2-Trimethylsilylethyl Sulfides in the von Braun Cyanogen Bromide Reaction: Selective Preparation of Thiocyanates and Application to Nucleoside Chemistry

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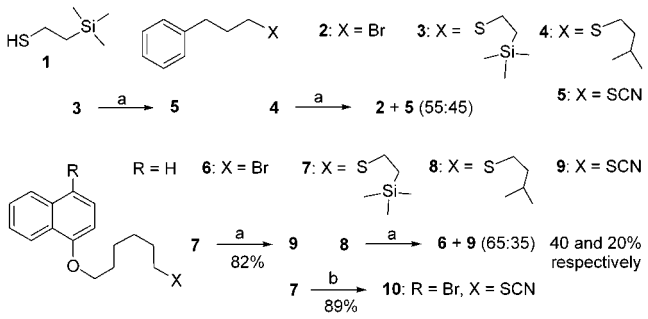
Mixed 2-(trimethylsilyl)ethyl sulfides were synthesized and used in the von Braun cyanogen bromide reaction for preparing selectively thiocyanates in high yield. We show here that this cleavage reaction is highly selective in methanol in comparison with the reaction of the corresponding non-silyl sulfide analogues. This reaction was applied to the synthesis of nucleosidic thiocyanates such as the new nucleosides **14** and **18** in the search for mechanism-based inhibitors of ribonucleoside diphosphate reductase and bioactive molecules. The selective cleavage is possible for sulfides bearing hydroxyl functions and aromatic rings. The reactions of cyanogen bromide as cyanating and brominating agent were observed for the first time under the same conditions with the naphthoxyhexyl 2-trimethylsilylethyl sulfide **7**, which, treated with cyanogen bromide in dichloromethane, led selectively to the *p*-bromonaphthoxyhexyl thiocyanate **10** in 89% yield. Another reaction induced by cyanogen bromide was observed in dichloromethane with the 2-(trimethylsilylethyl)thio nucleoside **13**, which gives the corresponding symmetrical disulfide **21** in good yield.

Introduction

Chemical modifications of naturally occurring nucleosides and nucleotides have led to a large number of analogues used for their therapeutic properties, especially their antiviral and antitumoral activities.[1] Among these modified nucleosides and nucleotides, many sulfur-containing molecules showed interesting biological activities and/or were used as tools for biochemical and biological studies.[2]

In the search for new bioactive nucleotides, we have shown that 2′-deoxy-2′-thiouridine 5′-diphosphate strongly inactivates in vitro *Escherichia coli* ribonucleoside diphosphate reductase (RDPR).[3] This enzyme catalyzes the reduction of the four natural ribonucleotides to the corresponding 2′-deoxyribonucleotides and thus is a key enzyme in the synthesis of DNA.[4] The thiol function of the modified nucleotide interacts with a cysteine residue at the active site to lead to a perthiyl radical on the enzyme. This nucleotide was obtained using a mixed propyl disulfide intermediate, which can be reduced easily in situ with dithiothreitol to lead to the active compound.[5] This protection appeared useful to introduce a diphosphate function at the 5′-position.

Scheme 1. Model Study of the Sulfide Cleavage with Cyanogen Bromide[a]



[a] Key: (a) BrCN, MeOH, rt; (b) BrCN, DCM, rt.

To improve the synthesis of nucleosides and nucleotides possessing a thiol function, we had previously developed a method for preparing methyl disulfides of thionucleosides such as 2′-thiouridine, cytidine, and 3′-thiothymidine using 2-(trimethylsilyl)ethanethiol **1** (Scheme 1).[6] Stable methyl disulfides, precursors of easily oxidable and unstable nucleosides possessing a thiol function on the sugar, were obtained by treatment of trimethylsilylethyl sulfide intermediates with dimethyl(methylthio)sulfonium tetrafluoroborate.[7] These methyl disulfides can be reduced under mild conditions to lead to the corresponding thiols.

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Cyanogen bromide is an interesting reagent that is able to induce selective cleavage of the methionyl peptide bond in proteins.[8a] It has been also used for sequence-specific cleavage of single-strand DNA[8c] and for ligation of DNA strands.[8b] Recently, homoserine lactone libraries were obtained through a BrCN-mediated cyclization process in the final cleavage step.[8d]

In the von Braun reaction, cyanogen bromide induces a nonselective cleavage of tertiary amines to yield alkyl bromides and disubstituted cyanamides.[8e] Alkyl sulfides also undergo nonselective cleavage in the presence of cyanogen bromide with formation of alkyl bromides and thiocyanates.[8e] In this reaction, mixed 2-trimethylsilylethyl sulfides could be interesting intermediates able to be cleaved selectively through a favored elimination of the 2-trimethylsilylethyl group.

We show here that such 2-trimethylsilylethyl sulfides are interesting reagents in the von Braun cyanogen bromide reaction for preparing selectively thiocyanates, especially nucleosidic thiocyanates in the search for bioactive compounds, and that the nature of the products can be dependent upon the solvent.

Thiocyanates undergo isomerization, substitution, elimination, addition, oxidation, and reduction reactions and, thus, are interesting intermediates in organic synthesis.[9] The photochemical homolytic fission of the S−CN bond has been reported.[10] As a consequence, nucleosides bearing a thiocyanate function could be interesting precursors in the search for nucleoside diphosphates that interfere with the radical reactions at the active site of RDPR. This function appears to be stable in vivo, for example, introduction of a thiocyanate function as a polar end group on aryloxyalkyl derivatives led to an improvement on the inhibition of *Trypanosoma cruzi* proliferation (Chagas' disease).[11] Thus, nucleosides bearing such a function could exhibit interesting biological activities.

