Structure-Activity Relationships of β-D-(2S,5R)- and α-D-(2S,5S)-1,3-Oxathiolanyl Nucleosides as Potential Anti-HIV Agents

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The β-D-(2S,5R)- and α-D-(2S,5S)-1,3-oxathiolanylpyrimidine and -purine nucleosides with natural nucleoside configuration were synthesized and evaluated against HIV-1 in human peripheral blood mononuclear (PBM) cells. The key intermediate **14**, which was utilized for the synthesis of various nucleosides, was synthesized from D-mannose or D-galactose. Condensation of the acetate **14** with thymine, uracil, cytosine, and 5-substituted uracils and cytosines gave various pyrimidine nucleosides. The acetate **14** was also condensed with 6-chloropurine and 6-chloro-2-fluoropurine which were converted to various purine nucleosides. In the case of thymine, uracil, and 5-substituted uracil derivatives, most of the compounds did not exhibit any significant anti-HIV activity except 5-fluorouracil (α-isomer) derivative **55**. Among 5-substituted cytosine analogues, 5-bromocytosine derivative (β-isomer) **68** was found to be the most potent anti-HIV agent. In the case of purine derivatives, inosine analogue (β-isomer) **78** was found to be the most potent anti-HIV agent in the 6-substituted purines and 2-amino-6-chloropurine derivative (β-isomer) **90** showed the most potent activity in the 2,6-disubstituted purine series. The β-isomers of 6-chloropurine (**74**), adenine (**76**), and N^6-methyladenine (**77**) derivatives showed similar potencies against HIV-1, and the corresponding α-isomers also exhibited significant anti-HIV activity, although they were generally less potent than the β-isomers.

Introduction

Since racemic dioxolanylthymine[1] and oxathiolanylcytosine[1,2] were first reported as potent anti-HIV agents, the syntheses of these compounds have been reported by Norbeck et al.[3] and Choi et al.[4] Our laboratories have been interested in the asymmetric syntheses and structure-activity relationships of both types of compounds. We have recently reported the enantiomeric syntheses of dioxolanylthymine and -cytosine as well as oxathiolanylcytosine utilizing various available carbohydrates, such as D-mannose,[5-8] D-galactose,[9] and L-gulose[10-12] (Figure 1).

From these studies, (−)-β-L-(2R,5S)-1,3-oxathiolanylcytosine,[10,13,15] the compound with the unnatural nucleoside configuration, was found to be more potent than its racemate[13] or (+)-β-D-(2S,5R)-isomer,[5] the compound with the natural nucleoside configuration, against HIV-1 in human peripheral blood mononuclear (PBM) cells. (−)-β-D-(2R,4R)-1,3-Dioxolanylthymine[6] was somewhat more or equally potent, compared to the (+)-β-L-(2S,4S)-isomer,[12] and it was less potent than (±)-1,3-dioxalanylthymine[6] in human PBM cells. 1,3-Dioxalanylcytosine showed a pattern similar to 1,3-oxathiolanylcytosine in that the (−)-β-L-(2S,4S)-enantiomer[12] with the unnatural nucleoside configuration was more potent than the (+)-β-D-(2R,4R)-enantiomer[7] with the natural nucleoside configuration.

On the basis of the above findings, our laboratories have reported the structure-activity relationships of various enantiomerically pure β-D-(2R,4R)- and α-D-(2R,4S)-1,3-dioxolanylpyrimidine[7] and purine[8] nucleosides. (+)-β-D-(2R,4R)-Dioxolanylcytosine was found to exhibit the most potent activity (EC_{50} = 0.016 μM) against HIV-1 among the pyrimidine series,[7] while (−)-β-D-(2R,4R)-dioxolanylguanine was the most potent compound (EC_{50} = 0.03 μM) among purine derivatives.[8]

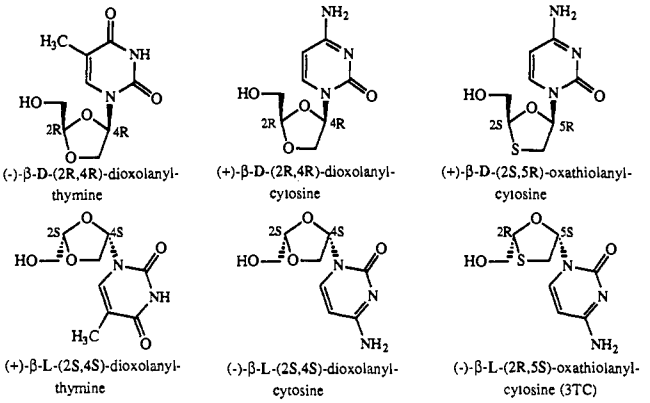

Figure 1. Structures of enantiomers of 1,3-dioxolanylthymine and -cytosine and 1,3-oxathiolanylcytosine.

We have also reported the syntheses of enantiomerically pure β-L-(2R,5S)- and α-L-(2R,5R)-1,3-oxathiolanylpyrimidine and purine nucleosides and their anti-HIV activities in human PBM cells,[11] in which (−)-β-L-(2R,5S)-oxathiolanylcytosine and -5-fluorocytosine were found to be excellent anti-HIV nucleosides (EC_{50} = 0.0018 and 0.0013 μM, respectively).[11] Among L-(2R,5S)-1,3-oxathiolanyl nucleosides, (−)-β-L-(2R,5S)-1,3-oxathiolanyl-5-fluorocytosine (FTC)[14] is undergoing preclinical toxicology and (−)-β-L-(2R,5S)-1,3-oxathiolanylcytosine (3TC)[15] is undergoing clinical trials.

Herein we wish to report the comprehensive structure-activity relationships of β-D-(2S,5R)- and α-D-(2S,5S)-1,3-

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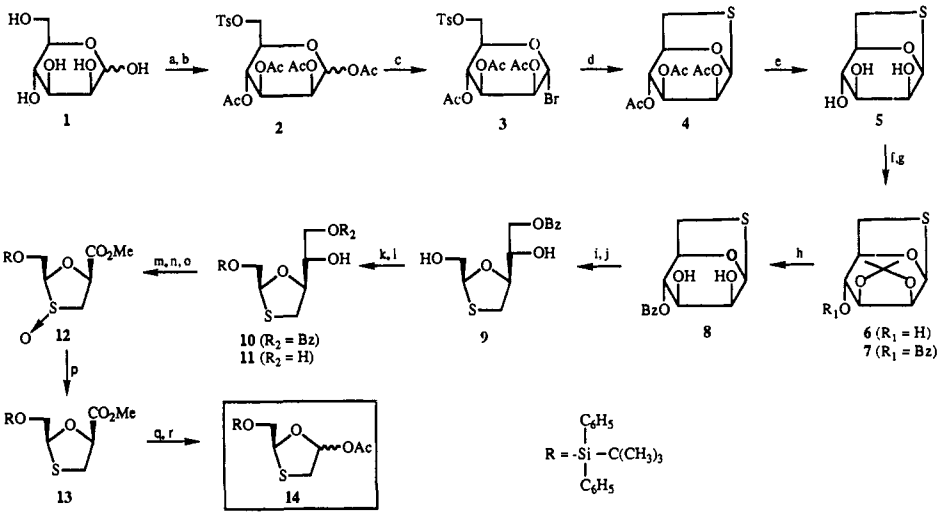
Scheme I[a]



[a] Reagents: (a) TsCl, pyridine, 0 °C; (b) Ac_2O, rt; (c) HBr, AcOH; (d) potassium *O*-ethylxanthate, DMF; (e) NH_4OH, MeOH; (f) $CH_3C(OMe)_2CH_3$, *p*-TsOH; (g) BzCl, pyridine; (h) 2% aqueous H_2SO_4/1,4-dioxane, 70 °C, (i) $Pb(OAc)_4$, EtOAc; (j) $NaBH_4$, EtOH; (k) *t*-$BuPh_2SiCl$, imidazole, DMF; (l) NH_4OH, MeOH; (m) $Pb(OAc)_4$, EtOAc; (n) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene; (o) $(CH_3)_2SO_4$, K_2CO_3, acetone; (p) $BHCl_2$, THF; (q) LiOH, THF–H_2O (4:1), (r) $Pb(OAc)_4$, pyridine, EtOAc.

oxathiolanyl nucleosides as potential anti-HIV agents. Furthermore, it was of interest to compare the anti-HIV activities of the D-(2*S*)-isomers[11] with those of L-(2*R*)-isomers.

Results and Discussion

The synthesis of key intermediate **14** starting from D-mannose (**1**) via 1,6-thioanhydro-D-mannopyranose (**5**) is shown in Scheme I.[5] D-Mannose (**1**) was converted in five steps to the 1,6-thioanhydro-D-mannopyranose (**5**), which possesses the desired 1,3-oxathiolanyl ring system as well as the desired stereochemistry. Selective tosylation of the primary hydroxyl group of D-mannose (**1**), peracetylation, and bromination afforded bromo sugar **3**. The bromo sugar **3** was treated with 3 molar equiv of potassium *O*-ethylxanthate in DMF to give 2,3,4-tri-*O*-acetyl-1,6-thioanhydro-D-mannopyranose (**4**). It was found that use of less than 2 molar equiv of potassium *O*-ethylxanthate afforded almost exclusively xanthate-substituted product, which can be further converted to the 1,6-thioanhydro-D-mannopyranose (**5**) by treatment with NaOMe. Treatment of compound **4** with NH_4OH gave the desired 1,6-thioanhydro-D-mannopyanose (**5**) in 39% yield from **3**.

Protection of the 2,3-cis diol of **5** as its isopropylidene derivative, benzoylation, and deprotection of isopropylidene group gave diol **8** (85% from **5**). Oxidative cleavage of **8** with $Pb(OAc)_4$ followed by reduction with $NaBH_4$ produced **9** after a secondary to primary benzoyl migration (97%). Selective silylation of **9** followed by debenzoylation with NH_4OH afforded diol **11** (83%). Treatment of the diol **11** with $Pb(OAc)_4$ gave an aldehyde, which was further treated with sodium chlorite[5] to obtain an acid derivative whose sulfur atom was oxidized (70%). Treatment of sulfoxide–acids with $Pb(OAc)_4$ failed to give the desired acetate, resulting in decomposition of the acid derivative. Therefore, the mixture of sulfoxide–acids was converted to their corresponding methyl esters **12** by treatment with dimethyl sulfate in order to facilitate the purification as well as the reduction of the sulfoxide to sulfide in organic solvent. The sulfoxide–esters **12** were then converted to sulfide **13** by reduction with dichloroborane[5]–dimethyl sulfide in anhydrous THF (80%). Hydrolysis of the ester **13** with LiOH in THF/H_2O (4:1) gave the acid, which was converted to the acetate **14** by treatment with $Pb(OAc)_4$.

