-Tri-*O*-acetyl-β-D-xylopyranosyl)-5-cyano-6-(2-naphthyl)-2-thiouracil (6). Yield 20%; mp 165–68°C; [α]=26.7; ^1H NMR δ 2.00–2.03 (3s, 9H), 3.65 (m, 1H), 4.10 (m, 1H), 4.09 (m, 1H), 5.06 (m, 1H), 5.33 (t, J=8.4 Hz, 1H), 6.03 (d, J=8.4 Hz, 1H, H1′), 7.63 (m, 2H), 8.07 (m, 4H), 8.51 (s, 1H). Anal. Calcd for $C_{26}H_{23}N_3O_8S{\cdot}H_2O$: C, 56.21; H, 4.54; N, 7.56; Found: C, 56.28; H, 4.38; N, 7.26.

1-(2′,3′,5′-Tri-*O*-acetyl-β-D-xylopyranosyl)-)-2-(2″,3″,5″-tri-*O*-acetyl-β-D-xylopyranosylthio)-6-(2-naphthyl)-pyrimidin-4(3*H*)-one (6′). Yield 35%; mp 123–25°C; [α]=21.6; ^{1}H NMR δ 1.99–2.06 (6s, 18H), 3.78 (t, *J*=9.3 Hz, 1H), 3.92 (t, *J*=5.4 Hz, 1H), 4.07 (t, *J*=9.3 Hz, 1H), 4.22 (t, *J*=5.4 Hz, 1H), 4.95 (m, 2H), 5.10 (m, 2H), 5.27 (t, *J*=9.0 Hz, 1H), 5.50 (t, *J*=4.5 Hz, 1H), 6.06 (d, *J*=9.0 Hz, 1H, H1′), 6.61 (d, *J*=4.5 Hz, 1H, H1″), 7.66 (m, 2H), 8.10 (m, 4H), 8.64 (s, 1H). Anal. Calcd for $C_{37}H_{37}N_3O_{15}S·H_2O$: C, 54.61; H, 4.79; N, 5.16; Found: C, 54.82; H, 4.65; N, 5.01.

The Silyl Method for 2–6 and 16. A mixture of a 2-thiouracil **7**–**9** (10 mmol), HMDS (60 mL), and $(NH_4)_2SO_4$ (125 mg) was heated under reflux for 6 h. Excess HMDS was removed by distillation and then residual HMDS was removed under a reduced pressure. A solution of the resultant silyl intermediate **15** in anhydrous MeCN (20 mL) was stirred and treated with a solution of β-D-glucose pentaacetate, β-D-galactose pentaacetate or β-D-xylose tetraacetate (9 mmol) in anhydrous MeCN (20 mL). Following cooling to 5°C and then addition of anhydrous $SnCl_4$ (1.6 mL), the mixture was stirred at 23°C for 16 h. The mixture was diluted with $CHCl_3$ (150 mL), washed with a saturated solution of $NaHCO_3$ (50 mL) and water (2×25 mL), and then dried (Na_2SO_4). Removal of solvent under a reduced pressure followed by crystallization (2×) of the residue by diluting an ether solution with hexanes and then from 95% EtOH gave an analytically pure compound **2**–**6**. Compound, yield: **2**, 65%; **3**, 65%; **4**, 62%; **5**, 61%; **6**, 60%. Only one crystallization was conducted before the subsequent ammonolysis of **2**–**6**.

In the synthesis of **16** the intermediate silyl derivative **15** was allowed to react with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose in the presence of $CF_3SO_3SiMe_3$ instead of $SnCl_4$ under otherwise identical conditions. Following a similar workup, product **16** was crystallized from 95% EtOH.

1-(2′,3′,5′-Tri-*O*-acetyl-β-D-ribofuranosyl)-5-cyano-6-phenyl-2-thiouracil (16). Yield 85%; mp 248–51°C; [α]=23.0; ^{1}H NMR δ 1.99–2.01 (3s, 9H), 4.09 (m, 1H, H4′), 4.33 (m, 2H, H_25'), 5.42 (m, 1H, H3′), 5.62 (m, 1H, H2′), 6.22 (d, *J*=2.7 Hz, 1H, H1′), 7.60 (m, 3H), 7.86 (m, 2H); ^{13}C NMR δ 20.1, 20.2, 20.5, 62.1, 69.7, 74.9, 79.5, 85.6, 93.6, 115.5, 128.2, 128.5, 131.7, 134.8, 161.5, 163.2, 166.0, 169.0, 169.3, 169.8. Anal. Calcd for $C_{22}H_{21}N_3O_8S·H_2O$: C, 52.27; H, 4.59; N, 8.31. Found: C, 52.12; H, 4.55; N, 8.22.

Ammonolysis of 2–6, 2–6/2′–6′, and 16. A solution of an individual nucleoside **2**–**6** (1 mmol), a mixture **2**–**6**/**2′**–**6′** (total 1 mmol) or **16** (1 mmol) in anhydrous MeOH (10 mL) was added at 0°C to a saturated solution of anhydrous NH_3 in anhydrous MeOH (25 mL) and the mixture was stirred at 0°C for 4 h and then at 23°C for an additional 12 h. Concentration followed by silica gel chromatography (MeOH/$CHCl_3$, 1:19) and then crystallization from 95% MeOH gave an analytically pure compound **10**–**14**. The yields for the ammonolysis of **2**–**6** or the corresponding mixture **2**–**6**/**2′**–**6′** were virtually identical.