Results and Discussion

Model Reactions. We began this work with model compounds in order to demonstrate the selectivity of cleavage of mixed 2-trimethylsilylethyl sulfides with cyanogen bromide. The 2-trimethylsilylethyl sulfides **3**[12] and **7** possessing an aromatic chromophore (Scheme 1) were prepared in good yields by reaction of 1-bromo-3-phenylpropane **2** and the naphthyloxybromoalkyl derivative **6**, respectively, with 2-trimethylsilylethanethiol in the presence of sodium hydride. To demonstrate an orientation effect of the silyl group in the cleavage of such sulfides with cyanogen bromide, the corresponding analogues without a silicon atom, the mixed 2-methylbutyl sulfides **4** and **8** were prepared by reaction of compounds **2** and **6** with 3-methylbutylthiol in the presence of sodium hydride, respectively (72 and 93% yields, respectively).

Treatment of the 3-phenylpropyl 2-trimethylsilylethyl sulfide **3** with 10 equiv of cyanogen bromide in methanol at room temperature during 45 min led selectively to only one aromatic compound (C18 reversed-phase HPLC, detection by UV absorption). This product was identified as the thiocyanate **5** (Scheme 1) by TLC and HPLC from an authentical sample prepared by reaction at room temperature of 1-bromo-3-phenylpropane **2** with 10 equiv of potassium thiocyanate in the presence of 18-crown-6 in 77% yield according to a method described by Pakulski et al.[9d] The bromide derivative formed in the cyanogen bromide reaction was not detected under our analysis conditions and was not isolated.

The same selectivity was observed in the cleavage of the naphthylsilyl sulfide **7** with an excess of cyanogen bromide in methanol at room temperature during 5 h (HPLC). The thiocyanate **9** (Scheme 1) was detected as the sole aromatic product and was isolated in 82% yield. The characteristic IR asymmetric stretching vibrations of the SCN group in compounds **5** and **9** were observed at 2150 and 2160 cm^{-1}, respectively.[9a,13]

Treatment with cyanogen bromide, under the conditions previously used, of the close analogue of the silyl sulfide **7**, the 3-methylbutyl sulfide **8**, without the silicon atom, led to a mixture of two aromatic products (HPLC). These products were characterized as the aromatic bromide **6** and the thiocyanate **9** detected as a mixture (65:35) by HPLC and isolated in 40 and 20% yields, respectively.

The reactivities of the sulfides **7** and **8** were compared, alone in solution or in mixture, at the same concentrations, by HPLC (10 equiv of cyanogen bromide). Clearly, the silyl sulfide **7** undergoes cleavage more rapidly than its 3-methylbutyl sulfide analogue **8** (see HPLC profiles in the Supporting Information: Figure 2). After standardization with naphthalene present in the reaction solution as an unreactive internal reference, the areas of the peaks detected by HPLC are proportional to the concentrations of the corresponding compounds present because (i) only the aromatic products in which the substituent on the alkyl chain has been modified were detected at 300 nm, and these modifications do not modify the absorption, and (ii) the spectrum of the aromatic chromophore is not affected by the composition of the eluent (methanol−water). In Figure 1, these areas were plotted as a function of the reaction time of the sulfides **7** and **8** in (50:50) mixture. This figure, and the other studies with the sulfides alone, revealed clearly the highest reactivity of the trimethylsilylethyl sulfide **7**.

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(11) Szajnman, S. H.; Yan, W.; Bailey, B. N.; Docampo, R.; Elhalem, E.; Rodriguez, J. B. *J. Med. Chem.* **2000**, *43*, 1826−1840.

(12) Compound **3** has been previously synthesized, but its characteristics were not reported.[7]

(13) *Tabulation of infrared spectral data*; Dolphin, D., Wick, A., Eds.; Wiley-Interscience: New York, London, Sidney, Toronto, 1977; pp 164−166.

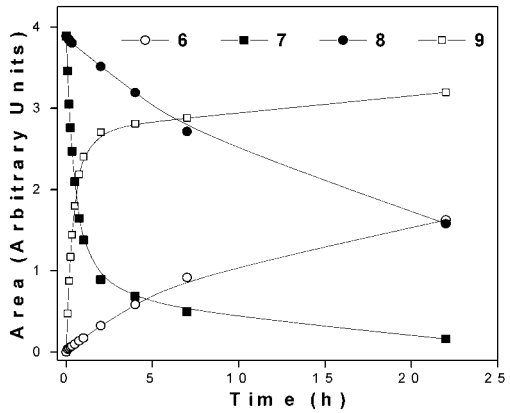


Figure 1. Cyanogen bromide cleavage of a (50:50) mixture of the model naphthyloxyalkyl sulfides **7** and **8** in methanol at room temperature (0.03 M for each sulfide, 0.42 M cyanogen bromide). Standardized areas of the HPLC peaks detected at 300 nm as a function of the reaction time. The silyl sulfide **7** leads selectively to the thiocyanate **9** more rapidly than its nonsilyl sulfide analogue **8**, which gives a mixture of the bromide **6** and the thiocyanate **9**.

Compound **7** is 22-fold more reactive than compound **8** under the initial conditions of reaction used (Figure 1). This points out the strong effect of the silyl group.

A lack of selectivity in the cyanogen bromide cleavage was also observed with the 3-methylbutyl sulfide **4**, analogue of the silyl sulfide **3**, under the conditions used previously. Two aromatic products were identified as 1-bromo-3-phenylpropane **2** and the thiocyanate **5** by comparison with authentic samples and were detected as a mixture (55:45) (HPLC). The kinetics of cleavage of the sulfides **3** and **4** were compared by HPLC. This study also showed a higher reactivity of the trimethylsilylethyl sulfide **3** than the one of the corresponding non silylated sulfide **4**.

Under the same conditions, the silyl sulfides **3** and **7** are cleaved more rapidly than the corresponding 3-methylbutyl sulfides **4** and **8**. These results indicate that, probably, from the cyanosulfonium intermediate, the 2-trimethylsilylethyl group is removed rapidly to give selectively a silylated carbenium ion intermediate stabilized by the β-silicon effect.[14]

Application to Nucleoside Chemistry. Nucleosides and nucleotides bearing a thiocyanate function could be interesting bioactive agents and/or tools for biochemical studies.