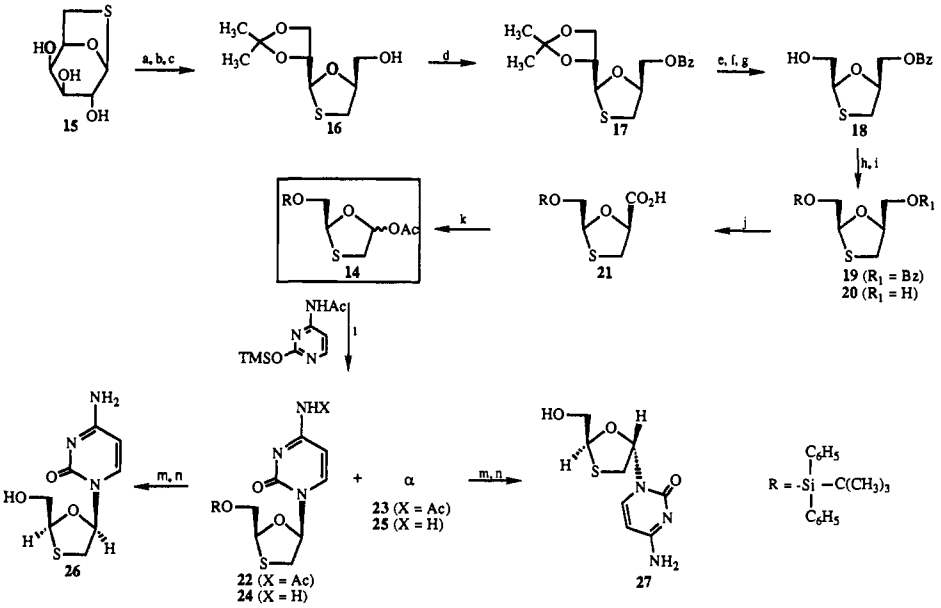
Although this approach resulted in an enantiomerically pure form of the acetate **14**, the synthetic steps were too lengthy and overall yield was not sufficiently high enough for large-scale synthesis. Thus, a more efficient and shorter synthetic route to the acetate **14** was developed starting from D-galactose (Scheme II).[9]

The key intermediate, 1,6-thioanhydro-D-galactopyranose (**15**),[16] is readily available in a preparative scale from D-galactose, and its use for the synthesis of the acetate **14** is illustrated in Scheme II.[9] Selective oxidative cleavage of 1,6-thioanhydro-D-galactopyranose (**15**) by $NaIO_4$ to the corresponding aldehyde and reduction with $NaBH_4$ followed by the protection of the resulting diol with 2,2-dimethoxypropane as an isopropylidene derivative yielded an 1,3-oxathiolane derivative **16** (79% from **15**). The primary hydroxyl group of **16** was benzoylated to give benzoate **17** (90%), which was converted to **18** by deprotection of the isopropylidene group with *p*-TsOH in MeOH at room temperature, oxidative cleavage of the resulting diol by $NaIO_4$ to the corresponding aldehyde, and reduction with $NaBH_4$ (80% from **17**). Silyl protection of **18** followed by debenzoylation of **19** with NaOMe in MeOH gave the silyl derivative **20** (95% from **18**). Treatment of **20** with pyridinium dichromate (PDC) in DMF[9] at room temperature gave crude acid **21** without oxidizing the sulfur of the ring, unlike $NaClO_2$ oxidation which produced a mixture of sulfoxides in the previously mentioned synthesis.[5] Without further purification, the acid **21** was converted to **14** with $Pb(OAc)_4$/pyridine in anhydrous THF (50% from **21**).[9]

Overall, this synthetic procedure afforded major advantages over the previously mentioned procedure starting from D-mannose,[5] including the large-scale preparation of key intermediate **15**, selective cleavage of the cis diol, and no sulfur oxidation during the preparation of the acid **21**.

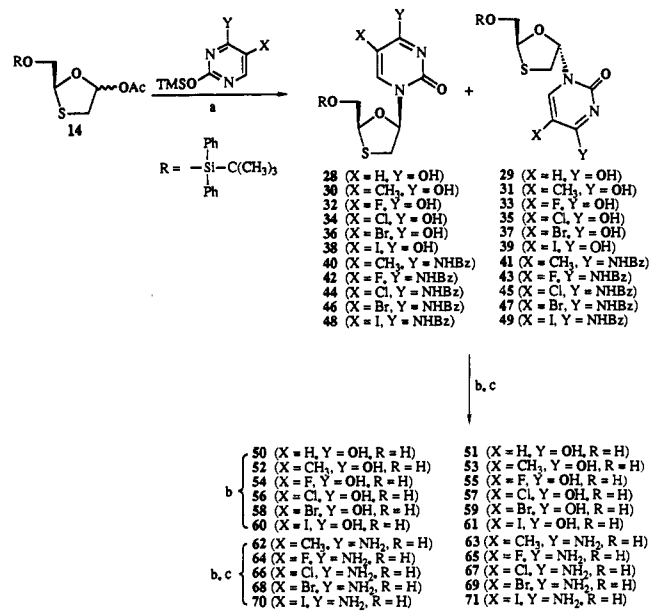
The acetate **14** was used for the synthesis of (+)-β-D-(2*S*,5*R*)-1,3-oxathiolanylcytosine and its α-isomer.[5,9] Condensation of **14** with silylated N^4-acetylcytosine in dry 1,2-dichloroethane in the presence of trimethylsilyl triflate gave a mixture of **22** (43%) and **23** (20%), which was

Scheme II[a]



[a] Reagents: (a) $NaIO_4$, $MeOH/H_2O$, 0 °C; (b) $NaBH_4$, $MeOH/H_2O$, 0 °C; (c) *p*-TsOH, acetone, rt; (d) BzCl, pyridine; (e) *p*-TsOH, MeOH, rt; (f) $NaIO_4$, 0 °C; (g) $NaBH_4$, 0 °C; (h) *t*-$BuPh_2SiCl$, DMF, imidazole; (i) NaOMe, MeOH, rt; (j) PDC, DMF, rt; (k) $Pb(OAc)_4$, THF, rt, (l) TMSOTf, $ClCH_2CH_2Cl$; (m) NH_3, MeOH; (n) *n*-Bu_4NF, THF.

Scheme III[a]



[a] Reagents: (a) TMSOTf, $ClCH_2CH_2Cl$, rt; (b) *n*-Bu_4NF, THF, rt; (c) NH_3, MeOH, rt.

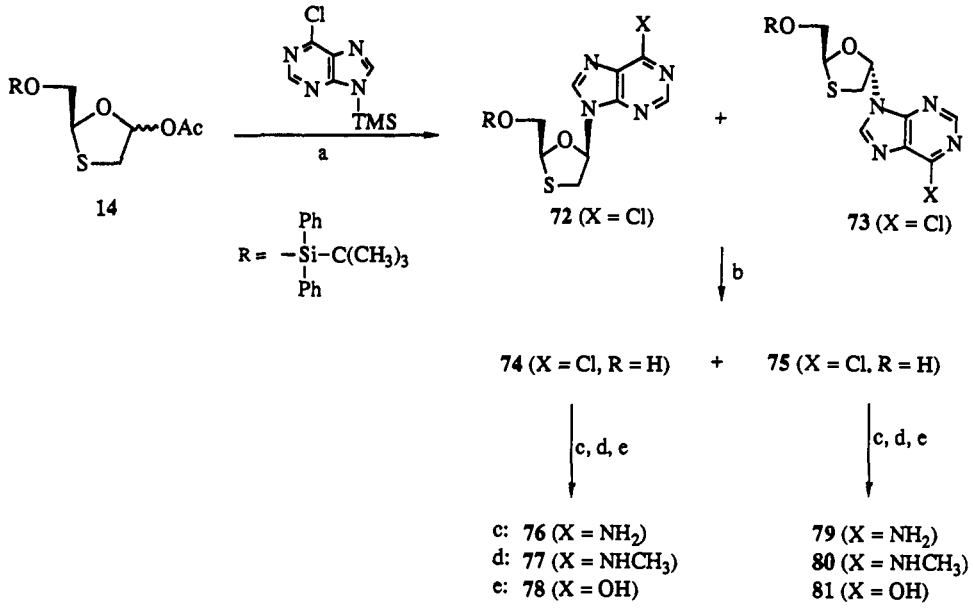
purified by silica gel column chromatography. Deacetylation of **22** and **23** with NH_3 in MeOH gave **24** and **25**, which were desilylated with tetra-*n*-butylammonium fluoride to give the desired (+)-β-D-(2*S*,5*R*)-1,3-oxathiolanylcytosine (**26**) and its α-isomer, (−)-α-D-(2*S*,5*S*)-1,3-oxathiolanylcytosine (**27**), respectively.

The synthesis of β-D-(2*S*,5*R*)- and α-D-(2*S*,5*S*)-1,3-oxathiolanylpyrimidine nucleosides **50–71** is illustrated in Scheme III. Condensation of **14** with silylated uracil, thymine, and 5-halouracils in the presence of TMSOTf afforded the fully protected (2*S*,5*RS*)-1,3-oxathiolanyluracil, -thymine, and -5-halouracil nucleosides **28–39** as inseparable α,β-anomeric mixtures. The protected nucleosides **28–39** were desilylated using tetra-*n*-butylammonium fluoride in THF and purified by silica gel column chromatography to give the final nucleosides **50–61**. The acetate **14** was also condensed with silylated N^4-benzoyl-5-substituted cytosines[11] to give β-D-(2*S*,5*R*)- and α-D-(2*S*,5*S*)-1,3-oxathiolanyl-5-substituted cytosine nucleosides **40–49**. Desilylation of the fully protected nucleosides **40–49** by tetra-*n*-butylammonium fluoride followed by debenzoylation using methanolic ammonia yielded the desired β-D-(2*S*,5*R*)- and α-D-(2*S*,5*S*)-1,3-oxathiolanyl-5-substituted cytosine nucleosides **62–71**.

The general synthetic route to β-D-(2*S*,5*R*)- and α-D-(2*S*,5*S*)-1,3-oxathiolanyl-6-substituted purine nucleosides **74–81** is shown in Scheme IV. The condensation of acetate **14** with silylated 6-chloropurine followed by desilylation afforded β-D-(2*S*,5*R*)- and α-D-(2*S*,5*S*)-1,3-oxathiolanyl-6-chloropurine nucleosides **74** and **75** which served as versatile intermediates for the synthesis of ddA, ddI, and N^6-MeddA derivatives. During the condensation, the initially formed N-3 adducts were converted to N-9 isomers while stirring overnight.[8,11] The 6-chloropurine derivative **74** was converted to the adenine derivative **76** by treatment with methanolic ammonia at 90 °C. Treatment of **74** with methylamine in methanol at 85 °C yielded N^6-methyladenine analogue **77**. The inosine derivative **78** was synthesized from **74** by refluxing with sodium methoxide and 2-mercaptoethanol in methanol. The corresponding α-anomers **79–81** were synthesized by procedures analogous to those used for the preparation of **76–78**.

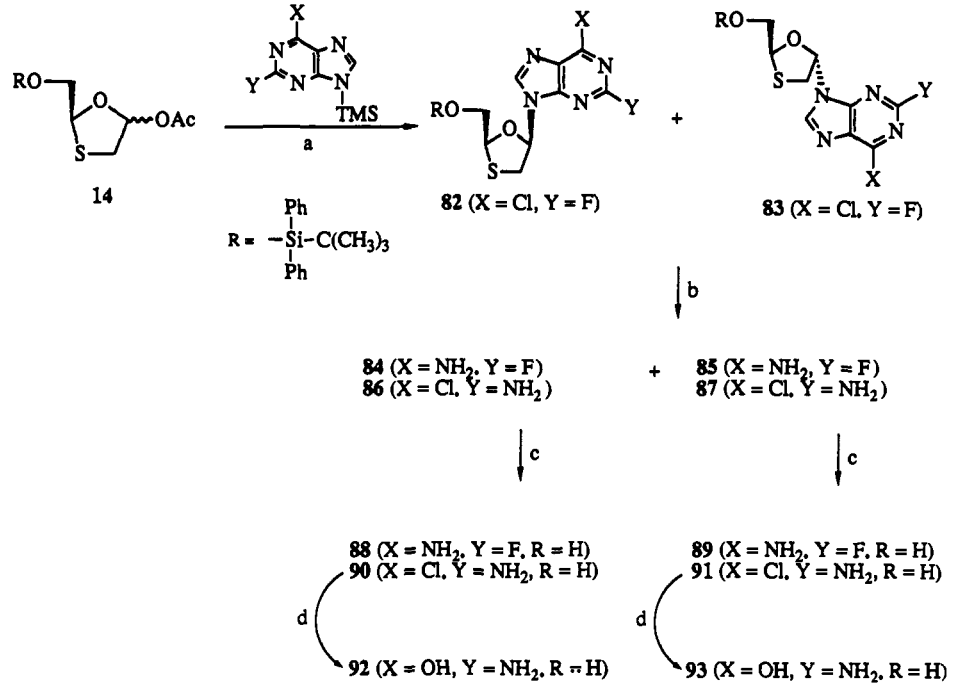
The acetate **14** was also used for the synthesis of 2,6-disubstituted purine analogues such as guanine derivative **92** (Scheme V). Condensation of the acetate **14** with 2-fluoro-6-chloropurine[17] gave an inseparable anomeric mixture of **82** and **83**. Similar to the case of 6-chloropurine, rearrangement of N-3 isomers to N-9 isomers occurred while refluxing for 4 h.[8,11] Bubbling ammonia into the mixture of **82** and **83** in DME at room temperature produced two pairs of α and β anomers **84–87**. The protected nucleosides **84** and **85** were separately treated with tetra-*n*-butylammonium fluoride to give β-D-(2*S*,5*R*)- and α-D-(2*S*,5*S*)-1,3-oxathiolanyl-2-fluoroadenine[18] nucleosides **88** and **89**. The anomeric mixture of 2-amino-6-chloro derivatives **86** and **87** was desilylated using tetra-

Scheme IV[a]



[a] Reagents: (a) TMSOTf, $ClCH_2CH_2Cl$, −20 °C to rt; (b) *n*-Bu_4NF, THF, rt; (c) NH_3, MeOH, 80–90 °C; (d) NH_2CH_3, MeOH, 80–90 °C; (e) NaOMe, $HSCH_2CH_2OH$, MeOH, reflux.