5-Cyano-1-(β-D-glucopyranosyl)-6-phenyl-2-thiocytosine (10). Yield 86%; mp 190–93°C; [α]=21.0; ^{1}H NMR (DMSO-d_6) δ 3.21 (m, 3H, H2′, H3′, H4′), 3.48 (m, 2H, H_26'), 3.68 (m, 1H, H5′), 4.80 (m, exchangeable with D_2O, 4H), 5.37 (d, *J*=10.0 Hz, 1H, H1′), 7.18 (bs, exchangeable with D_2O, 2H), 7.47 (m, 3H), 7.80 (m, 2H). Anal. Calcd for $C_{17}H_{18}N_4O_5S·1.5H_2O$: C, 48.92; H, 5.03; N, 13.42; S, 7.67; Found: C, 48.84; H, 5.10; N, 13.33; S, 7.73.

5-Cyano-1-(β-D-glucopyranosyl)-6-(4-tolyl)-2-thiocytosine (11). Yield 86%; mp 190–93°C; [α]=25.5; ^{1}H NMR (DMSO-d_6) δ 2.36 (s, 3H), 3.15 (m, 2H, H2′, H3′), 3.46 (m, 4H, H4′, H5′, H_26'), 4.80 (m, exchangeable with D_2O, 4H), 5.35 (d, *J*=10.2 Hz, 1H, H1′), 7.15 (bs, exchangeable with D_2O, 2H), 7.26 (d, *J*=8.0 Hz, 2H), 7.72 (d, *J*=8.0 Hz, 2H). Anal. Calcd for $C_{18}H_{20}N_4O_5S·2H_2O$: C, 49.08; H, 5.49; N, 12.72. Found: C, 48.95; H, 5.60; N, 12.65.

5-Cyano-1-(β-D-glucopyranosyl)-6-(2-naphthyl)-2-thiocytosine (12). Yield 83%; mp 198–201°C; [α]=19.3; ^{1}H NMR (DMSO-d_6) δ 3.15 (m, 5H, H2′, H3′, H4′, H_26'), 4.00 (m, 1H, H5′), 4.91 (m, exchangeable with D_2O, 4H), 5.39 (d, *J*=10.4 Hz, 1H, H1′), 7.18 (bs, exchangeable with D_2O, 2H), 7.60 (m, 2H), 7.98 (m, 4H), 8.22 (s, 1H). Anal. Calcd for $C_{21}H_{20}N_4O_5S·2H_2O$: C, 52.93; H, 5.08; N, 11.76. Found: C, 52.86; H, 5.22; N, 11.64.

5-Cyano-1-(β-D-galactopyranosyl)-6-phenyl-2-thiocytosine (13). Yield 87%; mp 192–95°C; [α]=22.6; ^{1}H NMR (DMSO-d_6) δ 3.54 (m, 6H, H2′, H3′, H4′, H5′, H_26'), 4.80 (m, exchangeable with D_2O, 4H,), 5.13 (d, *J*=10.0 Hz, 1H, H1′), 7.02 (bs, exchangeable with D_2O, 2H), 7.46 (m, 3H), 7.78 (m, 2H). Anal. Calcd for $C_{17}H_{18}N_4O_5S·1.5H_2O$: C, 48.92; H, 5.03; N, 13.42. Found: C, 49.18; H, 4.75; N, 13.17.

5-Cyano-6-(2-naphthyl)-(1-β-D-xylopyranosyl)-2-thiocytosine (14): Yield 84%; mp 196–98°C; [α]=16.8; ^{1}H NMR (DMSO-d_6) δ 3.12 (dd, *J*=8.8, 9.9 Hz, 1H, H2′), 3.20 (t, *J*=9.9 Hz, 1H, H3′), 3.39 (m, 2H, H_25'), 3.79 (m, 1H, H4′), 5.07 (bs, exchangeable with D_2O, 3H), 5.46 (d, *J*=8.8 Hz, 1H, H1′), 7.20 (bs, exchangeable with D_2O, 2H), 7.60 (m, 2H), 7.90 (m, 1H), 8.00 (m, 3H), 8.38 (s, 1H). Anal. Calcd for $C_{20}H_{18}N_4O_4S·2H_2O$: C, 53.81; H, 4.93; N, 12.55. Found: C, 54.18; H, 4.98; N, 12.20.

5-Cyano-6-phenyl-1-(β-D-ribofuranosyl)-2-thiocytosine (17). Yield 86%; mp 192–195°C; [α]=21.0; ^{1}H NMR δ 3.47 (m, 1H), 3.76 (m, 1H), 3.87 (m, 1H), 4.00 (m, 1H), 4.76 (br s, 1H), 4.97 (m, 1H), 5.38 (br s, 1H), 5.86 (d, *J*=3.6 Hz, H1′), 6.65 (br s, 1H), 7.24 (br s, 2H), 7.47 (m, 3H), 7.75 (m, 2H). Anal. Calcd for $C_{16}H_{16}N_4O_4S·2H_2O$: C, 48.48; H, 5.09; N, 14.13. Found: C, 48.15; H, 5.25; N, 13.95.

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