Previously, in the search for antiviral agents, 3′-deoxy-3′-thiocyanatothymidine **12** has been prepared in 21% yield by reaction of 1-(2-deoxy-3-*O*-mesyl-5-*O*-trityl-β-D-threopentofuranosyl)thymine with potassium thiocyanate in DMF at 100 °C and then deprotection. This nucleoside showed very low protection of MT4 cells against HIV.[15] The 3′-(2-trimethylsilylethyl)thiothymidine derivative **11** prepared by us previously[6] was treated with an excess of cyanogen bromide in methanol at room temperature to form selectively one nucleoside that was characterized as the thiocyanate **12** isolated in 77% yield (Scheme 2).

Ribonucleoside diphosphate reductase (RDPR) functions through radical reactions[4] and nucleoside 5′-diphosphates possessing a thiocyanate function on the sugar could interfere with the radical processes. To prepare a uridine derivative bearing a thiocyanate function at the 2′-position, a precursor of a diphosphate potentially mechanism-based inhibitor of RDPR, we used the 2′-(2-trimethylsilylethyl)thiouridine derivative **13** prepared previously.[6] Its cleavage with cyanogen bromide in methanol also appeared selective with formation of one nucleoside detected by TLC (Scheme 2). However, after complete reaction, during isolation of the product, decomposition reactions were observed. The thiocyanate **14** was finally obtained in 34% yield by precipitation from the reaction mixture and rapid chromatography on silica gel. At room temperature, this compound was found to be unstable in water, on silica gel, or on alumina; it decomposes to lead to several products.[16] Formation of the thiocyanate **14** was not detected when 2,2′-anhydrouridine **15** was heated in the presence of potassium thiocyanate and 18-crown-6 in DMF (80 °C, 120 °C, or reflux).

To introduce a thiocyanate function in the xylo configuration of the sugar that could interfere with the thiyl radical of RDPR formed from the 439 cysteine, we synthesized the corresponding 2-trimethylsilylethyl sulfide **17** using the interesting and versatile route described recently by Reese and co-workers for preparing xylo 2′-deoxy-2′-ethylthio and benzylthio uridine derivatives (Scheme 2).[17a] 2,2′-Anhydrouridine **15** was first converted into the 2′,3′-isomeric epoxide **16** by treatment with sodium hydride in excess in DMF and then addition of 2-trimethylsilylethanethiol led to the xylo sulfide **17** in 78% yield. The presence of the alkylthio group in the xylo configuration was confirmed by ^{1}H NMR experiments.[17b] The silyl sulfide **17** obtained was treated with an excess of cyanogen bromide at room temperature in methanol for obtaining selectively the corresponding new thiocyanate **18** in 69% yield.

Some 5′-modified adenosine derivatives are mechanism-based inhibitors of *S*-adenosyl-L-homocysteine hydrolase, and some of them present interesting antiviral activities, for example, 5′-deoxy-5′-methylthioadenosine.[2a,b,18] To confirm the cleavage selectivity of 2-trimethylsilylethyl sulfides in nucleosides, the 5′-thiocyanato adenosine derivative **20** was synthesized from 5′-deoxy-5′-(2-trimethylsilylethanethio)adenosine **19**. This latter was prepared from the corresponding 5′-tosyl adenosine derivative in 96% yield. The silyl sulfide **19** was treated with an excess of cyanogen bromide in methanol at room temperature for obtaining selectively the corresponding nucleosidic thiocyanate **20** in 80% yield (Scheme 3).[19]

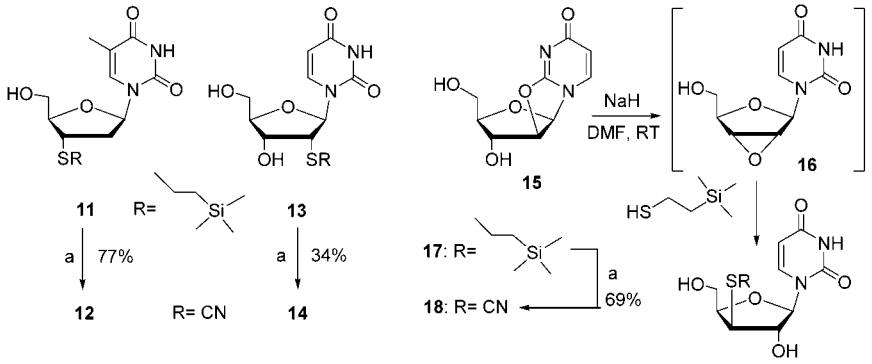
(14) Wierschke, S. G.; Chandrasekhar, J.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1985**, *107*, 1496−1500.

(15) Herdewijn, P.; Balzarini, J.; De Clercq, E.; Pauwels, R.; Baba, M.; Broder, S.; Vanderhaeghe, H. *J. Med. Chem.* **1987**, *30*, 1270−1278.

(16) The instability of thiocyanate **14** could be explained by an intramolecular reaction of the 2′-thiocyano group with the 3′-hydroxyl function. Such an instability was not observed for the xylo isomer of compound **14** described here and has not been reported for 3′-deoxy-3′-thiocyanatoarabinofuranosyl pyrimidine nucleosides previously prepared: Hollenberg, D. H.; Watanabe, K. A.; Fox, J. J. *J. Med. Chem.* **1977**, *20*, 113−116.

