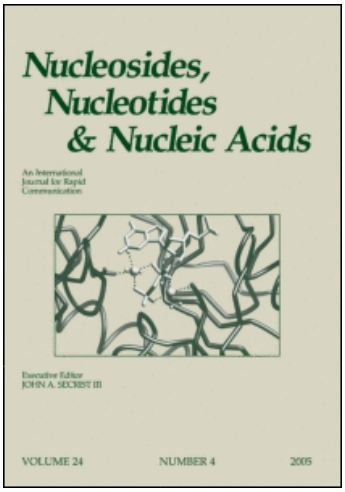

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Synthetic Studies with Thiosugar Nucleosides[1]

G. Wayne Craig[a]; John G. Moffatt[a]
[a] Institute of Bio-Organic Chemistry, Palo Alto, CA

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SYNTHETIC STUDIES WITH THIOSUGAR NUCLEOSIDES[1]

G. Wayne Craig and John G. Moffatt*
Institute of Bio-Organic Chemistry, Syntex Research
Palo Alto, CA 94304

ABSTRACT

Reactions using tri-n-butylphosphine and dialkyldisulfides have been investigated for the synthesis of several types of thiosugar nucleosides. Thus the reaction of N^6-benzoyl-2',3'-O-isopropylideneadenosine with a large excess of diisobutyldisulfide leads, after simple deprotection, to the transmethylation inhibitor SIBA (3) in quite good yield. Using limiting amounts of disulfide, the reaction leads instead to a pyrimidine ring-opened cyclonucleoside (11). The hydrate of 2',3'-O-cyclohexylideneuridine 5'-aldehyde reacts with the same reagents to give a 77% yield of the corresponding diisobutyl dithioacetal. The hydrate of N^6-benzoyl-2',3'-O-isopropylideneadenosine 5'-aldehyde, however, gave only a single diastereomer of the 5'-alkylthio derivative of 11.

In a recent paper[2] we have described the synthesis of variously protected and free dithioacetals (1) derived from nucleoside 5'-aldehydes. Appropriate derivatives in the adenosine series were then efficiently converted into the structurally unique vinylthioether (2), which shares structural features of the transmethylation inhibitors 5'-isobutylthio-5'-deoxyadenosine (SIBA, 3)[3] and the sinefungin related fungal metabolite A9145C (4).[4,5]

While seemingly trivial, the conversion of appropriately substituted nucleoside 5'-aldehydes[6] into simple dithioacetals proved to be more difficult than expected. Simple acid catalyzed reactions with thiols gave very poor yields, but Lewis acid promoted condensations with alkylthiotrimethylsilanes[7] were relatively successful although isolated yields of pure products were still only in the 50% range. Even using these methods the reactions were quite dependent upon the nature of the alkylthio group, giving dimethyl thioacetals

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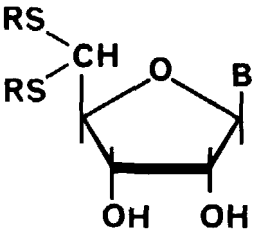

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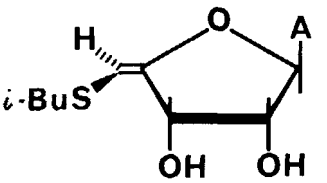

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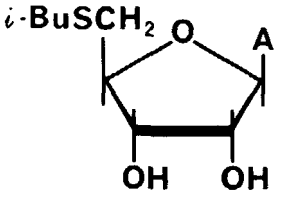

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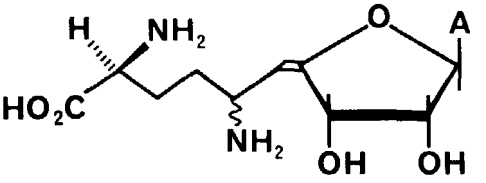