Scheme V[a]



[a] Reagents: (a) TMSOTf, $ClCH_2CH_2Cl$, −20 °C to reflux; (b) NH_3, DME, rt; (c) *n*-Bu_4NF, THF, rt; (d) NaOMe, $HSCH_2CH_2OH$, MeOH, reflux.

n-butylammonium fluoride to give β-D-(2*S*,5*R*)- and α-D-(2*S*,5*S*)-1,3-oxathiolanyl-2-amino-6-chloropurine nucleosides **90** and **91**, respectively. 2-Amino-6-chloro derivatives **90** and **91** were seperately treated with sodium methoxide and 2-mercaptoethanol in methanol to give β-D-(2*S*,5*R*)- and α-D-(2*S*,5*S*)-1,3-oxathiolanylguanine[19] derivatives **92** and **93**.

The assignments of anomeric configurations of (+)-β-D-(2*S*,6*R*)-1,3-oxathiolanylcytosine (**26**) and (−)-α-D-(2*S*,5*S*)-1,3-oxathiolanylcytosine (**27**) were based on NOE experiments[11] in which irradiation of 4′-H in **26** and **27** resulted in enhancement of the 1′-H peak in **26**, confirming the β-configuration, while no enhancement was observed in **27** upon similar irradiation, indicating the α-configuration. Anomeric configurations of other 1,3-oxathiolanyl nucleosides were assigned based on a comparison of the ^1H NMR patterns to those of **26** and **27** as well as the chemical shifts of the anomeric protons, in which the β-anomeric proton appeared upfield relative to the α anomeric proton. Furthermore, the 4′-proton of the β anomers appeared upfield from that observed for the α anomer, and the 5′-protons of the β anomer appeared downfield from those observed for the α anomers.[11,20]

Table I shows melting points, optical rotations, and elemental analysis data of synthesized β-D-(2*S*,5*R*)- and α-D-(2*S*,5*S*)-1,3-oxathiolanyl nucleosides.[21] Optical rotations of D-(2*S*)-nucleosides were the same as those of the corresponding L-(2*R*)-nucleosides, but of opposite sign.[11]

Table I. Optical Rotations and Melting Points

compds	mp, °C (solv)[a]	$[\alpha]^{25}_D$, deg	formula	anal.
4	98–99 (A)	−133.0 (c 1.22, MeOH)	$C_{12}H_{16}O_7S$	C, H, S
5	220 dec. (F)	−122.9 (c 1.0, MeOH)	$C_8H_{10}O_4S$	C, H, S
6	124–125 (E)	−49.1 (c 0.82, MeOH)	$C_9H_{14}O_4S$	C, H, S
7	94–95 (I)	103.5 (c 1.17, MeOH)	$C_{18}H_{18}O_6S$	C, H, S
8	103–104 (A)	−166.0 (c 1.06, MeOH)	$C_{13}H_{14}O_6S$	C, H, S
9	58–60 (A)	−14.6 (c 1.05, MeOH)	$C_{13}H_{16}O_6S$	C, H, S
10	oil	−31.9 (c 0.5, MeOH)	$C_{29}H_{34}O_5SSi$	C, H, S
11	oil	−19.4 (c 1.13, MeOH)	$C_{22}H_{30}O_4SSi$	C, H, S
12	108–110 (A)	73.6 (c 1.14, MeOH)	$C_{22}H_{28}O_5SSi$	C, H, S
16	oil	−13.2 (c 1.14, MeOH)	$C_8H_{16}O_4S$	C, H, S
17	oil	−11.9 (c 1.0, MeOH)	$C_{18}H_{20}O_6S$	C, H, S
18	oil	−11.5 (c 0.59, MeOH)	$C_{12}H_{14}O_4S$	C, H, S
19	oil	−21.8 (c 0.35, $CHCl_3$)	$C_{28}H_{32}O_4SSi$	C, H, S
20	oil	−16.7 (c 0.55, MeOH)	$C_{21}H_{28}O_4SSi$	C, H, S
24	135 dec. (A)	37.4 (c 0.5, MeOH)	$C_{24}H_{29}N_3O_3SSi·0.25H_2O$	C, H, N, S
25	190 dec. (E)	−51.7 (c 0.8, MeOH)	$C_{24}H_{28}N_3O_3SSi$	C, H, N, S
26	145–147 (B)	121.0 (c 1.06, MeOH)	$C_8H_{11}N_3O_3S$	C, H, N, S
27	154–156 (H)	−143.2 (c 0.62, MeOH)	$C_8H_{11}N_3O_3S$	C, H, N, S
28 and 29	foam	mixture	$C_{24}H_{28}N_2O_4SSi·0.1Et_2O$	C, H, N, S
30 and 31	foam	mixture	$C_{25}H_{30}N_2O_4SSi·0.1H_2O$	C, H, N, S
32 and 33	foam	mixture	$C_{24}FH_{27}N_2O_4SSi$	C, H, N, S
34 and 35	foam	mixture	$C_{24}ClH_{27}N_2O_4SSi$	C, Cl, H, N, S
36 and 37	foam	mixture	$C_{24}BrH_{27}N_2O_4SSi$	C, Br, H, N, S
38 and 39	foam	mixture	$C_{24}H_{27}IN_2O_4SSi$	C, H, I, N, S
40	foam	75.2 (c 0.80, $CHCl_3$)	$C_{32}H_{35}N_3O_4SSi$	C, H, N, S
41	foam	−98.3 (c 0.25, $CHCl_3$)	$C_{32}H_{35}N_3O_4SSi$	C, H, N, S
42	foam	105.2 (c 0.50, $CHCl_3$)	$C_{31}FH_{32}N_3O_4SSi$	C, H, N, S
43	foam	−99.2 (c 0.55, $CHCl_3$)	$C_{31}FH_{32}N_3O_4SSi$	C, H, N, S
44	foam	85.4 (c 1.0, MeOH)	$C_{31}ClH_{32}N_3O_4SSi$	C, Cl, H, N, S
45	foam	104.5 (c 0.54, MeOH)	$C_{31}ClH_{32}N_3O_4SSi$	C, Cl, H, N, S
46	foam	80.3 (c 0.60, $CHCl_3$)	$C_{31}BrH_{32}N_3O_4SSi·0.4C_4H_{10}O$	C, Br, H, N, S
47	foam	−93.0 (0.60, $CHCl_3$)	$C_{31}BrH_{32}N_3O_4SSi$	C, Br, H, N, S
48	foam	69.3 (c 0.53, MeOH)	$C_{31}H_{32}IN_3O_4SSi·0.3C_6H_{14}$	C, H, N, S
49	foam	−84.2 (c 0.66, MeOH)	$C_{31}H_{32}IN_3O_4SSi$	C, H, N, S
50	131–133 (A)	80.2 (c 0.41, MeOH)	$C_8H_{10}N_2O_4S$	C, H, N, S
51	foam	−91.0 (c 0.37, MeOH)	$C_8H_{10}N_2O_4S$	C, H, N, S
52	foam	59.7 (c 0.35, MeOH)	$C_9H_{12}N_2O_4S·0.1H_2O$	C, H, N, S
53	foam	−69.5 (c 0.7, MeOH)	$C_8H_{12}N_2O_4S·0.1H_2O$	C, H, N, S
54	187–190 (C)	67.1 (c 0.44, MeOH)	$C_8FH_9N_2O_4S$	C, H, N, S
55	152–155 (C)	−95.2 (c 0.40, MeOH)	$C_8FH_9N_2O_4S$	C, H, N, S
56	182–183 (C)	69.8 (c 0.52, MeOH)	$C_8ClH_9N_2O_4S$	C, Cl, H, N, S
57	133–134 (C)	−98.1 (c 0.52, MeOH)	$C_8ClH_9N_2O_4S$	C, Cl, H, N, S
58	173–174 (C)	62.7 (c 0.51, MeOH)	$C_8BrH_9N_2O_4S$	C, Br, H, N, S
59	154–155 (C)	−77.4 (c 0.50, MeOH)	$C_8BrH_9N_2O_4S$	C, Br, H, N, S
60	156–157 (B)	45.3 (c 0.5, MeOH)	$C_8H_{27}IN_2O_4S$	C, H, I, N, S
61	146–147 (B)	−63.1 (c 0.52, MeOH)	$C_8H_{27}IN_2O_4S$	C, H, I, N, S
62	69–72 (B)	109.9 (c 0.29, MeOH)	$C_9H_{13}N_3O_3S$	C, H, N, S
63	162–165 (B)	−136.3 (c 0.22, MeOH)	$C_9H_{13}N_3O_3S$	C, H, N, S
64	136–140 (B)	135.1 (c 0.31, MeOH)	$C_8FH_{10}N_3O_3S$	C, H, N, S
65	151–53 (B)	−78.5 (c 0.34, MeOH)	$C_8FH_{10}N_3O_3S$	C, H, N, S
66	148–151 (B)	101.2 (c 0.54, MeOH)	$C_8ClH_{10}N_3O_3S$	C, Cl, H, N, S
67	162–164 (B)	−155.2 (c 0.33, MeOH)	$C_8ClH_{10}N_3O_3S·0.08CH_2Cl_2$	C, Cl, H, N, S
68	170–174 (B)	100.1 (C 0.36, MeOH)	$C_8BrH_{10}N_3O_3S$	C, Br, H, N, S
69	155–159 (B)	−120.3 (c 0.32, MeOH)	$C_8BrH_{10}N_3O_3S$	C, Br, H, N, S
70	160–162 (B)	69.2 (c 0.58, MeOH)	$C_8H_{10}IN_3O_3S·0.2H_2O$	C, H, I, N, S
71	191–193 (B)	−96.2 (c 0.59, MeOH)	$C_8H_{10}IN_3O_3S$	C, H, I, N, S
72 and 73	mixture	mixture	$C_{25}ClH_{27}N_4O_2SSi$	C, Cl, H, N, S
74	114–115 (C)	−13.5 (c 0.34, MeOH)	$C_9ClH_9N_4O_2S$	C, Cl, H, N, S
75	113–116 (C)	−10.6 (c 0.41, MeOH)	$C_9ClH_9N_4O_2S$	C, Cl, H, N, S
76	170–172 (C)	−9.4 (c 0.12, MeOH)	$C_8H_{11}N_5O_2S$	C, H, N, S
77	112–114 (C)	−5.2 (c 0.63, MeOH)	$C_{10}H_{13}N_5O_2S$	C, H, N, S
78	>172 dec (C)	−7.7 (c 0.40, MeOH)	$C_9H_{10}N_4O_3S$	C, H, N, S
79	190–192 (B)	−4.9 (c 0.21, MeOH)	$C_8H_{11}N_5O_2S$	C, H, N, S
80	143–148 (E)	−6.2 (c 0.12, MeOH)	$C_{10}H_{13}N_5O_2S$	C, H, N, S
81	>200 dec	−13.6 (c 0.09, MeOH)	$C_8H_{10}N_4O_3S$	C, H, N, S
82 and 83	106–110 (G)	mixture	$C_{25}ClFH_{28}N_4O_2SSi$	C, Cl, H, N, S
84	166–167 (F)	−9.8 (c 0.14, $CHCl_3$)	$C_{25}FH_{28}N_5O_2SSi$	C, F, H, N, S
85	164–166 (F)	−11.2 (c 0.10, $CHCl_3$)	$C_{25}FH_{28}N_5O_2SSi$	C, F, H, N, S
86 and 87	75–80 (F)	mixture	$C_{25}ClH_{28}N_5O_2SSi$	C, Cl, H, N, S
88	206–209 (F)	ND	$C_8FH_{10}N_5O_2S$	C, H, N, S
89	262–263 (D)	−10.0 (c 0.25, MeOH)	$C_9FH_{10}N_5O_2S$	C, H, N, S
90	88–90 (F)	−8.6 (c 0.29, MeOH)	$C_9ClH_{10}N_5O_2S·1.7H_2O$	C, Cl, H, N, S
91	119–120 (F)	19.2 (c 0.23, MeOH)	$C_9ClH_{10}N_5O_2S·1.7H_2O$	C, Cl, H, N, S
92	>220 dec (B)	−58.7 (c 0.21, H_2O)	$C_9H_{11}N_5O_3S$	C, H, N, S
93	>270 (D)	38.2 (c 0.22, H_2O)	$C_9H_{11}N_5O_3S$	C, H, N, S

[a] Crystallized or silica gel column solvents: A, ether–hexanes; B, ether–methanol; C, ether; D, methanol; E, hexane–methylene chloride; F, chloroform–methanol; G, hexanes–ethyl acetate; H, 2-propanol–ether; I, cyclohexanes; ND; could not be determined because of poor solubility. Optical rotations of purines were not accurate due to poor solubility.