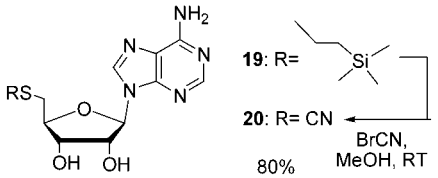
(17) (a) Miah, A.; Reese, C. B.; Song, Q. *J. Chem. Soc., Chem. Commun.* **1997**, 407−408. (b) Chemical shifts analysis and homodecoupling experiments showed the presence of the silylethylthio group at the 3′-position of the sugar. In DMSO-d_6, the 3′-H proton was detected at 3.34 ppm as a pseudo triplet (doublet of doublet, $J_{3',2'} = J_{3',4'} = 7.2$ Hz). These data are close to those reported in the same solvent for the corresponding benzylthio derivative, 1-(3-benzylthio-β-D-xylofuranosyl)uracil described by Reese et al.[a] and characterized by X-ray crystal analysis: Miah, A.; Reese, C. B.; Song, Q.; Sturdy, Z.; Neidle, S.; Simpson, I. J.; Read, M.; Rayner, E. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3277−3284.

Scheme 2. Preparation of Thiocyanates 12, 14, and 18 by Cyanogen Bromide Cleavage of the Corresponding 2-Trimethylsilylethylthio Derivatives 11, 13, and 17[a]



[a] Key: (a) BrCN, MeOH, rt.

Scheme 3. Preparation of Thiocyanate 20 by Cyanogen Bromide Cleavage of the Corresponding 2-Trimethylsilylethylthio Derivative 19

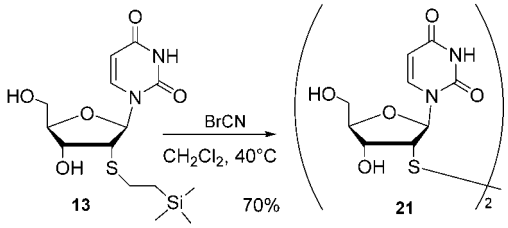


Solvent Effects on the Cyanogen Bromide Reactivity. The reactivity of the trimethylsilylethyl sulfides prepared with cyanogen bromide was studied in dichloromethane instead of methanol as a solvent.

In dichloromethane, the phenyl sulfide **3** led selectively to the thiocyanate **5** (HPLC), whereas the naphthyl sulfide **7** led selectively to an aromatic compound different of the thiocyanate **9** obtained in methanol. This compound was isolated and characterized as the thiocyanate **10** (Scheme 1), which results from a selective electrophilic bromination on the naphthyl ring at the para position and a selective cleavage of the trimethylsilylethyl sulfide function (Scheme 1). It was isolated in 89% yield. Thus, in dichloromethane the polarization of cyanogen bromide can be inverted to generate an electrophilic bromine species. The brominating action of cyanogen bromide has been reported previously, for example, in the synthesis of α-bromo-*β*-aminoenones from *β*-aminoenones.[20]

Concerning the trimethylsilylethylthio nucleosides prepared, an interesting reaction of the 2′-uridine sulfide **13** was observed in dichloromethane. The low solubility of these compounds in this solvent led us to conduct the reaction with cyanogen bromide at reflux. A white precipitate appeared slowly. The corresponding product was purified by chromatography and obtained in 70% yield. It was characterized as the symmetric uridine disulfide **21** by comparison with an authentical sample prepared (Scheme 4).[5,21] This reaction is an alternative to the preparation of reductible and stable precursors of 2′-thiouridine from compound **13**.[5,6,21]

Scheme 4. Preparation of the Symmetrical Disulfide 21 by Reaction of the 2-Trimethylsilylethylthio Derivative 13 with Cyanogen Bromide



This behavior was also observed with the trimethylsilylethylthio nucleoside **17**, which gave the corresponding symmetrical disulfide in dichloromethane under the same conditions but not selectively (^{1}H NMR, LRMS). Formation of the corresponding thiocyanates as minor products was observed by CCM.

Conclusion

These results show that 2-trimethylsilylethyl sulfides can be cleaved with cyanogen bromide in methanol to lead selectively to the corresponding thiocyanates in excellent yields. This reaction is possible and selective for compounds possessing an aromatic ring such as phenyl, alkoxynaphthyl, pyrimidine (uracil), and purine (adenine) rings and in the presence of hydroxyl functions.

Different potentially bioactive nucleosides bearing a thiocyanate function were prepared in good yields using this method, among them the new xylo uridine derivative **18**. 2′-Deoxy-2′-thiocyanatouridine **14** was also obtained for the first time despite its instability under different conditions.

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(19) During this work, Guillerm et al. synthesized this compound using another way and showed that it is an irreversible inhibitor of *S*-adenosyl-L-homocysteine hydrolase (unpublished results; for examples, see ref 18).

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A study in another solvent, dichloromethane, revealed the remarkable interest of cyanogen bromide in the reaction of electron-rich, aromatic trimethylsilylethyl sulfides, which can be selectively brominated on the aromatic ring and cleaved at the sulfur atom to generate a thiocyanate function as illustrated with the preparation of compound **10** from compound **7** in 89% yield. Thus, the dual reactivity of cyanogen bromide resulting from opposite polarizations can be observed on a molecule under the same conditions. Another interesting effect of the solvent and temperature was observed with the trimethylsilylethylthio nucleoside **13**, which led in dichloromethane to the symmetrical disulfide **21** in good yield.

In conclusion, cyanogen bromide is a powerful reagent for selectively modifying trimethylsilylethyl sulfides. It will be interesting to investigate the corresponding reactions of trimethylsilylethylamines. 2-(Trimethylsilyl)-ethyl sulfides are versatile intermediates that can be selectively converted into their corresponding methyl disulfides,[6,7] thiols,[6,22a] and thioacetates.[22b] We show here that they can also be selectively transformed to their corresponding thiocyanates.

Experimental Section

General Procedures. Melting points are reported uncorrected. Chemical shifts are in parts per million relative to the residual signal of the solvent. NMR peak assigments and conditions for the study of cyanogen bromide cleavage of the model sulfides by HPLC (Figure 2) can be obtained as Supporting Information.