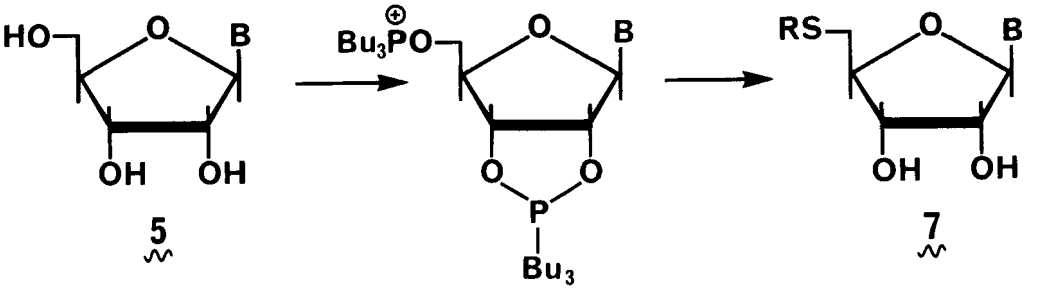
4

quite readily with trimethylsilyl triflate catalysis. Extension to even the diisobutyl thioacetal analogs, however, required the use of trimethylsilyl triflate together with traces of zinc iodide or triflic acid. The nature of the aglycone was also significant, 2',3'-O-cyclohexylideneuridine 5'-aldehyde being converted to the dimethyl thioacetal using methylthiotrimethylsilane in the presence of zinc iodide alone while the more basic N^6-benzoyl-2',3'-O-isopropylideneadenosine 5'-aldehyde did not react satisfactorily under these conditions and required trimethylsilyl triflate catalysis.

In the course of the above work we also briefly explored several tributylphosphine mediated reactions for the preparation of thioether or thioacetal derivatives of nucleosides, and these are the subject of this paper.

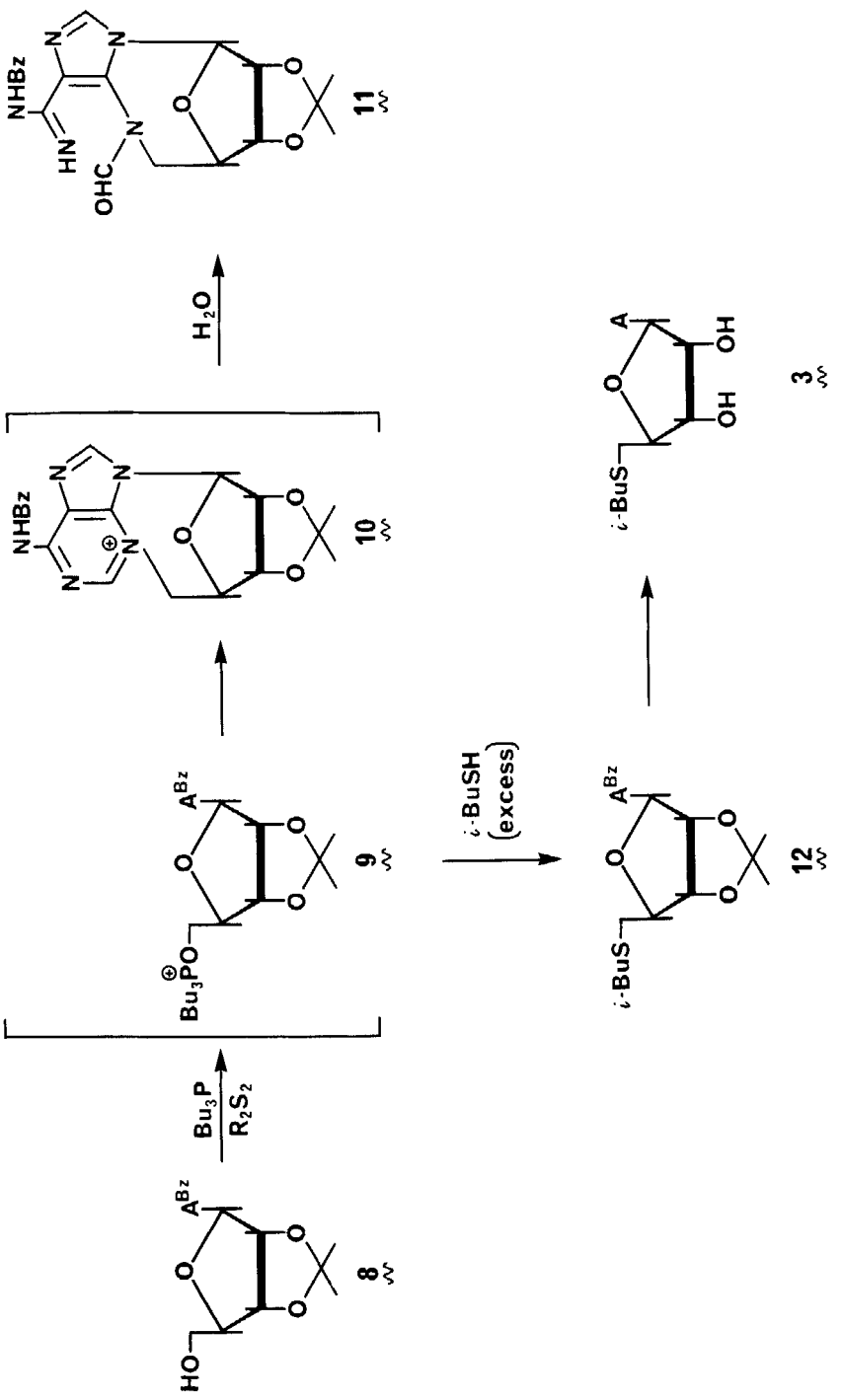
In order to evaluate the biological properties of 2, it was necessary to prepare a reference sample of 5'-deoxy-5'-(isobutylthio)adenosine (SIBA, 3). Originally this compound was prepared[3]