Table II. Median Effective (EC_{50}) and Inhibitory (IC_{50}) Concentration of β-D-(2S,5R)- and α-D-(2S,5S)-Oxathiolanylpyrimidine and Purine Nucleosides in PBM Cells and Vero Cells

compds base no.	anomer	anti-HIV-1 in PBM cells EC_{50}[a] (μM)	cytotoxicity in PBM cells IC_{50}[a] (μM)	cytotoxicity in Vero cells IC_{50}[a] (μM)
cytosine **26**	(+)-β	0.21	>100	>100
cytosine **27**	(−)-α	>100	>100	>100
uracil **50**	(+)-β	94.7	>100	>100
uracil **51**	(−)-α	>100	>100	>100
thymine **52**	(+)-β	11.6	>100	>100
thymine **53**	(−)-α	>100	>100	>100
5-fluorouracil **54**	(+)-β	6.3	>100	>100
5-fluorouracil **55**	(−)-α	2.3	>100	>100
5-chlorouracil **56**	(+)-β	30.4	>100	>100
5-chlorouracil **57**	(−)-α	>100	>100	>100
5-bromouracil **58**	(+)-β	>100	>100	>100
5-bromouracil **59**	(−)-α	>100	>100	>100
5-iodouracil **60**	(+)-β	29.3	>100	>100
5-iodouracil **61**	(−)-α	112.1	>100	>100
5-methylcytosine **62**	(+)-β	0.172	>100	>100
5-methylcytosine **63**	(−)-α	>100	>100	>100
5-fluorocytosine **64**	(+)-β	0.38	>100	>100
5-fluorocytosine **65**	(−)-α	77.5	>100	>100
5-chlorocytosine **66**	(+)-β	0.28	>100	>100
5-chlorocytosine **67**	(−)-α	>100	>100	31.15
5-bromocytosine **68**	(+)-β	0.012	>100	>100
5-bromocytosine **69**	(−)-α	>100	>100	>100
5-iodocytosine **70**	(+)-β	1.9	>100	>100
5-iodocytosine **71**	(−)-α	0.28	>100	>100
6-chloropurine **74**	(−)-β	0.48	>100	46.5
6-chloropurine **75**	(−)-α	2.7	>100	86.1
adenine **76**	(−)-β	0.28	>100	>100
N-methyladenine **77**	(−)-β	1.1	>100	>100
inosine **78**	(−)-β	0.05	>100	>100
adenine **79**	(−)-α	11.9	>100	>100
N-methyladenine **80**	(−)-α	11.7	>100	>100
inosine **81**	(−)-α	>100	>100	>100
2-fluoroadenine **88**	(−)-β	2.8	>100	5.6
2-fluoroadenine **89**	(−)-α	61.9	>100	45.4
2-amino-6-chloropurine **90**	(−)-β	0.52	>100	>100
2-amino-6-chloropurine **91**	(+)-α	5.6	>100	>100
guanine **92**	(−)-β	0.83	>100	>100
guanine **93**	(+)-α	7.62	>100	63.6
AZT		0.004	>100	>100

[a] Mean of triplicate values; EC_{50} values are for 50% inhibition of virus production as indicated by supernatant RT levels; IC_{50} values indicates 50% inhibition of cell growth.[22,23]

Antiviral and cytotoxicity assays were performed according to the methods described previously.[11,13,22,23] EC_{50} and IC_{50} values were calculated by the medium method.[23] β-D-(2S,5R)- and α-D-(2S,5S)-1,3-oxathiolanylpyrimidine and purine nucleosides were evaluated for anti-HIV activity in human PBM cells infected with HIV-1 strain LAV, and the biological data are shown in Table II.

In the case of uracil, thymine, and 5-substituted uracil derivatives, most of the compounds did not exhibit significant anti-HIV activity except the 5-fluorouracil derivatives **54** and **55**. The order of anti-HIV potency is as follows: 5-fluorouracil (α-isomer) **55** > 5-fluorouracil (β-isomer) **54** > thymine (β-isomer) **52** > 5-iodouracil (β-isomer) **60** ≈ 5-chlorouracil (β-isomer) **56** > uracil (β-isomer) **50**. 5-Bromouracil (β-isomer) **58** and other α-isomers were found to be inactive.

Among 5-substituted cytosine analogues, the 5-bromocytosine derivative (β-isomer) **68** was found to be the most potent anti-HIV agent. The antiviral potency of the cytosine analogues was found to be in the following decreasing order: 5-bromocytosine (β-isomer) **68** > 5-methylcytosine (β-isomer) **62** > cytosine (β-isomer) **26** > 5-chlorocytosine (β-isomer) **66** ≈ 5-iodocytosine (α-isomer) **71** > 5-fluorocytosine (β-isomer) **64** > 5-iodocytosine (β-isomer) **70** > 5-fluorocytosine (α-isomer) **65**. Interestingly, the α-isomer of 5-iodocytosine analogue **71** exhibited potent anti-HIV activity. All the 5-substituted cytosine analogues were nontoxic up to 100 μM in PBM as well as Vero cells. However, it is difficult to find a correlation between the substituents at the 5-position of cytosine and their anti-HIV activity. In general, in the pyrimidine series, the 5-substituted cytosine analogues exhibited greater potency than the 5-substituted uracil derivatives.

When the anti-HIV activities of these D-(2S)-pyrimidine nucleosides were compared with those of corresponding L-(2R)-pyrimidine nucleosides,[11] cytosine **26** and 5-fluorocytosine **64** derivatives (EC_{50} = 0.21 and 0.38 μM, respectively) were less potent than the corresponding (EC_{50} = 0.0018 and 0.0013 μM, respectively) L-(2R)-nucleosides. The 5-chlorocytosine **66**, 5-bromocytosine **68**, and 5-iodocytosine **70** derivatives of D-(2S)-nucleosides were more potent than the corresponding L-(2R)-pyrimidine nucleosides. It is interesting to note that L-(2R)-nucleosides are more active than D-(2S)-nucleosides in the case of a small size atom (H, F) at 5-position of cytosine, whereas the D-(2S)-nucleosides are more potent than the L-(2R)-nucleosides when the 5-position of cytosine was substituted by large atoms (Cl, Br, I).

In the case of 6-substituted purine derivatives, the β-isomers of 6-chloropurine (**74**), adenine (**76**), N^6-methyladenine (**77**), and inosine (**78**) derivatives also showed significant anti-HIV activity. Interestingly, the α-isomers of 6-chloropurine (**75**), adenine (**79**), and N^6-methyladenine (**80**) derivatives also exhibited good anti-HIV activity, although they were less potent than the corresponding β-isomers. The inosine analogue (β-isomer) **78** was found to be the most potent anti-HIV agent against HIV-1 among the 6-substituted purines tested. All 6-substituted purine nucleosides were nontoxic in PBM and Vero cells up to 100 μM except 6-chloropurine (**74** and **75**) and 2-fluoroadenine (**88** and **89**) analogues, which showed cytotoxicity in Vero cells.

When the anti HIV activities in these D-(2S)-6-substituted purine nucleosides were also compared with those of L-(2R)-6-substituted purine nucleosides, all the D-(2S)-isomers were found to be more potent than the corresponding L-(2R)-isomers.[11] Among 2,6-disubstituted purines, the 2-amino-6-chloropurine (β-isomer) derivative **90** showed the most potent activity. The antiviral potency of other 2,6-disubstituted purine analogues was found to be in the following decreasing order: guanine (β-isomer) **92** > 2-fluoroadenine (β-isomer) **88** > 2-amino-6-chloropurine (α-isomer) **91** > guanine (α-isomer) **93**.

In summary, the 5-substituted cytosine analogues exhibited more potencies than the 5-substituted uracil analogues, and the 6-substituted purine derivatives were more potent than the 2,6-disubstituted purine derivatives. In general, the D-(2S)-isomers were more potent than the corresponding L-(2R)-isomers except cytosine and 5-fluorocytosine derivatives. In some cases, the α-isomers were more potent than the corresponding β-isomers. Other instances where an α-isomer has greater potency than the

corresponding β-isomer occur in nucleosides containing a heteroatom in the sugar moiety in place of a methylene group.[8,11]

Experimental Section

Melting points were determined on a Mel-temp II laboratory device and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL FX 90Q Fourier transform spectrometer or Bruker AM300 with Me_4Si as internal standard; chemical shifts (δ) are reported in parts per million, and signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). UV spectra were obtained on a Beckman DU-7 spectrophotometer. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. TLC was performed on Uniplates (silica gel) purchased from Analtech Co. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA, or Galbraith Laboratories, Inc., Knoxville, TN. Dry 1,2-dichloroethane and methylene chloride were obtained by distillation from CaH_2 immediately prior to use.

1,2,3,4-Tetra-*O*-acetyl-6-*O*-tosyl-D-mannopyranose (2). A solution of *p*-toluenesulfonyl chloride (158.73 g, 0.84 mol) in pyridine (600 mL) was added dropwise to a suspension of D-mannose (1) (100 g, 0.56 mol) in dry pyridine (800 mL). The internal temperature was maintained between 18 and 20 °C during the addition. Upon completion of the addition, the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was cooled, and acetic anhydride (250 mL, 2.69 mol) was added dropwise, again maintaining the internal temperature between 18 and 20 °C. Upon completion of the addition, the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure and the residue partitioned between ethyl acetate and water. The organic layer was washed with 1% aqueous H_2SO_4 and saturated $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated. The residue was dried under high vacuum to give **2** (269.75 g, 97%) as a foam, which was used in the next step without further purification.

A small quantity was purified by preparative TLC for a NMR sample: ^{1}H NMR ($CDCl_3$) δ 1.99 (s, 3 H, Ac), 2.03 (s, 3 H, Ac), 2.13 (s, 3 H, Ac), 2.14 (s, 3 H, Ac), 2.45 (s, 3 H, CH_3Ar), 4.12 (d, J = 1.8 Hz, 2 H, 6-H), 4.21 (m, 1 H, 5-H), 5.01–5.53 (m, 3 H, 2-H, 3-H, 4-H), 6.02 (d, J = 1.8 Hz, 1 H, 1-H), 7.34 (d, J = 8.4 Hz, 2 H, Ar), 7.78 (d, J = 8.57 Hz, 2 H, Ar).