Synthesis. 2-(Trimethylsilyl)ethanethiol (commercially available) was synthesized from vinyltrimethylsilane and thiolacetic acid according to the procedures described previously.[7,23] 2,2′-Anhydrouridine **15** was obtained using the method reported by Hampton and Nichol and improved by Mofatt et al.[24]

3-Phenylpropyl 2-(Trimethylsilyl)ethyl Sulfide 3. To a solution of 2-(trimethylsilyl)ethanethiol **1** (250 μL, 1.56 mmol) in THF (5 mL) was added sodium hydride (65% suspension, 200 mg, 5.42 mmol). The mixture was stirred for 30 min at room temperature under nitrogen, and then 1-bromo-3-phenylpropane (300 μL, 1.97 mmol) was added. The mixture was stirred at room temperature for 15 h and then cooled at 0 °C. Water was added slowly (40 mL), followed by an aqueous ammonium chloride solution (5 M, 5 mL). The resulting solution was extracted with dichloromethane (150 mL). The organic solution was dried over Na_2SO_4 and then evaporated at room temperature. The residue was chromatographed on silica gel in hexane−CH_2Cl_2 (9:1) to afford compound **3** (liquid, 269 mg, 68%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.29−7.18 (5 H, m), 2.73 (2 H, t), 2.55 (4 H, m), 1.91 (2 H, m, CH_2), 0.65 (2 H, m), 0.02 (9 H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.7, 128.5, 128.3, 125.8, 34.9, 31.2, 31.1, 27.6, 17.4, −1.7; LRMS (DCI+, NH_3 + isobutane) m/z = 253 $[M + H]^+$. Anal. Calcd for $C_{14}H_{24}SSi$: C, 66.60; H, 9.58; S, 12.70. Found: C, 66.49; H, 9.66; S, 12.82.

3-Methylbutyl 3-Phenylpropyl Sulfide 4. To a solution of 3-methylbutanethiol (2 mL, 16 mmol) in THF (20 mL) was added sodium hydride (65% suspension, 1 g, 27 mmol) at room temperature. The mixture was stirred for 30 min under nitrogen, and then 1-bromo-3-phenylpropane (3.65 mL, 25 mmol) was added. The mixture was stirred for 15 h at room temperature and then was cooled at 0 °C. An aqueous NaH_2PO_4 (10%, 200 mL) was added slowly, and the resulting solution was extracted with dichloromethane (250 mL). The organic layer was dried over Na_2SO_4 and then was evaporated at room temperature. The residue was chromatographed on silica gel in pentane−CH_2Cl_2 (9:1) to lead to compound **4** (liquid, 2.57 g, 72%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.29−7.18 (5 H, m), 2.76 (2 H, t), 2.56 (4 H, m), 1.95 (2 H, m), 1.71 (1 H, m), 1.50 (2 H, m), 0.94 (6 H, d); ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.5, 128.4, 128.3, 125.8, 38.6, 34.8, 31.4, 31.1, 30.0, 29.6, 27.4, 22.2; LRMS (EI) m/z = 222 $[M]^{\bullet+}$. Anal. Calcd for $C_{13}H_{22}S$: C, 75.61; H, 9.97; S, 14.42. Found: C, 75.51; H, 10.01; S, 14.94.

1-Bromo-6-(1-naphthoxy)hexane 6. To a solution of 1-naphthol (1 g, 6.9 mmol in acetonitrile (6 mL) were added potassium carbonate (2 g, 14.5 mmol) and then 1,6-dibromohexane (6.4 mL, 41.4 mmol). The mixture was stirred at 50 °C under nitrogen for 15 h. After filtration to remove the mineral salts and evaporation, the residue was dissolved in dichloromethane (100 mL). The solution was washed with water (100 mL), dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel in pentane−CH_2Cl_2 (9:1) to lead to compound **6** (liquid, 1.935 g, 91%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.26 (1 H, m), 7.77 (1 H, m), 7.50−7.30 (4 H, m), 6.79 (1 H, d), 4.13 (2 H, t), 3.42 (2 H, t), 1.99−1.65 (4 H, m), 1.68−1.51 (4 H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.8, 134.5, 127.4, 126.3, 125.9, 125.7, 125.1, 122.0, 120.0, 104.6, 67.7, 33.7, 32.7, 29.1, 28.0, 25.5; LRMS (EI) m/z = 308 $[M(^{81}Br)]^{\bullet+}$, 306 $[M(^{79}Br)]^{\bullet+}$, 144 $[naphthol]^{\bullet+}$. Anal. Calcd for $C_{16}H_{19}BrO$: C, 62.55; H, 6.23. Found: C, 62.81; H, 6.32.

6-(1-Naphthyl)oxyhexyl 2-(Trimethylsilyl)ethyl Sulfide 7. To a solution of the bromonaphthyl derivative **6** (1 g, 3.25 mmol) in DMF (5 mL) were added potassium carbonate (2 g, 14.5 mmol) and then 2-(trimethylsilyl)ethanethiol (0.63 mL, 3.9 mmol). The mixture was stirred at 50 °C under nitrogen for 15 h. After filtration to remove the mineral salts and evaporation, the residue was dissolved in dichloromethane (100 mL). The solution was washed with water (100 mL), dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel in pentane−CH_2Cl_2 (8:2) to led to compound **7** (liquid, 1.06 g, 90%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.26 (1 H, m), 7.77 (1 H, m), 7.50−7.29 (4 H, m), 6.78 (1 H, dd), 4.13 (2 H, t), 2.54 (4 H, m), 1.92 (2 H, m), 1.71−1.45 (6 H, m), 0.85 (2 H, m), 0.01 (9 H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.8, 134.5, 127.4, 126.2, 125.8, 125.7, 125.0, 122.0, 120.0, 104.5, 68.0, 31.6, 29.5, 29.2, 28.7, 27.6, 25.9, 17.4, −1.8; LRMS (EI) m/z = 360 $[M]^{\bullet+}$, 144 $[naphthol]^{\bullet+}$. Anal. Calcd for $C_{21}H_{32}OSSi$: C, 69.94; H, 8.94. Found: C, 70.24; H, 9.07.