using the general method of Baddiley and Jamieson[8] via reaction of 2',3'-O-isopropylidene-5'-O-tosyladenosine with the sodium salt of isobutylthiol in liquid ammonia followed by acidic hydrolysis. More recently, a potentially attractive method for the preparation of 5'-alkylthio-5'-deoxynucleosides (7) was described by Nakagawa, et al.,[9] via direct reaction of free nucleosides (5) with disulfides and tri-n-butylphosphine. Most of the examples cited utilized di-2-pyridyldisulfide in pyridine and gave quite good yields of the corresponding 5'-deoxy-5'-2-pyridylthionucleosides (7, R = 2-pyridyl) after 1-24 hr reaction at room temperature. The single example of a simple dialkyldisulfide, however, was that of the reaction of dimethyldisulfide with adenosine and tri-n-butylphosphine in dimethylformamide, which gave the desired 5'-deoxy-5'-methylthioadenosine (7, R = Me) in only 38% yield after 10 days reaction. Such reactions are presumed to proceed via the 5'-oxyphosphonium intermediate 6 in which the 2'- and 3'-hydroxyl groups are blocked as a cyclic dioxyphosphorane. Similar intermediates have been recognized in related reactions by Kimura, et al.[10]



5 6 7

It occurred to us that the synthesis of compounds related to SIBA (3) by this route might well be substantially improved by using a readily available protected derivative rather than adenosine itself. The use of 2',3'-O-isopropylideneadenosine was ruled out by the known ease of formation of the N^3,5'-cyclonucleoside upon