2,3,4-Tri-*O*-acetyl-1-bromo-1-deoxy-6-*O*-tosyl-α-D-mannopyranose (3). A 1-L round-bottom flask containing **2** (40 g, 0.079 mol) and HBr in acetic acid (45% w/v, 210 mL) cooled in an ice–water bath was fitted with a $CaCl_2$ tube and stirred at 0 °C for 30 min and then at room temperature for 15 h. The solvent was removed under reduced pressure and the residue partitioned between ethyl ether and cold water. The organic layer was washed with cold water and saturated $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated. The residue was dried under high vacuum to give **3** (40.64 g, 98%) as a hygroscopic foam which was used without further purification. A small quantity was purified by preparative TLC for use as an NMR sample: ^{1}H NMR ($CDCl_3$) δ 1.99 (s, 3 H, Ac), 2.07 (s, 3 H, Ac), 2.14 (s, 3 H, Ac), 2.45 (s, 3 H, CH_3Ar), 4.16 (d, J = 1.8 Hz, 2 H, 6-H), 4.20 (m, 1 H, 5-H), 5.42 (m, 2 H, 2-H and 3-H), 5.65 (dd, J = 3.3 and 10.1 Hz, 1 H, 4-H), 6.19 (d, J = 1.5 Hz, 1 H, 1-H), 7.35 (d, J = 7.9 Hz, 2 H, Ar), 7.79 (d, J = 8.4 Hz, 2 H, Ar).

(−)-2,3,4-Tri-*O*-acetyl-1,6-dideoxy-1,6-thioanhydro-D-mannopyranose (4). Potassium *O*-ethylxanthate (37.34 g, 0.23 mol) was added to a stirred solution of **3** (40.64 g, 0.078 mol) in dry DMF (50 mL) cooled in an ice bath for 45 min and the reaction mixture stirred at room temperature for 15 h. Solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and water. The organic layer was washed with water, dried ($MgSO_4$), and evaporated. The residue was used in the next step without further purification. An analytical sample was obtained by chromatography over silica gel using EtOAc/hexanes (3:7) as the eluant and then crystallization from Et_2O/hexanes: ^{1}H NMR ($CDCl_3$) δ 2.04 (s, 3 H, Ac), 2.13 (s, 3 H, Ac), 2.15 (s, 3 H, Ac), 3.21 (s, 1 H, 6-H_a), 3.25 (d, J = 2.9 Hz, 1 H, 6-H_b), 4.80 (d, J = 1.5 Hz, 1 H, 3 H), 4.85 (m, 1 H, 5-H), 5.19 (m, 1 H, 4-H), 5.29 (pseudo t, J = 4.0 and 5.3 Hz, 1 H, 2-H), 5.48 (d, J = 4.0 Hz, 1 H, 1-H).

(−)-1,6-Dideoxy-1,6-thioanhydro-D-mannopyranose (5). Concentrated NH_4OH (75 mL) was added to a solution of the crude residue **4** in methanol (200 mL) and the reaction mixture stirred at room temperature for 15 h. The reaction mixture was concentrated under reduced pressure and coevaporated several times with absolute ethanol. The residue was purified by silica gel column chromatography to give **5** (5.46 g, 39% from **3**): ^{1}H NMR (DMSO-d_6) δ 2.90 (d, J = 13.0 Hz, 1 H, 6-H_a), 3.05 (dd, J = 3.5, 13.0 Hz, 1 H, 6-H_b), 3.55 (m, 2 H, H-2 and H-3), 3.81 (m, 1 H, H-4), 4.30 (d, J = 3.7 Hz, 1 H, OH), 4.65 (m, 1 H, H-5), 4.82 (d, J = 7.0 Hz, OH), 5.10 (d, J = 4.8 Hz, 1 H, H-1), 5.22 (d, J = 3.7 Hz, 1 H, OH).

(−)-2,3-*O*-Isopropylidene-1,6-dideoxy-1,6-thioanhydro-D-mannopyranose (6). 2,2-Dimethoxypropane (100 mL) and *p*-toluenesulfonic acid (2.5 g) were added to a solution of **5** (10 g, 0.0562 mol) in acetone (500 mL), the reaction mixture heated to 55 °C for 2 h, and methanol added to get a clear solution if necessary. After the reaction mixture was stirred at room temperature for 16 h, it was neutralized with triethylamine and concentrated to dryness. The residue was purified by chromatography over silica gel using EtOAc/hexanes (2:3) as eluant to give **6** (9.92 g, 81%) as a crystalline solid, which was recrystallized from CH_2Cl_2/hexanes: ^{1}H NMR (DMSO-d_6) δ 1.23 (s, 3 H, CH_3), 1.55 (s, 3 H, CH_3), 2.79 (dd, J = 1.8 and 9.9 Hz, 1 H, 6-H_a), 2.92 (dd, J = 7.0 and 9.9 Hz, 1 H, 6-H_b), 3.73 (d, J = 4.4 Hz, on D_2O exchange goes to s, 1 H, 4-H), 3.98 (d, J = 6.8 Hz, 1 H, 3-H), 4.29 (pseudo t, J = 5.3 and 6.8 Hz, 1 H, 2-H), 4.65 (d, J = 7.0 Hz, 1 H, 5-H), 5.45 (d, J = 4.8 Hz, 2 H, 4-OH and 1-H, on D_2O exchange, d, J = 5.3 Hz, 1 H, 1-H).

(−)-4-*O*-Benzoyl-2,3-*O*-isopropylidene-1,6-dideoxy-1,6-thioanhydro-D-mannopyranose (7). Benzoyl chloride (5.6 mL, 0.046 mol) was added dropwise to a stirred solution of **6** (6.25 g, 0.029 mol) in pyridine (50 mL) cooled to 0 °C in an ice bath. The reaction mixture was allowed to come to room temperature and stirred for 2 h at which time TLC indicated the absence of starting material. Ice was added to decompose excess benzoyl chloride, the reaction mixture was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate and water. The organic layer was washed with 1% aqueous H_2SO_4 and saturated $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated to give a solid, which was recrystallized from cyclohexane to yield **7** (7.03 g, 75%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 3 H, CH_3), 1.69 (s, 3 H, CH_3), 3.12 (s, 1 H, 6-H_a), 3.16 (d, J = 3.1 Hz, 1 H, 6-H_b), 4.25 (d, J = 7.0 Hz, 1 H, 3-H), 4.51 (pseudo t, J = 5.5 and 6.8 Hz, 1 H, 2-H), 4.87 (m, 1 H, 5-H), 5.16 (s, 1 H, 4-H), 5.55 (d, J = 5.3 Hz, 1 H, 1-H), 7.32-8.21 (m, 5 H, C_6H_5).

(−)-4-*O*-Benzoyl-1,6-dideoxy-1,6-thioanhydro-D-mannopyranose (8). A solution of **7** (7.0 g, 0.022 mol) and 2% aqueous H_2SO_4 (40 mL) in 1,4-dioxane (200 mL) was heated to 70 °C for 5 h at which time TLC indicated the absence of starting material. The reaction mixture was cooled and neutralized by the addition of solid $NaHCO_3$. The solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and H_2O. The organic layer was washed with H_2O, dried ($MgSO_4$), and evaporated. The residue was purified by chromatography over silica gel using EtOAc/hexane (3:7) as the eluant to give **8** (5.28 g, 85%) as white crystals after crystallization from Et_2O/hexanes: ^{1}H NMR (DMSO-d_6) δ 3.13 (d, J = 6.4 Hz, 2 H, 6-H), 3.65–4.05 (m, 2 H, 2-H and 3-H), 4.84–5.21 (m, 4 H, 2-OH, 3-OH, 4-H, 5-H), 5.38 (d, J = 4.8 Hz, 1 H, 1-H), 7.41–8.12 (m, 5 H, C_6H_5).

(−)-[2*S*[2α,5α(*R*)]]-2-Benzoyl-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,2-ethanediol (9). $Pb(OAc)_4$ (4.04 g, 0.0089 mol) was added to a stirred solution of **8** (2.3 g, 0.008 mol) in ethyl acetate (50 mL) and the mixture stirred for 5 min at 0 °C. The reaction mixture was filtered, and the lead salts were washed with ethyl acetate thoroughly. The organic layer was washed with saturated aqueous $NaHCO_3$ to remove any unreacted $Pb(OAc)_4$ and concentrated under reduced pressure. The residue was dissolved in ethanol (50 mL) and cooled in an ice bath. Excess $NaBH_4$ (1.23 g, 0.032 mol) was added to this cold solution until TLC indicated the disappearance of starting material and the complete conversion of the secondary benzoate to the primary benzoate. The reaction was quenched by the careful addition of glacial acetic acid, and the reaction mixture was poured into water (200 mL) and extracted with EtOAc. The combined organic

layers were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated to give a residue, which was purified by chromatography over silica gel using EtOAc/hexanes (1:1) as eluant to yield **9** (2.25 g, 98%) as white crystals after crystallization from hexanes/Et_2O: ^1H NMR (DMSO-d_6) δ 2.87 (dd, $J_{5,4a}$ = 8.4 Hz, $J_{4a,4b}$ = 10.3 Hz, 1 H, 4-H_a), 3.12 (dd, $J_{5,4b}$ = 5.1 Hz, $J_{4a,4b}$ = 10.3 Hz, 1 H, 4-H_b), 3.41 (dd, J = 5.7 and 11.4 Hz on D_2O exchange goes to J = 5.2 and 11.4 Hz, 1 H, 2-CH_aOH), 3.65 (dd, J = 5.7 and 11.4 Hz on D_2O exchange goes to dd, J = 5.2 and 11.4 Hz, 1 H, 2-CH_bOH), 3.80–4.24 (m, 2 H, 5-H and 1'-H), 4.32 (dd, $J_{1',2'a}$ = 5.6 Hz, $J_{2'a,2'b}$ = 11.2 Hz, 1 H, 2'-H_a), 4.61 (dd, $J_{1',2'b}$ = 3.3 Hz, $J_{2'a,2'b}$ = 11.2 Hz, 1 H, 2'-H_b), 5.06 (t, $J_{2\text{-}CH_2OH,OH}$ = 5.7 Hz, 1 H, 2-CH_2OH), 5.15 (t, $J_{2,2\text{-}CH_2OH}$ = 5.3 Hz, 1 H, 2-H), 5.5 (d, J = 5.3 Hz, 1 H, 1'-OH), 7.32–8.21 (m, 5 H, C_6H_5).

(−)-[2*S*[2α,5α(*R*)]]-2-Benzoyl-1-[2-(*tert*-butyldiphenylsilyl)-1,3-oxathiolan-5-yl]-1,2-ethanediol (10). Imidazole (1.61 g, 0.024 mol) and *tert*-butyldiphenylsilyl chloride (2.25 mL, 0.0087 mol) were added to a solution of **9** (2.25 g, 0.0079 mol) in DMF (50 mL) and the reaction mixture stirred at room temperature until TLC indicated the absence of starting material. DMF was removed under reduced pressure and the residue partitioned between EtOAc and H_2O. The organic layer was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated to give a residue, which was purified by chromatography over silica gel using EtOAc/hexanes (1:9) as eluant to yield **10** (3.76 g, 91%) as an oil: ^1H NMR (DMSO-d_6) δ 0.98 (s, 9 H, *tert*-butyl), 2.93 (dd, J = 9.5 and 10.6 Hz, 1 H, 4-H_a), 3.21 (dd, J = 5.5 and 10.6 Hz, 1 H, 4-H_b), 3.61–4.62 (m, 6 H, 2-CH_2OR, 1'-H, 2'-H_a, 2'-H_b, 5-H), 5.29 (pseudo t, J = 5.1 and 5.3 Hz, 1 H, 2-H), 5.52 (d, J = 5.5 Hz, 1 H, 1'-OH), 7.31–8.13 (m, 15 H, 3 × C_6H_5).

(−)-[2*S*[2α(*R*),5α]]-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]-1,2-ethanediol (11). Concentrated NH_4OH (10 mL) was added to a solution of **10** (3.76 g, 7.203 mmol) in methanol (75 mL) and the reaction mixture stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure and the residue purified by chromatography over silica gel using EtOAc/hexanes (2:3) as eluant to give **11** (2.79 g, 93%) as an oil: ^1H NMR (DMSO-d_6) δ 1.01 (s, 9 H, *tert*-butyl), 2.76 (d, $J_{4a,4b}$ = 10.1 Hz, 1 H, 4-H_a), 3.08 (dd, $J_{5,4b}$ = 5.4 Hz, $J_{4a,4b}$ = 10.1 Hz, 1 H, 4-H_b), 3.42–3.21 (m, 6 H, 1'-H, 2'-H, 5-H, 2-CH_2OR), 4.56 (t, J = 5.4 Hz, 1 H, 2'-OH), 4.93 (d, J = 4.8 Hz, 1'-OH), 5.25 (pseudo t, J = 5.1 and 5.5 Hz, 1 H, 2-H), 7.32–7.81 (m, 10 H, 2 × C_6H_5).