3-Methylbutyl 6-(1-Naphthyl)oxyhexyl Sulfide 8. To a solution of the bromonaphthyl derivative **6** (1 g, 3.25 mmol) in DMF (5 mL) were added potassium carbonate (2 g, 14.5 mmol) and 3-methylbutanethiol (0.49 mL, 3.9 mmol). The mixture was stirred at 50 °C under nitrogen for 15 h before being filtered and evaporated to dryness. After filtration to remove the mineral salts and evaporation, the residue was dissolved in dichloromethane (100 mL). The solution was washed with water (100 mL), dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel in pentane−CH_2Cl_2 (8:2) to lead to compound **8** (liquid, 0.997 g, 93%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.28 (1 H, m), 7.79 (1 H, m), 7.52−7.31 (4 H, m), 6.80 (1 H, dd), 4.15 (2 H, t), 2.52 (4 H, m), 1.95 (2 H, m), 1.72−1.39 (9 H, m), 0.91 (6 H, d); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.8, 134.4, 127.3, 126.2, 125.8, 125.7, 124.9, 122.0, 120.0, 104.5, 68.0, 38.7, 32.0, 30.1, 29.6, 29.5, 29.2, 27.4, 25.9, 22.2; LRMS (DCI+, NH_3 + isobutane) m/z = 331 $[M + H]^+$. Anal. Calcd for $C_{21}H_{30}OS$: C, 76.31; H, 9.15; S, 9.70. Found: C, 76.18; H, 9.15; S 9.65.

Thiocyanates. 3-Phenylpropyl Thiocyanate 5. To a solution of 1-bromo-3-phenylpropane (200 μL, 1.32 mmol) in acetone (2 mL) was added KSCN (1.3 g, 13.3 mmol) and 18-crown-6 (350 mg, 1.32 mmol). The mixture was stirred for 15 h at room temperature under nitrogen. After filtration to remove the mineral salts and evaporation, the residue was dissolved in dichloromethane (50 mL). The solution was washed with water (20 mL), dried over Na_2SO_4, and evapo-

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rated. The residue was chromatographed on silica gel in dichloromethane to lead to compound **5** (liquid, 180 mg, 77%): IR_{max} (KBr) 2150 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.35−7.19 (5 H, m), 2.93 (2 H, t), 2.81 (2 H, t), 2.17 (2 H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.6, 128.5, 128.2, 126.3, 111.7 (SCN), 33.5, 32.9, 31.0; LRMS (EI) $m/z = 177$ $[M]^{\bullet+}$. Anal. Calcd for $C_{10}H_{11}NS$: C, 67.75; H, 6.25; N, 7.90; S, 18.09. Found: C, 67.92; H, 6.22; N, 7.99; S, 17.82.

General Procedure for the Cyanogen Bromide Cleavage. To a solution of sulfide (∼0.6 mmol) in methanol (4 mL) was added cyanogen bromide (∼6 mmol). The mixture was stirred for 5−15 h at room temperature, and then aqueous phosphate buffer (0.5 M, pH 7, 4 mL) was added. The mixture was stirred for 30 min, and water (20 mL) was added. The solution was extracted with dichloromethane (150 mL), and the organic phase was dried over Na_2SO_4. The residue was chromatographed on silica gel to afford the corresponding thiocyanate.

6-(1-Naphthoxy)hexyl Thiocyanate 9. Starting silyl sulfide **7**: 205 mg, 0.59 mmol; cyanogen bromide (630 mg, 5.95 mmol); reaction time, 5 h; eluent for chromatography, pentane−dichloromethane (50:50). Thiocyanate **9**: 139 mg, 82%; mp 44−45 °C; IR_{max}(KBr) 2160 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.27 (1 H, m, Ar-H), 7.80 (1 H, m, Ar-H), 7.50−7.29 (4 H, m, Ar-H), 6.81 (1 H, dd, Ar-H), 4.16 (2 H, t), 2.98 (2 H, t), 2.04−1.64 (4 H, m), 1.75−1.54 (4 H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.7, 134.5, 127.5, 126.3, 125.8, 125.7, 125.1, 121.9, 120.1, 112.3 (SCN), 104.6, 67.7, 33.9, 29.8, 29.1, 27.7, 25.7; LRMS (EI) $m/z = 285$ $[M]^{\bullet+}$, 144 $[naphthol]^{\bullet+}$. Anal. Calcd for $C_{17}H_{19}ONS$: C, 71.54; H, 6.71; N, 7.91; S, 11.24. Found: C, 71.47; H, 6.75; N, 7.93; S, 11.53.

Cleavage of the Sulfide 8. Starting sulfide **8**: 195 mg, 0.59 mmol; cyanogen bromide (650 mg, 6.13 mmol); reaction time, 15 h. Bromide **6**: eluent, pentane−dichloromethane (70:30); 70 mg, 40%. Thiocyanate **9**: eluent, pentane−dichloromethane (50:50); 34 mg, 60%.