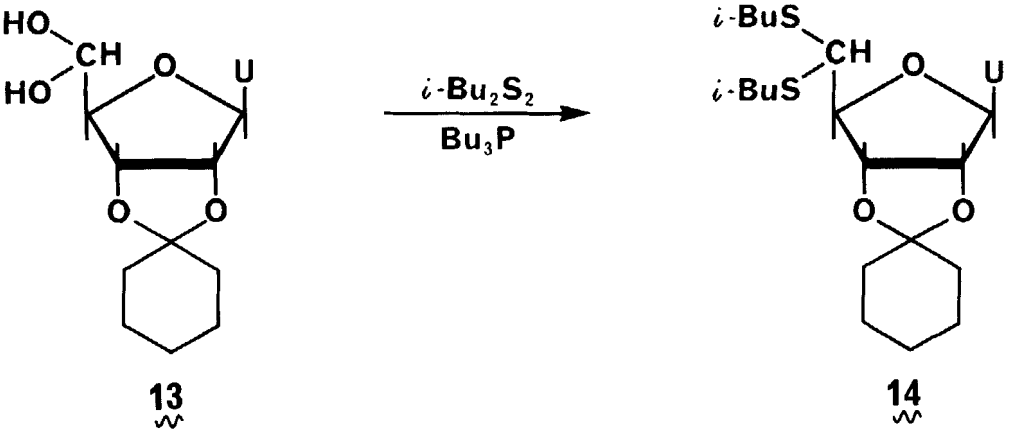


generation of a 5'-oxyphosphonium intermediate in this series.[11] It is, however, known that the propensity for cyclonucleoside formation is greatly reduced by acylation of the amino group on the adenine ring.[12] Hence we reacted N^6-benzoyl-2',3'-O-isopropylideneadenosine (8)[6b] with an excess of both di-n-butyldisulfide and tri-n-butylphosphine in dimethylformamide at room temperature for 12 hr. The major product, isolated in crystalline form in 71% yield following chromatography on silica gel, proved to be the pyrimidine ring-opened cyclonucleoside (11) that was physically and spectroscopically identical to the previously characterized product.[12b,13] Clearly, as was the case in the mechanistically related reaction of 8 with methyltriphenoxyphosphonium iodide in dimethylformamide,[12b] generation of the initial 5'-oxyphosphonium intermediate (9) led to intramolecular displacement giving the N^3,5'-cyclonucleoside 10 despite the deactivating influence of the N^6-benzoyl group. Such N^6-acyl-N^3,5'-cycloadenosine derivatives are known to be hydrolytically sensitive, readily leading to the observed N-formyl product 11.[12b]

Qualitatively similar results were obtained using diisobutyldisulfide, and it was hoped that by doing the reaction in a less polar solvent[12b] and in the presence of excess isobutylthiol, intermediate 9 could be driven to the desired thioether 12. In methylene chloride, however, the reaction was very slow, and even in a mixture of methylene chloride and dimethylformamide the reaction had to be heated to 60° to see accumulation of the desired product. Better results were obtained using a mixture of dimethylformamide and isobutylthiol (1:4) as the solvent, and after 2 days at room temperature the desired crystalline N^6-benzoyl-5'-deoxy-5'-isobutylthio-2',3'-O-isopropylideneadenosine (12) was isolated in 57% yield as a crystalline solid following chromatography. A 9% yield of 11 was also isolated from this reaction. It is interesting that the 300 MHz ^{1}H-NMR spectrum of 12 shows the methyl groups of the isobutyl moiety as a pair of doublets (J = 6.6 Hz) centered at 0.94 and 0.95 ppm, indicating a hindrance to rotation, presumably by the purine ring. Deprotection of 12 was achieved by sequential treatment with 90% trifluoroacetic acid and ammonium hydroxide

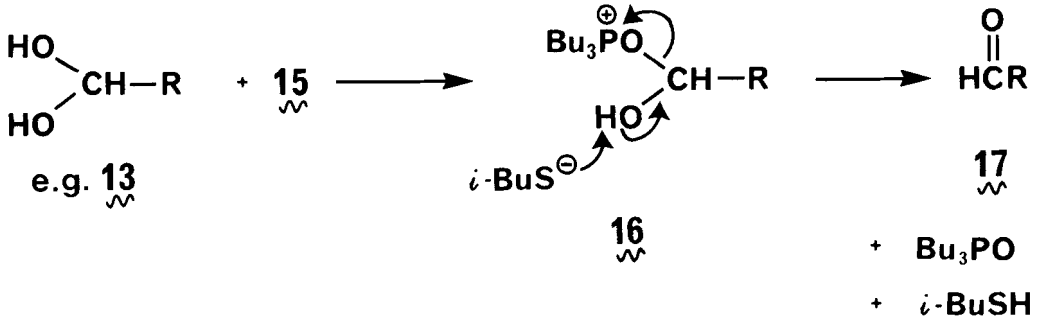
giving a 92% yield of crystalline SIBA (3) with physical properties similar to those in the literature.[3] Removal of the protecting groups almost completely restores free rotation, the terminal methyl groups now appearing as only a slightly broadened doublet. The above method provides a fairly convenient alternative to the published synthesis of SIBA, a compound which has proved to exhibit a broad array of biological activities based upon its ability to inhibit S-adenosylhomocysteine hydrolase and thus S-adenosylmethionine mediated transmethylation.[5,14]

In our previous work we showed that 2',3'-O-cyclohexylideneuridine 5'-aldehyde (13) could be converted into its 5'-diisobutylthioacetal derivative (14) through reaction with isobutylthiotrimethylsilane, zinc iodide and trimethylsilyl triflate in an isolated yield of 45%. Since the aldehyde occurs as a stable hydrate (13) that can be azeotropically dehydrated to the free aldehyde,[6a] we considered the possibility that treatment of 13 under the conditions of Nakagawa, et al.,[9] could lead sequentially to the dithioacetal (14). Indeed, treatment of 13 with excess diisobutyldisulfide and tributylphosphine in dimethylformamide at room temperature for 8 hr led to the isolation of 14, identical to that described earlier,[1] in a yield of 77% following chromatography on silica gel. This clearly constitutes a substantial improvement in the synthesis of that compound.