[2*S*(2α,3β,5α)- and [2*S*(2α,3α,5α)]-2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolane-5-carboxylic Acid Methyl Ester 3-Oxide (12). $Pb(OAc)_4$ (5.46 g, 0.0123 mol) was added to a solution of **11** (4.7 g, 0.0112 mol) in ethyl acetate (50 mL) cooled in an ice bath and the reaction mixture stirred for 2 min at which time TLC indicated the absence of starting material and the presence of the aldehyde (positive to 2,4-DNP). The reaction mixture was filtered and the filtrate diluted with 150 mL of EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated to give a crude aldehyde derivative (4.22 g) as a syrup which was used in the next step without further purification.

An aqueous solution of $NaH_2PO_4 \cdot H_2O$ (3.0 g in 30 mL) and 2-methyl-2-butene (1 mL) was added to a solution of crude aldehyde (4.22 g, 0.0109 mol) in acetonitrile (150 mL). The reaction mixture was cooled in an ice bath and treated dropwise with an aqueous solution of $NaClO_2$ (80%, 1.35 g in 30 mL). After the addition was complete, the ice bath was removed and the reaction mixture stirred at room temperature. The progress of the reaction was monitored by TLC. After 3 h, TLC indicated the disappearance of starting material. The reaction was quenched by the addition of $NaHSO_3$ and the acetonitrile removed under reduced pressure. The aqueous residue was adjusted to pH ~4 and extracted with ethyl acetate (200 mL × 2). The combined organic layers were washed with water, dried ($MgSO_4$), and evaporated to give 4.24 g of crude acid derivative (~70% endo and exo sulfoxide acid) which was used in the next step without further purification.

Anhydrous K_2CO_3 (3.0 g, 21.7 mmol) and dimethyl sulfate (1.02 mL, 10.7 mmol) were added to a solution of the crude mixture of sulfoxide–acids (3.0 g, 7.15 mmol) in acetone (50 mL) and the reaction mixture stirred until TLC indicated complete disappearance of starting material. The reaction mixture was filtered through a Celite pad and the filtrate evaporated. The residue was dissolved in ethyl acetate, washed with water and saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated. The residue was purified by chromatography over silica gel using ethyl acetate/hexanes (1:1) as eluant to give pure ester **12** (2.1 g) as a mixture of sulfoxides. Crystallization from ethyl ether/hexanes (9:1) gave one sulfoxide as a crystalline solid: ^1H NMR ($CDCl_3$) δ 1.03 (s, 9 H, *tert*-butyl), 2.85 (dd, $J_{5,4a}$ = 11.5 Hz and $J_{4a,4b}$ = 13.2 Hz, 1 H, 4-H_a), 3.42 (dd, $J_{5,4b}$ = 4.2 Hz and $J_{4a,4b}$ = 13.2 Hz, 1 H, 4-H_b), 3.83 (s, 3 H, OCH_3), 3.91 (dd, $J_{2,2\text{-}CH_2OR}$ = 4.0 Hz and $J_{CH_a,bOR}$ = 11.6 Hz, 1 H, 2-CH_aOR), 4.19 (dd, $J_{2,2\text{-}CH_2OR}$ = 2.6 Hz and $J_{CH_a,bOR}$ = 11.6 Hz, 1 H, 2-CH_bOR), 4.83 (pseudo t, J = 3.1 and 3.5 Hz, 1 H, 2-H), 5.25 (dd, J_{5-4a} = 4.2 Hz and J_{5-4b} = 11.4 Hz, 1 H, 5-H), 7.31–7.82 (m, 10 H, 2 × C_6H_5).

[2*S*(2α,5α)-2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolane-5-carboxylic Acid Methyl Ester (13). A solution of **12** (0.5 g, 1.16 mmol) and $BHCl_2 \cdot (CH_3)_2S$ (0.16 mL, 1.39 mmol) in dry THF (25 mL) was stirred at 5 °C for 15 min under argon and then allowed to warm to room temperature. After 1.5 h, the reaction was completed, quenched with saturated $NaHCO_3$ solution (5 mL), and diluted with ethyl acetate (75 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (25 mL × 2) and H_2O (25 mL × 2), dried (Na_2SO_4), and evaporated. The residue was separated by chromatography over silica gel using 5% EtOAc/hexanes as eluant to give **13** (0.38 g, 80%) as an oil: ^1H NMR ($CDCl_3$) δ 1.06 (s, 9 H, *tert*-butyl), 3.16 (d, $J_{5,4a}$ = 7.6 Hz, 1 H, 4-H_a), 3.21 (d, $J_{5,4b}$ = 6.2 Hz, 1 H, 4-H_b), 3.73 (s, 3 H, OCH_3), 3.79 (dd, $J_{2,2\text{-}CH_2OR}$ = 6.2 Hz, $J_{CH_a,bOR}$ = 10.6 Hz, 1 H, 2-CH_aOR), 4.06 (dd, $J_{2,2\text{-}CH_2OR}$ = 5.0 Hz, $J_{2\text{-}CH_a,bOR}$ = 10.6 Hz, 1 H, 2-CH_bOR), 4.59 (dd, $J_{5,4a}$ = 6.2 Hz, $J_{5,4b}$ = 7.6 Hz, 1 H, 5-H), 5.31 (dd, $J_{2,2\text{-}CH_aOR}$ = 5.0 Hz, $J_{2,2\text{-}CH_bOR}$ = 6.2 Hz, 1 H, 2-H), 7.32–7.85 (m, 10 H, 2 × C_6H_5).

[2*S*(2α,5α)]- and [2*S*(2α,5β)]-2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-ol Acetate (14). LiOH (0.048 g, 1.13 mmol) was added to a solution of the sulfide ester **13** (0.43 g, 1.03 mmol) in THF/H_2O (4:1) (50 mL) and the reaction mixture stirred at room temperature until TLC indicated the disappearance of starting material. The reaction mixture was neutralized with acetic acid and THF removed under reduced pressure. The residue was extracted with EtOAc, and the organic layer was washed three times with H_2O, dried ($MgSO_4$), and evaporated to give 0.373 g (90%) of the crude acid which was used without further purification. To a solution of the crude acid (0.6 g, 1.49 mmol) in dry ethyl acetate (50 mL) were added pyridine (0.24 mL, 2.98 mmol) and $Pb(OAc)_4$ (0.92 g, 2.08 mmol), and the mixture was stirred at room temperature for 2 h. The reaction mixture was filtered through a Celite pad and the solvent removed under reduced pressure. The residue was separated by chromatography over silica gel using 5% ethyl acetate in hexanes to give **14** (0.4 g, 64%) as syrup: ^1H NMR ($CDCl_3$) δ 1.06 and 1.09 (s, 9 H, *tert*-butyl), 1.85 and 2.06 (s, 3 H, Ac), 3.01–4.03 (m, 4 H, 4-H, 2-CH_2OR), 5.47 (t, 1 H, 2 H), 6.58 (d, 1 H, 5-H), 7.31–7.92 (m, 10 H, 2 × C_6H_5).

(−)-[2*S*[2α(*S*),5α]]-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)-1,3-oxathiolane-5-methanol (16). An aqueous solution (200 mL) of $NaIO_4$ (16.82 g, 0.0784 mol) was added dropwise at 0 °C over a period of 25 min to a solution of 1,6-thioanhydro-D-galactopyranose[16] (**15**) (10 g, 0.056 mol) in MeOH (150 mL) and the mixture stirred at 0 °C for 10 min. $NaBH_4$ (4.24 g, 0.112 mol) was added at 0 °C and stirred for an additional 10 min. After being filtered through a Celite pad, the mixture was neutralized with 1 N HCl, solvents were evaporated, and the residue was dried overnight under high vacuum. The dried residue was treated with MeOH (20 mL) and acetone (300 mL) followed by *p*-toluenesulfonic acid (3 g). After 1 h, most of the starting materials were converted to product. After neutralization with triethylamine and evaporation of solvents, the residue was dissolved in ethyl acetate (500 mL), washed with water (100 mL × 2), dried ($MgSO_4$), and evaporated to give crude residue (10 g). The mother liquor was evaporated and the reside dried overnight. The above procedure was repeated to give another 3 g of crude residue. The combined residues were purified by silica gel column chromatography to give **16** (8.0 g, 65%) as a colorless oil: ^1H NMR (DMSO-d_6) δ 1.26 and 1.32 (2 × s, 6 H, isopropyl), 2.71 (pseudo t, J = 9.2 and 10.1 Hz, 1 H, 4-H_a), 3.53

(d, 2 H, J = 5.1 Hz, 2 H, CH_2OC), 3.72–4.17 (m, 4 H, 5-H, CH_2OH and CHO), 4.34 (br s, 1 H, CH$_2$OH), 5.05 (d, J = 6.2 Hz, 1 H, 2-H).

(-)-[2*S*[2α(*S*),5α]]-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)-1,3-oxathiolane-5-methanol Benzoate (17). Benzoyl chloride (4.224 mL, 0.036 mol) was added to a solution of **16** (8 g, 0.036 mol) in pyridine (30 mL) and the reaction mixture stirred at room temperature for 1 h. Pyridine was removed under high vacuum, and the residue was dissolved in ethyl acetate (300 mL), washed with water (100 mL) and brine (100 mL), dried (MgSO$_4$), and evaporated. The residue was purified by silica gel column chromatography to give **17** (10.5 g, 89%) as a colorless oil: ^{1}H NMR (CDCl$_3$) δ 1.35 and 1.43 (2 × s, 6 H, isopropyl), 2.90 (pseudo t, J = 8.6 Hz, 1 H, 4-H$_a$), 3.15 (dd, J = 4.8 and 10.3 Hz, 1 H, 4-H$_b$), 3.91–4.43 (m, 3 H, CH_2OC and CHO), 4.50–4.61 (m, 2 H, CH_2-OBz), 5.17 (d, J = 5.7 Hz, 1 H, 2-H), 7.32–7.85 (m, 5H, C$_6H_5$).

(-)-[2*S*(2α,5α)]-1,3-Oxathiolane-2,5-dimethanol 5-Benzoate (18). p-Toluenesulfonic acid (1.76 g, 0.0093 mol) was added to a solution of **17** (10 g, 0.031 mol) in MeOH (40 mL) and the mixture stirred at room temprature for 7 h. After neutralization with triethylamine, the aqueous solution (100 mL) of NaIO$_4$ (9.95 g, 0.0465 mol) was added dropwise and the mixture stirred for 10 min. NaBH$_4$ (2.345 g, 0.062 mol) was added and the mixture stirred for further 5 min. After neutralization with triethylamine, the mixture was filtered, and solvents were evaporated to a half volume. The aqueous mixture was extracted with ethyl acetate (300 mL × 2), and the organic layer was washed with water (100 mL) and brine (100 mL), dried (MgSO$_4$), and evaporated. The residue was purified by silica gel column chromatography to give **18** (15.88 g, 75%) as a colorless oil: ^{1}H NMR (DMSO-d_6) δ 2.82 (pseudo t, J = 8.6 and 10.1 Hz, 1 H, 4-H$_a$), 3.18 (dd, J = 4.8 and 10.2 Hz, 1 H, 4-H$_b$), 3.45 (dd, J = 6.4 and 11.5 Hz, 1 H, CH_aOH), 3.65 (dd, J = 5.7 and 11.7 Hz, 1 H, CH_bOH), 4.25–4.57 (m, 3 H, 5-H and CH_2OBz), 5.10 (t, J = 5.5 Hz, 1 H, CH$_2$OH), 5.15 (t, J = 4.8 Hz, 1 H, 2-H), 7.41–8.05 (m, 5 H, C$_6H_5$).