6-(1-(4-Bromonaphthyl)oxy)hexyl Thiocyanate 10. To a solution of the silyl sulfide **7** (360 mg, 1 mmol) in dichloromethane (10 mL) was added cyanogen bromide (1 g, 9.4 mmol). Monitoring of the reaction by HPLC revealed the formation of only one compound absorbing in the UV. The mixture was stirred for 20 h at room temperature, and then aqueous phosphate buffer (0.5 M, pH 7, 15 mL) was added. The mixture was stirred for 30 min, and water (10 mL) was added. The mixture was extracted with dichloromethane (100 mL). The organic layer was dried over Na_2SO_4 and evaporated. The residue was chromatographed on silica gel in pentane−dichloromethane (50:50) to lead to the thiocyanate **10** (325 mg, 89%): mp 64−66 °C; IR_{max} (KBr) 2160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.28 (1 H, m), 8.25 (1 H, m), 7.63−7.48 (3 H, m), 6.64 (1 H, d), 4.09 (2 H, t), 2.93 (2 H, t), 1.97−1.82 (4 H, m), 1.65−1.54 (4 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 132.4, 129.4, 127.7, 126.8, 126.7, 125.9, 122.4, 113.0, 112.2 (SCN), 105.2, 67.9, 33.9, 29.8, 28.9, 27.7, 25.6; LRMS (FAB+, NBA) $m/z = 365$ $[M(^{81}Br) + H]^+$, 363 $[M(^{79}Br) + H]^+$, 224 $[(naphthol - Br)+H]^+$. Anal. Calcd for $C_{17}H_{18}BrONS$: C, 56.05; H, 4.98; N, 3.84; S, 8.80. Found: C, 56.05; H, 4.96; N, 3.89; S, 8.55.

3′-Deoxy-3′-thiocyanatothymidine 12. Starting silyl sulfide **11**: 100 mg, 0.28 mmol; methanol (1.5 mL), cyanogen bromide (300 mg, 2.83 mmol); reaction time, 24 h; eluent, dichloromethane−methanol (95:5). Thiocyanate **12**: 61 mg, 77%; mp 112−113 °C; IR_{max} (KBr) 2160 cm^{-1}; ^1H NMR (200 MHz, pyridine-d_5) δ 7.56 (1 H, s), 6.65 (1 H, dd), 4.53−4.04 (4 H, m), 2.85 (2 H, m), 1.83 (3 H, s); ^{13}C NMR (75 MHz, pyridine-d_5) δ 164.7, 151.6, 136.3, 111.0 (SCN), 110.6, 86.4, 84.7, 60.3, 43.0, 39.1, 12.6; LRMS (FAB+, glycerol) $m/z = 284$ $[M + H]^+$, 127 $[thymine + H]^+$.

2-Deoxy-2′-thiocyanatouridine 14. To a solution of the silyl sulfide **13** (800 mg, 1.26 mmol) in methanol (3 mL) was added cyanogen bromide (1.35 g, 12.7 mmol). The mixture was stirred for 48 h at room temperature and then was poured slowly into diethyl ether (250 mL). The precipitate was collected by filtration and washed with diethyl ether. It was rapidly flash chromatographed on silica gel in dichloromethane−methanol (80:20) to afford the thiocyanate **14** (215 mg, 34%): mp dec; IR_{max} (KBr) 2150 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.48 (1 H, d), 7.79 (1 H, d), 6.00 (1 H, d), 5.66 (1 H, dd), 5.28 (1 H, ls, 5′-OH), 5.18 (1 H, m), 4.55 (1 H, dd), 4.28 (1 H, m), 3.65 (2 H, m), 3.16 (1 H, ls); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.1, 150.5, 140.6, 110.5 (SCN), 101.9, 91.9, 86.1, 83.9, 60.7, 53.6; LRMS (DCI+, NH_3 + isobutane) $m/z = 286$ $[M + H]^+$, 227 $[M - HSCN + H]^+$, 113 $[uracil + H]^+$; HRMS (FAB$^+$, MCA) calcd for $[C_{10}H_{12}O_5N_3S + H]^+$ 286.0498, found 286.0495.

1-(3-(2-(Trimethylsilyl)ethyl)-β-D-xylofuranosyl)uracil 17. To a suspension of 2,2′-anhydrouridine **15** (2 g, 8.84 mmol) in anhydrous DMF (50 mL) was added sodium hydride (65% suspension, 4 g, 108 mmol). The mixture was stirred for 3 h at room temperature under nitrogen, and then 2-(trimethylsilyl)ethanethiol (2.5 mL, 13.2 mmol) was added. The mixture was stirred for 3 h at room temperature, and then, after cooling at 0 °C, an aqueous ammonium chloride solution (10%, 20 mL) was added slowly. The mixture was evaporated to dryness. The residue was dissolved in dichloromethane (300 mL). The solution was washed with water (100 mL), and the aqueous layer was extracted with dichloromethane (2 × 200 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated. The residue was chromatographed on silica gel in dichloromethane−methanol (95:5) to lead to the silyl sulfide **17** (2.47 g, 6.85 mmol, 78%): mp 165−167 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 11.33 (1 H, s), 7.91 (1 H, d), 5.79 (1 H, d), 5.68 (1 H, d), 5.66 (1 H, d), 5.04 (1 H, t, $J = 4$ Hz, 5′-OH), 4.28 (1 H, m, 4′-H), 4.11 (1 H, m, 2′-H), 3.62 (2 H, m, 5′-H), 3.34 (1 H, t), 2.63 (2 H, m), 0.81 (2 H, m), −0.01 (9 H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.1, 150.8, 140.8, 101.8, 88.0, 80.3, 78.6, 61.4, 50.5, 27.8, 17.2, −1.6; LRMS (FAB+, glycerol) $m/z = 721$ $[2M + H]^+$, 361 $[M + H]^+$. Anal. Calcd for $C_{14}H_{24}O_5N_2SiS$: C, 46.64; H, 6.71; N, 7.77; S, 8.89. Found: C, 46.26; H, 6.71; N, 7.72; S, 8.88.