13 14

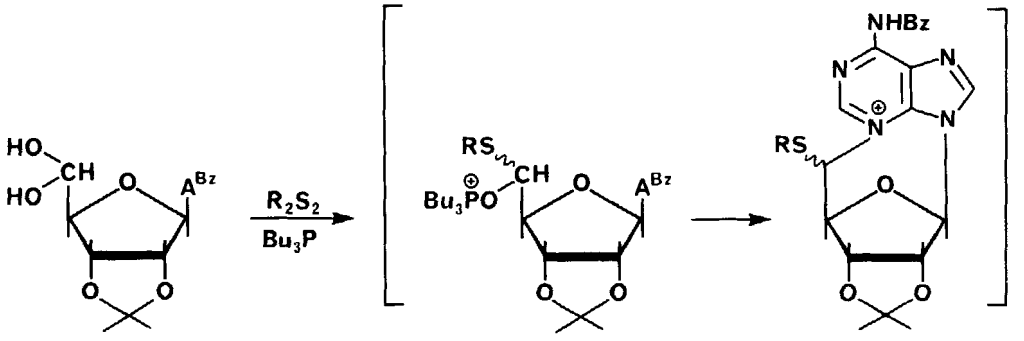
After completing this reaction we realized that Tazaki and Takagi[15] have already briefly described the conversion of free aldehydes to dithioacetals using dialkyldisulfides and tributylphosphine in the absence of solvent. Their proposed mechanism suggests a nucleophilic attack of the thiolate anion in the initial complex $Bu_3\overset{\oplus}{P}-SR\ \overset{\ominus}{S}R$ (15) upon the carbonyl group as an early event and would appear to be inoperable with the aldehyde hydrate. It is entirely possible, however, that the initial adduct (16) from the hydrate and 15 could lose tributylphosphine oxide to generate the free aldehyde (17), which could then participate in the Tazaki and Takagi mechanism. We have not sought a clarification as to which mechanism actually occurs.



An attempt to extend this reaction into the adenosine series led to quite different results. Thus reaction of the hydrate of N^6-benzoyl-2',3'-O-isopropylideneadenosine 5'-aldehyde (18) with excess of both diisobutyldisulfide and tributylphosphine in dimethylformamide at room temperature led to one major product which was isolated in crystalline form in 65% yield by chromatography on silica gel. The ultraviolet and NMR spectra of this compound showed that it was undoubtedly the 5'-isobutylthio derivative (20a) of the previously obtained ring-opened cyclonucleoside (11). The ultraviolet spectra of 11 and 20a were essentially identical, while the ^{1}H-NMR spectra were very similar except that one of the extremely magnetically non-equivalent $C_{5'}$-protons in 11 was missing and was replaced by an isobutylthio group. The ^{13}C-NMR spectrum was also confirmatory of this structure. A similar reaction using di-n-

butyldisulfide gave the related crystalline cyclonucleoside 20b in 58% yield. An extraordinary feature of these reactions is that in each case only a single $C_{5'}$-diastereomer was apparent in the NMR spectra, although we cannot rule out the removal of a minor second isomer during crystallization. The 300 MHz ^{1}H-NMR spectra of 20a and 20b show $C_{4'}$H and $C_{5'}$H as clean doublets with a value of $J_{4',5'}$ of 2.2 Hz, suggesting a dihedral angle of roughly 60° or 120° if one does not consider the effects due to electronegative substituents.[16] An examination of Dreiding models of 20 shows that largely unhindered conformers of the "anhydro" ring can be achieved with either diastereomer. The isomer with the S-configuration at $C_{5'}$ can adopt unhindered conformers with dihedral angles of roughly 120° or 30°, while that with the $C_{5'}$-R configuration can only adopt a 90° angle if major hindrance is to be avoided. Based upon this, we tentatively assign the S-configuration to $C_{5'}$ in the isolated products 20a and b.