(-)-[2*S*(2α,5α)]-2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolane-5-methanol Benzoate (19). *tert*-Butyldiphenylsilyl chloride (12.29 mL, 0.0473 mol) was added to a solution of **18** (10 g, 0.0394 mol) in DMF (30 mL) followed by imidazole (13.41 g, 0.197 mol) and the reaction mixture stirred at room temperature for 1 h. DMF was removed under high vacuum, and the residue was dissolved in ethyl acetate (300 mL), washed with water (100 mL) and brine (100 mL), dried (MgSO$_4$), and evaporated. The residue was purified by silica gel column chromatography to give **19** (17.0 g, 98%) as a colorless oil: ^{1}H NMR (CDCl$_3$) δ 1.05 (s, 9 H, *tert*-butyl), 2.85 (pseudo t, J = 9.0 and 10.2 Hz, 1 H, 4-H$_a$), 3.11 (dd, J = 4.8 and 10.0 Hz, 1 H, 4-H$_b$), 3.78 (dd, J = 5.3 and 11.1 Hz, 1 H, CH_aOSi), 3.95 (dd, J = 5.3 and 10.6 Hz, 1 H, CH_bOSi), 4.33–4.55 (m, 3 H, 1-H and CH_2OBz), 5.32 (dd, J = 5.3 and 10.6 Hz, 1 H, 2-H), 7.34–8.05 (m, 15 H, 3 × C$_6H_5$).

(-)-[2*S*(2α,5α)]-2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolane-5-methanol (20). NaOMe (0.33 g, 0.0061 mol) was added to a solution of **19** (15 g, 0.0305 mol) in MeOH (30 mL) and the reaction mixture stirred at room temperature for 2 h. After the mixture was neutralized with glacial acetic acid, MeOH was removed under high vacuum and the residue dissolved in ethyl acetate (350 mL), washed with water (200 mL) and brine (100 mL), dried (MgSO$_4$), and evaporated. The residue was purified by silica gel column chromatography to give **20** (10.65 g, 90%) as a colorless oil: ^{1}H NMR (DMSO-d_6) δ 1.00 (2, 9 H, *tert*-butyl), 2.68 (dd, J = 9.2 and 4.4 Hz, 1 H, 4-H$_a$), 3.04 (dd, J = 5.3 and 10.1 Hz, 1 H, 4-H$_b$), 3.53 (d, J = 5.3 Hz, 2 H, CH_2OSi), 3.56–4.18 (m, 4 H, 5-H, CH_2OH and CH$_2$OH), 5.26 (t, J = 5.5 Hz, 1 H, 2-H), 7.36–7.71 (m, 10 H, 2 × C$_6H_5$).

(-)-[2*S*(2α,5α)]-2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolane-5-carboxylic Acid (21). Pyridinium dichromate (PDC) (26.66 g, 0.070 mol) was added to a solution of **20** (5 g, 0.0129 mol) in dry DMF (300 mL) and the reaction mixture stirred at room temperature for 15 h. The reaction mixture was poured into water (300 mL), extracted with diethyl ether (500 mL × 5), dried (MgSO$_4$), and evaporated. The residue (5 g) was dried for 2 days and then used for the next reaction without further purification. For identification, **21** was esterified by treating with dimethyl sulfate and K$_2$CO$_3$ in acetone for 1 h. After acetone was evaporated, the residue was dissolved in ethyl acetate, washed with water and brine, dried (MgSO$_4$), and evaporated to give a residue which was purified by silica gel column chromatography to yield methyl ester of **21**, which was identical with the methyl ester synthesized from D-mannose.

[2*S*(2α,5α)]- and [2*S*(2α,5β)]-2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-ol Acetate (14). Pb(OAc)$_4$ (8.58 g, 0.0194 mol) was added to a solution of **21** (5 g) in dry THF (60 mL) followed by pyridine (1.57 mL, 0.0194 mol) and the reaction mixture stirred at room temperature for 30 min. After filtration through a Celite pad, THF was removed under high vacuum. The residue was purified by silica gel column chromatography to give **14** (2.41 g, 45%) as a colorless oil, which was identical with D-1,3-oxathiolanyl acetate synthesized from D-mannose.

General Procedure A for the Condensation of Pyrimidine Bases with the Acetate 14. A stirred suspension of pyrimidine bases (1.5 equiv) and (NH$_4$)$_2$SO$_4$ (10 mg) in hexamethyldisilazane (HMDS) (25 mL) was heated to reflux under argon until a clear solution was obtained. The solution was allowed to cool to room temperature and the HMDS removed under reduced pressure using anhydrous conditions. Dry 1,2-dichloroethane (10 mL) was added to the silylated pyrimidine bases followed by the acetate **14** (1.0 equiv) in 1,2-dichloroethane (20 mL). This suspension was cooled in an ice/water bath to 5 °C and treated with trimethylsilyl triflate (1.5 equiv), and the reaction mixture was stirred at room temperature for 1–3 h. The reaction mixture was poured into ethyl acetate (200 mL) and 5% NaHCO$_3$ solution (50 mL) and the resulting mixture stirred for 20 min. The organic layer was separated, washed with saturated NaHCO$_3$ solution and H$_2$O, dried over MgSO$_4$, and evaporated. The residue was purified by silica gel column chromatography using the appropriate solvents.

General Procedure B for the Desilylation of Protected Nucleosides. A solution of protected nucleosides (1.0 equiv) and tetra-*n*-butylammonium fluoride (1 M in THF) (1.2 equiv) in THF (25 mL) was stirred at room temperature until TLC indicated the disappearance of starting material (0.5–1 h). The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography using the appropriate solvents.

(+)-(2*S*,5*R*)-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]-*N*^{4}-acetylcytosine (22) and (-)-(2*S*,5*S*)-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]-*N*^{4}-acetylcytosine (23). General Procedure A. **22** (0.33 g, 43%): UV (MeOH) λ$_{max}$ 297 nm, 311 nm (pH 2). **23** (0.15 g, 20%): UV (MeOH) λ$_{max}$ 297 nm, 311 nm (pH 2).

(+)-(2*S*,5*R*)-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]cytosine (24). A solution of the β anomer **22** (0.15 g, 0.294 mmol) in MeOH (10 mL) was treated with NH$_3$/MeOH (saturated solution 0.5 mL), and the reaction mixture was stirred at room temperature until the disappearance of starting material was observed (3 h). The reaction mixture was concentrated under reduced pressure and the residue purified by preparative TLC using 5% MeOH/CHCl$_3$ as the eluant. The material obtained from the plate gave **24** (0.10 g, 73%) as a white solid on trituration with hexanes and Et$_2$O: UV (MeOH) λ$_{max}$ 271.5 nm, 283.5 nm (pH 2).

(-)-(2*S*,5*S*)-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]cytosine (25). The α anomer **23** (0.10 g, 0.196 mmol) and NH$_3$/MeOH (saturated solution, 0.5 mL) in MeOH (10 mL) were reacted according to procedure described for **24** to give **25** (0.07 g, 76%) as a white crystalline solid: UV (MeOH) λ$_{max}$ 271 nm, 283 nm (pH 2).

(+)-(2*S*,5*R*)-1-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]-cytosine (26). General Procedure B. White crystalline solid (0.055 g, 75%): UV (H$_2$O) λ$_{max}$ 270 nm (pH 7) (ε 9500), 279 (pH 2) (ε 13 700), 270 (pH 11) 270 (ε 9600).

(-)-(2*S*,5*S*)-1-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (27). General Procedure B. White solid (0.036 g, 76%): UV (H$_2$O) λ$_{max}$ 271 nm (pH 7) (9800), 279 (pH 2) (ε14 000), 271 (pH 11) (ε 10 000).

(2*S*,5*RS*)-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]uracil (28 and 29). General Procedure A. Inseparable mixture of anomers **28** and **29** (R_f = 0.62, chloroform–methanol (20:1), 0.32 g, 81%) as a white foam: UV (MeOH) λ$_{max}$ 261.0 nm.

(2*S*,5*RS*)-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]thymine (30 and 31). General Procedure A. Inseparable anomeric mixture of **30** and **31** (R_f = 0.65, chloroform–methanol (20:1), 0.40 g, 85%) as a white foam: UV (MeOH) λ_{max} 265.0 nm.

(2*S*,5*RS*)-5-Fluoro-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]uracil (32 and 33). General Procedure A. Inseparable mixture of anomers **32** and **33** (R_f = 0.64, chloroform–methanol (20:1), 0.41 g, 82%) as a white foam: UV (MeOH) λ_{max} 266.0 nm.

(2*S*,5*RS*)-5-Chloro-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]uracil (34 and 35). General Procedure A. Inseparable mixture of anomers **34** and **35** (R_f = 0.65, chloroform–methanol (20:1), 0.29 g, 60%) as a white foam: UV (MeOH) λ_{max} 272.0 nm.

(2*S*,5*RS*)-5-Bromo-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]uracil (36 and 37). General Procedure A. Inseparable mixture of anomers **36** and **37** (R_f = 0.64, chloroform–methanol (20:1), 0.29 g, 57%) as a white foam: UV (MeOH) λ_{max} 278.0 nm.

(2*S*,5*RS*)-5-Iodo-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]uracil (38 and 39). General Procedure A. Inseparable mixture of anomers **38** and **39** (R_f = 0.67, chloroform–methanol (20:1), 0.367 g, 64%) as a white foam: UV (MeOH) λ_{max} 283.0 nm.

(+)-(2*S*,5*R*)-5-Methyl-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]-*N*⁴-benzoylcytosine (40) and (−)-(2*S*,5*S*)-5-Methyl-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]-*N*⁴-benzoylcytosine (41). General Procedure A. **40** (R_f = 0.25, hexanes–ethyl acetate (5:1), 0.285 g, 41%) as a white foam: UV ($CHCl_3$) λ_{max} 330.0 nm. **41** (R_f = 0.29, hexanes–ethyl acetate (5:1), 0.19 g, 27%) as a white foam: UV ($CHCl_3$) λ_{max} 330.2 nm.

(+)-(2*S*,5*R*)-5-Fluoro-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]-*N*⁴-benzoylcytosine (42) and (−)-(2*S*,5*S*)-5-Fluoro-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]-*N*⁴-benzoylcytosine (43). General Procedure A. (R_f = 0.13, hexanes–ethyl acetate (4:1), 0.29 g, 41%) as a white foam: UV ($CHCl_3$) λ_{max} 330.7 nm. **43** (R_f = 0.20, hexanes–ethyl acetate (4:1), 0.18 g, 25%) as a white foam: UV ($CHCl_3$) λ_{max} 331.2 nm.

(+)-(2*S*,5*R*)-5-Chloro-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]-*N*⁴-benzoylcytosine (44) and (−)-(2*S*,5*S*)-5-Chloro-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]-*N*⁴-benzoylcytosine (45). General Procedure A. **44** (R_f = 0.21, hexanes–ethyl acetate (4:1), 0.42 g, 58%), as a white foam: UV (isopropanol) λ_{max} 333.2 nm. **45** (R_f = 0.28, hexanes–ethyl acetate (4:1), 0.23 g, 32%) as a white foam: UV (2-propanol) λ_{max} 333.1 nm.

(+)-(2*S*,5*R*)-5-Bromo-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]-*N*⁴-benzoylcytosine (46) and (−)-(2*S*,5*S*)-5-Bromo-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]-*N*⁴-benzoylcytosine (47). General Procedure A. **46** (R_f = 0.44, hexanes–ethyl acetate (3:1), 0.26 g, 33%) as a white foam: UV ($CHCl_3$) λ_{max} 334.7 nm. **47** (R_f = 0.50, hexanes–ethyl acetate (3:1), 0.20 g, 26%) as a white foam: UV ($CHCl_3$) λ_{max} 333.7 nm.

(+)-(2*S*,5*R*)-5-Iodo-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]-*N*⁴-benzoylcytosine (48) and (−)-(2*S*,5*S*)-5-Iodo-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]-*N*⁴-benzoylcytosine (49). General Procedure A. **48** (R_f = 0.31, hexanes–ethyl acetate (4:1), 0.26 g, 31%) as a white foam: UV ($CHCl_3$) λ_{max} 339.7 nm. **49** (R_f = 0.38, hexanes–ethyl acetate (4:1), 0.18 g, 21%) as a white foam: UV ($CHCl_3$) λ_{max} 340.1 nm.