1-(3-Thiocyanato-β-D-xylofuranosyl)uracil 18. To a solution of sulfide (100 mg, 0.28 mmol) in methanol (1.5 mL) was added cyanogen bromide (500 mg, 4.72 mmol) in parts. The mixture was stirred for 48 h at room temperature, and then aqueous phosphate buffer (0.5 M, pH 7, 4 mL) and water (10 mL) were added. The mixture was extracted with dichloromethane (60 mL) and then ethyl acetate (150 mL). The ethyl acetate solution obtained were dried over Na_2SO_4 and evaporated. The residue was chromatographed on silica gel in dichloromethane−methanol (50:50) to afford to the thiocyanate **18** (55 mg, 69%): mp 176−178 °C dec; IR_{max} (KBr) 2150 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 11.33 (1 H, s), 7.81 (1 H, d), 6.26 (1 H, d), 5.75 (1 H, d), 5.69 (1 H, d), 5.54 (1 H, t), 4.47 (1 H, m), 4.17 (2 H, m), 3.68 (2 H, m); ^{13}C NMR (50 MHz, DMSO-d_6) δ 162.9, 150.7, 140.1, 113.0 (SCN), 102.2, 86.5, 77.8, 77.7, 60.9; LRMS (DCI+, NH_3 + isobutane) $m/z = 303$ $[M + NH_3 + H]^+$, 286 $[M + H]^+$, 113 $[uracil + H]^+$, (DCI−, NH_3 + isobutane) $m/z = 569$ $[2M - H]^-$, 284 $[M - H]^-$. Anal. Calcd for $C_{10}H_{11}O_5N_3S$: C, 42.10; H, 3.89; N, 14.73; S, 11.24. Found: C, 41.80; H, 4.10; N, 14.70; S, 11.19.

5′-Deoxy-5′-(2-(trimethylsilyl)ethyl)adenosine 19. To a solution of 5′-tosyladenosine (500 mg, 1.19 mmol) in anhydrous DMF (10 mL) were added potassium carbonate (1 g, 7.23 mmol) and then 2-(trimethylsilyl)ethanethiol (0.4 mL, 2.49 mmol). The mixture was stirred at 50 °C under nitrogen for 15 h. After filtration to remove the mineral salts and evaporation, the residue was chromatographed on silica gel in dichloromethane−methanol (90:10) to afford compound **19** (438 mg, 96%). This compound was finally crystallized from methanol: mp 125−127 °C; ^1H NMR (200 MHz, DMSO-d_6) δ 8.31 (1 H, s), 8.13 (1 H, s), 7.22 (2 H, s), 5.86 (1 H, d), 5.43 (1 H, d), 5.23 (1 H, d), 4.75 (1 H, m), 4.14 (1 H, m), 3.99 (1 H, m), 2.84 (2 H, m), 2.50 (2 H, m), 0.71 (2 H, m), −0.12 (9 H, s); ^{13}C NMR (50 MHz, DMSO-d_6) δ 156.0, 152.5, 149.4, 139.8, 119.2, 87.5, 84.5, 72.6, 72.5, 33.6, 27.5, 16.6, −1.9; LRMS (FAB+, glycerol) $m/z = 384$ $[M + H]^+$, 136 $[adenine + H]^+$. Anal. Calcd for $C_{15}H_{25}O_3N_5SiS \cdot {}^1/_2MeOH$: C, 46.59; H, 6.81; N, 17.53; S, 8.03. Found: C, 46.39; H, 6.75; N, 17.53; S, 8.53.

5′-Deoxy-5′-thiocyanatoadenosine 20. Starting silyl sulfide **19**: 100 mg, 0.26 mmol; methanol (2 mL); cyanogen bromide (500 mg, 4.7 mmol); reaction time 15 h; chromatog-

raphy on C18 reversed-phase, eluent water−methanol (70:30). Thiocyanate **20**: 64 mg, 80%: mp 103−105 °C; IR_{max} (KBr) 2160 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 8.33 (1 H, s), 8.14 (1 H, s), 7.23 (2 H, s), 5.93 (1 H, d), 5.55 (1 H, d), 5.46 (1 H, d), 4.78 (1 H, m), 4.25 (1 H), 4.12 (1 H, m), 3.51 (2 H, m); ^{13}C NMR (50 MHz, DMSO-d_6) δ 156.0, 152.5, 149.2, 139.9, 119.2, 112.9 (SCN), 87.7, 82.5, 72.6, 72.3, 35.7; LRMS (DCI+, NH_3 + isobutane) m/z = 309 $[M + H]^+$, 136 [adenine + H]$^+$; HRMS (FAB$^+$, MCA) calcd for $[C_{11}H_{12}O_3N_6S + H]^+$ 309.0770, found 309.0788. Anal. Calcd for $C_{11}H_{12}O_3N_6S \cdot {}^2/_3H_2O$: C, 41.24; H, 4.20; N, 26.24; S, 10.01. Found: C, 41.41; H, 4.17; N, 25.92; S, 10.29.

Bis(2′-deoxyuridin-2′-yl) Disulfide 21. To a solution of the silyl sulfide **13** (200 mg; 0.55 mmol) in dichloromethane (3 mL) was added a cyanogen bromide solution in dichloromethane (3 M; 0.7 mL; 2.1 mmol) at reflux under nitrogen. The resulting solution was stirred for 48 h at 40 °C. From this solution, the disulfide **21** precipitated slowly. After evaporation, the residue was dissolved in water, and the disulfide **21** was chromatographed on a reversed-phase column (C_{18}-Sep-Pak, 10 g cartridge) in water−methanol (90:10) (98 mg; 0.19 mmol; 70%): mp 160−163 °C (lit.[5,20b] mp 157−158 °C, lit.[20a] mp 161−164 °C); ^1H NMR (200 MHz, DMSO-d_6) δ 11.29 (1 H, s), 7.76 (1 H, d), 6.15 (1 H, d), 5.74 (1 H, d), 5.67 (1 H, d), 5.04 (1 H, t), 4.15 (1 H, m), 3.81 (1 H, m), 3.53 (2 H, m); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.0; 150.8; 140.5; 102.4; 87.8; 86.6; 72.1; 61.3; 55.3; LRMS (FAB+, glycerol) m/z = 519 $[M + H]^+$.

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Supporting Information Available: ^1H and ^{13}C NMR data for all compounds synthesized and conditions for the study of cyanogen bromide cleavage of the model sulfides by HPLC (Figure 2). This material is available free of charge via the Internet at http://pubs.acs.org.

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