There are clearly several different sequences of steps through either the aldehyde hydrate (18) or its dehydration product (as in 13 → 17) that can lead to the 5'-functionalized cyclonucleoside 19 and thence, by rapid hydrolysis, to the observed product 20. We have not as yet explored modified reaction conditions, such as those employed in the preparation of 14, in order to subvert the above pathway and permit conversion of 18 into the related thioacetals since the latter compounds are readily available by other routes.[2] The use of phosphorus based reagents in the synthesis of other thiosugar nucleosides remains an interesting area of research.



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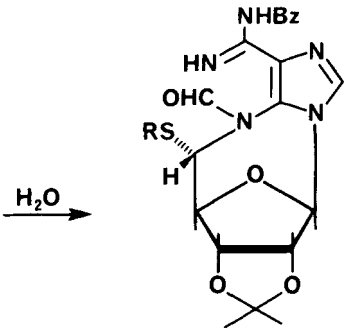

20(a) R = *i*-Bu
(b) R = *n*-Bu

EXPERIMENTAL

The spectroscopic and analytical methodology used in this work is essentially as described in previous work.[2] We are grateful to the staff of the Analytical Research Laboratories of Syntex Research for their input, and in particular to Dr. M. L. Maddox and Mrs. J. Nelson for their considerate help with NMR spectroscopy.

5'-N^5-Anhydro-4-(N-benzoylformamidino)-5-formamido-1-(2,3-O-isopropylidene-β-D-ribofuranosyl)imidazole (11).

A solution of N^6-benzoyl-2',3'-O-isopropylideneadenosine (8, 411 mg, 1 mmol),[6b] tri-n-butylphosphine (2.5 mL, 10 mmol), and diisobutyldisulfide (1.9 mL, 10 mmol) in dimethylformamide (10 mL) was stirred under nitrogen at room temperature for 12 hr. The mixture was then partitioned between chloroform and brine and the organic phase was washed with water, dried ($MgSO_4$), evaporated and chromatographed on silica gel using chloroform-ethyl acetate (3:1) giving 292 mg (71%) of 11 with mp 239-240° (gas evolution) from methanol-chloroform (reported mp 236°,[12b] 245°[13]): $[\alpha]_D^{25}$ -178.2° (c 0.27, $CHCl_3$); λ_{max} (MeOH) 264 nm (ε 15,000), 306 (16,000); NMR (d_6-DMSO) 1.28 and 1.46 ppm (s, 3, CMe_2), 3.07 (dd, 1, $J_{4',5'a}$ = 0.5 Hz, J_{gem} = 14.4 Hz, $C_{5'a}H$), 4.58 (d, 1, $J_{2',3'}$ = 5.8 Hz, $C_{3'}H$), 4.77 (br s, 1, $C_{4'}H$), 4.90 (dd, 1, $J_{4',5'b}$ = 2.2 Hz, $C_{5'b}H$), 5.03 (d, 1, $C_{2'}H$), 6.26 (s, 1, $C_{1'}H$), 7.3-8.05 (m, 5, Bz), 8.09 (s, C_2H), 8.43 (s, 1, NCHO), 8.80, 10.30 (br s, 1, NH). Calcd. for $C_{20}H_{21}N_5O_5$ (411.41): C, 58.38; H, 5.15; N, 17.02. Found: C, 58.15; H, 5.19; N, 16.95.

N^6-Benzoyl-5'-deoxy-5'-isobutylthio-2',3'-O-isopropylidene-adenosine (12).

A solution of 8 (300 mg, 0.73 mmol), tri-n-butylphosphine (1.8 mL, 7.2 mmol), and diisobutyldisulfide (1.3 mL, 7.2 mmol) in a mixture of dimethylformamide (1 mL) and isobutylthiol (4 mL) was stirred under nitrogen for 2 days at room temperature. The mixture was partitioned between chloroform and water and the organic phase was washed with water, dried (Na_2SO_4) and evaporated to dryness. The residue was chromatographed on silica gel using hexane-chloroform (2:1) to remove excess sulfides, etc., followed by a gradient of 1 to 5% methanol in methylene chloride giving 27 mg (9%) of 11 and 201 mg (57%) of 12 with mp 220° (d) from ethanol: λ_{max} (MeOH) 233 nm (ε 11,200), 280 (18,300); NMR ($CDCl_3$) 0.94, 0.95 ppm (d, 3, J = 6.6 Hz, $CH\underline{Me}_2$), 1.42, 1.64 (s, 3, CMe_2), 1.78 (m, 1, $\underline{CH}Me_2$), 2.40 (d, 2, J = 6.9 Hz, SCH_2), 2.76 (dd, 1, $J_{4',5'a}$ = 6.2 Hz, J_{gem} = 13.5 Hz, $C_{5'a}H$), 2.84 (dd, 1, $J_{4',5'b}$ = 7.3 Hz, $C_{5'b}H$), 4.44 (m, 1, $C_{4'}H$), 5.06 (dd, 1, $J_{2',3'}$ = 6.4 Hz, $J_{3',4'}$ = 3.1 Hz, $C_{3'}H$), 5.52 (dd, 1, $J_{1',2'}$ = 2.3 Hz, $C_{2'}H$), 6.15 (d, 1, $C_{1'}H$), 7.5-8.1 (m, 5, Bz), 8.18, 8.83 (s, 1, C_2H, C_8H), 9.1 (br s, 1, NH). Calcd. for $C_{24}H_{29}N_5O_4S$ (483.47): C, 59.57; H, 6.05; N, 14.48. Found: C, 59.44; H, 6.16; N, 14.21.

5'-Deoxy-5'-isobutylthioadenosine (3).

A solution of 12 (100 mg, 0.2 mmol) in 90% trifluoroacetic acid (10 mL) was kept at room temperature for 30 min and then neutralized with aqueous bicarbonate. The mixture was extracted into chloroform, washed with water, dried and evaporated. The residue was dissolved in methanol (3 mL) and tetrahydrofuran and conc. ammonium hydroxide (1 mL) was added. After storage overnight the mixture was evaporated to dryness and chromatographed on silica gel using methylene chloride-methanol (9:1) giving 62 mg (92%) of 3 with mp 127-128° from ethanol (reported[3] mp 126-128°); $[\alpha]_D^{25}$ 2.6° (c 0.15, $CHCl_3$); λ_{max} (MeOH) 259 nm (ε 14,100); NMR ($CDCl_3$-d_4-MeOH) 0.98 ppm (d, 6, J = 6.7 Hz, $CH\underline{Me}_2$), 1.82 (m, 1, $\underline{CH}Me_2$), 2.49 (d, 2, J = 6.9 Hz, SCH_2), 2.88 (dd, 1, $J_{4',5'a}$ = 5.2 Hz, J_{gem} = 14.1 Hz, $C_{5'a}H$),

3.00 (dd, 1, $J_{4',5'b}$ = 4.6 Hz, $C_{5'b}H$), 4.30 (m, 2, $C_{3'}H$, $C_{4'}H$), 4.53 (dd, 1, $J_{1',2'}$ = 3.9 Hz, $J_{2',3'}$ = 4.6 Hz, $C_{2'}H$), 5.97 (d, 1, $C_{1'}H$), 8.19, 8.26 (s, 1, C_2H, C_8H). Calcd. for $C_{14}H_{21}N_5O_3S \cdot 0.5\ H_2O$ (348.43): C, 48.26; H, 6.36; N, 20.10. Found: C, 48.40; H, 6.39; N, 19.75.

2',3'-O-Cyclohexylidene-5'-deoxy-5'-bis(isobutylthio)uridine (14). A solution of 13 (200 mg, 0.59 mmol),[6a] diisobutyldisulfide (1.1 mL), and tri-n-butylphosphine (1.4 mL) in dimethylformamide (3 mL) was stirred under nitrogen for 8 hr and then partitioned between chloroform and brine. The organic phase was washed with water, dried and evaporated. The resulting oil was filtered through a pad of silica gel in methylene chloride and then subjected to Chromatotron[17] chromatography on silica gel using methylene chloride giving 220 mg (77%) of 14 as a homogeneous foam identical chromatographically and spectroscopically to that prepared by a different route.[2]

5',N^5-Anhydro-4-N-benzoylformamidino-5-formamido-5'-(S)-isobutylthio-1-(2,3-O-isopropylidene-β-D-ribofuranosyl)imidazole (20a). A solution of the aldehyde hydrate 18 (260 mg, 0.6 mmol), tri-n-butylphosphine (1.53 mL, 6.2 mmol), and diisobutyldisulfide (1.15 mL, 6.2 mmol) in dimethylformamide (3.5 mL) was stirred under nitrogen for 12 hr and then partitioned between chloroform and brine. The organic phase was washed with water, dried and evaporated. The residue was chromatographed on silica gel using methylene chloride to give 195 mg (65%) of 20a with mp 183-184° from methanol-chloroform: $[\alpha]_D^{25}$ 138° (c 0.6, $CHCl_3$); λ_{max} (MeOH) 266 nm (ε 14,000), 307 (16,100); ^{1}H-NMR ($CDCl_3$) 0.54, 0.58 ppm (d, 3, J = 6.7 Hz, $CH\underline{CH}_3$), 1.32, 1.53 (s, 3, CMe_2), 1.55 (m, 1, $\underline{CH}Me_2$), 2.52 (m, 2, CH_2S), 4.74, 4.79 (d, 1, $J_{2',3'}$ = 5.6 Hz, $C_{2'}H$, $C_{3'}H$), 4.83 (d, 1, $J_{4',5'}$ = 2.2 Hz, $C_{4'}H$), 5.88 (s, 1, $C_{1'}H$), 6.14 (d, 1, $C_{5'}H$), 7.35-7.5 and 8.15 (m, 5, Bz), 7.59 (s, 1, C_2H), 8.89 (s, 1, NCHO), 7.98, 10.80 (br s, 1, NH); ^{13}C-NMR ($CDCl_3$) 21.22, 21.75 ($CHMe_2$), 24.71, 26.17 ($O_2C\underline{Me}_2$), 27.99 ($\underline{CH}Me_2$), 39.01 (CH_2S), 59.24 ($C_{5'}$), 82.54 ($C_{3'}$), 85.01 ($C_{2'}$), 89.27 ($C_{4'}$), 91.70 ($C_{1'}$), 113.78

($O_2\underline{C}Me_2$), 128-137 (Arom.), 134.07 (C_2), 161.64 (CO), 164.46 (CHO), 181.50 (NC=N). Calcd. for $C_{24}H_{29}N_5O_5S$ (499.26): C, 57.71; H, 5.81; N, 14.03. Found: C, 57.64; H, 5.81; N, 13.95.

5',N^5-Anhydro-4-N-benzoylformamidino-5-formamido-5'-(S)-n-butylthio-1-(2,3-O-isopropylidene-β-D-ribofuranosyl)imidazole (20b).

A reaction between 18 (260 mg, 0.6 mmol), di-n-butyldisulfide (1.15 mL, 6.2 mmol) and tri-n-butylphosphine (1.53 mL, 6.2 mmol) in dimethylformamide (3.5 mL) for 8 hr at room temperature was worked up as for 20a. Crystallization from chloroform-methanol gave 174 mg (58%) of 20b with mp 193-194°: $[\alpha]_D^{25}$ 105° (c 0.57, $CHCl_3$); λ_{max} (MeOH) 266 nm (ε 12,700), 307 (14,500); ^{1}H-NMR ($CDCl_3$) 0.63 ppm (t, 3, J = 7.3 Hz, CH_3), 0.9, 1.3 (m, 2, CH_2's), 1.32, 1.52 (s, 3, CMe_2), 2.48, 2.69 (m, 1, SCH_2), 4.72, 4.79 (d, 1, $J_{2',3'}$ = 5.6 Hz, $C_{2'}H$, $C_{3'}H$), 4.82 (d, 1, $J_{4',5'}$ = 2.2 Hz, $C_{4'}H$), 5.88 (s, 1, $C_{1'}H$), 6.18 (d, 1, $C_{5'}H$), 7.35-7.5, 8.1 (m, 5, Bz), 7.59 (s, 1, C_2H), 8.86 (s, 1, CHO), 8.0, 8.8 (br s, 1, NH); ^{13}C-NMR ($CDCl_3$) 13.43, 21.41, 29.75, 31.00 (butyl), 24.70, 26.15 ($C\underline{Me}_2$), 58.68 ($C_{5'}$), 82.54 ($C_{3'}$), 85.00 ($C_{2'}$), 89.23 ($C_{4'}$), 91.68 ($C_{1'}$), 113.72 ($O_2\underline{C}Me_2$), 128-137 (Arom.), 133.90 (C_2), 161.50 (CO), 164.31 (CHO), 181.39 (N=C-N). Calcd. for $C_{24}H_{29}N_5O_5S$ (499.26): C, 57.71; H, 5.81; N, 14.03. Found: C, 57.72; H, 5.89; N, 13.82.

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