(+)-(2*S*,5*R*)-1-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]uracil (50) and (−)-(2*S*,5*S*)-1-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]uracil (51). General Procedure B. **50** (0.067 g, 34%, R_f = 0.55) as a white solid: UV (H_2O) λ_{max} 261.5 nm (ε 14 090) (pH 7), 261.5 (ε 13 500) (pH 2), 260.9 (ε 9700) (pH 11). **51** (0.060 g, 31%, R_f = 0.51) as a white foam: UV (H_2O) λ_{max} 262.3 nm (ε 14 100) (pH 7), 262.3 (ε 15 000) (pH 2), 261.3 (ε 11 470) (pH 11).

(+)-(2*S*,5*R*)-1-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]thymine (52) and (−)-(2*S*,5*S*)-1-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]thymine (53). General Procedure B. **52** (0.074 g, 41%, R_f = 0.58) as a white solid: UV (H_2O) λ_{max} 266.8 nm (ε 14 550) (pH 7), 266.8 (ε 14 300) (pH 2), 265.8 (ε 12 100) (pH 11). **53** (0.057 g, 32%, R_f = 0.53) as a white foam: UV (H_2O) λ_{max} 267.3 nm (ε 11 500) (pH 7), 267.3 (ε 12 470) (pH 2), 266.8 (ε 9090) (pH 11).

(+)-(2*S*,5*R*)-5-Fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]uracil (54) and (−)-(2*S*,5*S*)-5-Fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]uracil (55). General Procedure B. **54** (0.08 g, 39%, R_f = 0.60) as a white solid: UV (H_2O) λ_{max} 268.5 (ε 10 100) (pH 7), 268.8 (ε 11 300) (pH 2), 267.8 (ε 11 150) (pH 11). **55** (0.075 g, 34%, R_f = 0.57) as a white solid: UV (H_2O) λ_{max} 268.8 nm (ε 13 510) (pH 7), 269.3 (ε 13 950) (pH 2), 268.3 (ε 11 510) (pH 11).

(+)-(2*S*,5*R*)-5-Chloro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]uracil (56) and (−)-(2*S*,5*S*)-5-Chloro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]uracil (57). General Procedure B. **56** (0.075 g, 52%, R_f = 0.35) as a white solid: UV (H_2O) λ_{max} 277.0 nm (ε 10 870) (pH 7), 277.0 (ε 11 110) (pH 2), 274.0 (ε 8670) (pH 11). **57** (0.05 g, 35%, R_f = 0.31) as a white solid: UV (H_2O) λ_{max} 277.0 nm (ε 10 390) (pH 7), 277.0 (ε 10 890) (pH 2), 274.0 (ε 7590) (pH 11).

(+)-(2*S*,5*R*)-5-Bromo-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]uracil (58) and (−)-(2*S*,5*S*)-5-Bromo-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]uracil (59). General Procedure B. **58** (0.076 g, 49%, R_f = 0.37) as a white solid: UV (H_2O) λ_{max} 279.0 nm (ε 9940) (pH 7), 279.0 (ε 10 590) (pH 2), 276.0 (ε 7290) (pH 11). **59** (0.052 g, 34%, R_f = 0.32) as a white solid: UV (H_2O) λ_{max} 279.0 nm (ε 10 140) (pH 7), 279.0 (ε 10 890) (pH 2), 276.0 (ε 8000) (pH 11).

(+)-(2*S*,5*R*)-5-Iodo-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]uracil (60) and (−)-(2*S*,5*S*)-5-Iodo-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]uracil (61). General Procedure B. **60** (0.090 g, 42%, R_f = 0.46) as a white solid: UV (H_2O) λ_{max} 288.0 nm (ε 8850) (pH 7), 288.0 (ε 9850) (pH 2), 278.5 (ε 6870) (pH 11). **61** (0.080 g, 38%, R_f = 0.42) as a white solid: UV (H_2O) λ_{max} 288.0 nm (ε 8140) (pH 7), 288.0 (ε 8900) (pH 2), 279.0 (ε 6590) (pH 11).

General Procedure for the Desilylation and Debenzoylation of Protected Nucleosides. A solution of protected nucleosides (1.0 equiv) and tetra-*n*-butylammonium fluoride (1 M in THF) (1.2 equiv) in THF (25 mL) was stirred at room temprature until TLC indicated the disappearance of starting material (0.5–1 h). The reaction mixture was concentrated under reduced pressure. The residue was treated with saturated methanolic ammonia (20 mL) and stirred at room temperature overnight. The solvent was evaporated and the residue purified by silica gel column chromatography (chloroform–methanol (10:1)).

(+)-(2*S*,5*R*)-5-Methyl-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (62). White solid (R_f = 0.31, 0.095 g, 90%) from ether and methanol: UV (H_2O) λ_{max} 277.0 nm (ε 10 100) (pH 7) 286.8 (ε 14 150) (pH 2), 276.8 (ε 9190) (pH 11).

(−)-(2*S*,5*S*)-5-Methyl-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (63). White solid (R_f = 0.31, 0.06 g, 90%) from ether and methanol; UV (H_2O) λ_{max} 277.5 nm (ε 10 110) (pH 7), 286.8 (ε 14 780) (pH 2), 276.8 (ε 9500) (pH 11).

(+)-(2*S*,5*R*)-5-Fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (64). White solid (R_f = 0.29, 0.065 g, 58%) from ether and methanol; UV (H_2O) λ_{max} 280.0 nm (ε 12 790) (pH 7), 287.8 (ε 15 450) (pH 2), 279.8 (ε 12 210) (pH 11).

(−)-(2*S*,5*S*)-5-Fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (65). White solid (R_f = 0.29, 0.04 g, 64%) from ether and methanol: UV (H_2O) λ_{max} 280.7 nm (ε 12 060) (pH 7), 287.8 (ε 15 010) (pH 2), 280.0 (ε 12 140) (pH 11).

(+)-(2*S*,5*R*)-5-Chloro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (66). White solid (R_f = 0.30, 0.065 g, 63%) from ether and methanol: UV (H_2O) λ_{max} 285.5 nm (ε 12 990) (pH 7), 295.5 (ε 16 640) (pH 2), 285.5 (ε 12 170) (pH 11).

(−)-(2*S*,5*S*)-5-Chloro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (67). White solid (R_f = 0.30, 0.04 g, 63%) from ether and methanol: UV (H_2O) λ_{max} 286.0 nm (ε 11 500) (pH 7), 295.5 (ε 15 550) (pH 2), 285.3 (ε 11 950) (pH 11).

(+)-(2*S*,5*R*)-5-Bromo-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (68). White solid (R_f = 0.32, 0.085 g, 56%) from ether and methanol: UV (H_2O) λ_{max} 287.0 nm (ε 8880) (pH 7), 298.0 (ε 12 750) (pH 2), 287.0 (ε 10 070) (pH 11).

(−)-(2*S*,5*S*)-5-Bromo-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (69). White solid (R_f = 0.32, 0.045 g, 68%) from

ether and methanol: UV (H_2O) λ_{max} 287.0 nm (ε 8000) (pH 7), 298.0 (ε 11 500) (pH 2), 287.5 (ε 8750) (pH 11).

(+)-(2S,5R)-5-Iodo-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (70). White solid (R_f = 0.33, 0.075 g, 67%) from ether and methanol: UV (H_2O) λ_{max} 293.3 nm (ε 8770) (pH 7), 308.0 (ε 11 940) (pH 2), 293.5 (ε 8750) (pH 11).

(−)-(2S,5S)-5-Iodo-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (71). White solid (R_f = 0.33, 0.059 g, 68%) from ether and methanol: UV (H_2O) λ_{max} 293.5 nm (ε 6550) (pH 7), 308.0 (ε 7270) (pH 2), 293.5 (ε 7100) (pH 11).

(−)-(2S,5R)-6-Chloro-9-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]purine (72) and (−)-(2S,5S)-6-Chloro-9-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]purine (73). A solution of 14 (2.1 g, 5.05 mmol) in dry CH_2Cl_2 (30 mL) and TMSOTf (1.46 mL, 7.62 mmol) were added to a solution of silylated 6-chloropurine (1.17 g, 7.62 mmol), prepared from 6-chloropurine (1.17 g, 7.62 mmol), and hexamethyldisilazane (50 mL), and ammonium sulfate (catalytic amount), in dry $ClCH_2CH_2Cl$ (20 mL) at room temperature. The mixture was stirred at room temperature for 14 h under N_2, during which time the intially formed N-3 isomer was converted to N-9 isomer. The same workup used in general procedure A and purification by silica gel column chromatography gave an anomeric mixture of 72 and 73 (R_f = 0.64, hexanes–ethyl acetate (1:1), 1.33 g, 52%) as a white foam: UV (MeOH) λ_{max} 265.0 nm. A small amount of sample was purified by preparative TLC (hexanes–ethyl acetate (1:1)) for ^1H NMR samples.

(−)-(2S,5R)-6-Chloro-9-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]purine (74) and (−)-(2S,5S)-6-Chloro-9-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]purine (75). General Procedure B. 74 (0.294 g, 41%) as a white solid from methylene chloride and hexanes: UV (H_2O) λ_{max} 264.9 nm (ε 12 730) (pH 7), 264.5 (ε 12 780) (pH 2), 264.3 (ε 13 010) (pH 11). 75 (0.274 g, 39%) as a white solid: UV (H_2O) λ_{max} 264.8 nm (ε 14 550) (pH 7), 264.5 (ε 14 980) (pH 2), 264.3 (ε 11 560) (pH 11).

(−)-(2S,5R)-9-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]adenine (76). A solution of 74 (0.07 g, 0.257 mmol) and NH_3/MeOH (15 mL) was heated at 90 °C in a steel bomb for 24 h. After cooling, the solvent was removed under vacuum and the residual syrup purified by column chromatography (silica gel 230–400 mesh) using chloroform–methanol (10:1) as the eluent to give 76 (R_f = 0.2, 0.048 g, 74%) as a white solid: UV (H_2O) λ_{max} 259.0 nm (ε 18 760) (pH 7), 258.0 (ε 17 790) (pH 2), 259.4 (ε 19 050) (pH 11).

(−)-(2S,5R)-N^6-Methyl-9-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]adenine (77). A solution of 74 (0.06 g, 0.22 mmol) and methylamine (40 wt % solution in H_2O, 5 mL) in MeOH (10 mL) was heated at 90 °C in a steel bomb for 15 h. After cooling, the solvents were removed under vacuum. The residual syrup was purified by column chromatography (silica gel 230–400 mesh) using chloroform–methanol (10:1) as the eluent to give 77 (R_f = 0.21, 0.04 g, 68%) as a white solid: UV (H_2O) λ_{max} 265.9 nm (ε 20 150) (pH 7), 262.3 (ε 24 070) (pH 2), 265.3 (ε 19 900) (pH 11).

(−)-(2S,5R)-9-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]-hypoxanthine (78). A mixture of 74 (0.05 g, 0.183 mmol), 2-mercaptoethanol (0.05 mL, 0.735 mmol), and NaOMe (0.039 g, 0.735 mmol) in MeOH (15 mL) was refluxed for 4 h under N_2. The mixture was cooled, neutralized with glacial AcOH, and evaporated to dryness under vacuum. The residue was purified by silica gel column chromatography (chloroform–methanol (10:1)) to give 78 (R_f = 0.15, 0.041 g, 88%) as a white leaflet, which was triturated with ether: UV (H_2O) λ_{max} 248.5 nm (ε 12 400) (pH 7), 249.0 (ε 12 990) (pH 2), 252.9 (ε 13 090) (pH 11).

(−)-(2S,5S)-9-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]adenine (79). A solution of 75 (0.072 g, 0.264 mmol) and NH_3/MeOH (10 mL) was treated according to the same procedure used for 76 to give 79 (R_f = 0.2, 0.05 g, 75%) as a white solid, which was triturated with ether/methanol: UV (H_2O) λ_{max} 258.9 nm (ε 21 050) (pH 7), 257.5 (ε 21 100) (pH 2), 259.4 (ε 22 550) (pH 11).

(−)-(2S,5S)-N^6-Methyl-9-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]adenine (80). A solution of 75 (0.06 g, 0.22 mmol) and methylamine (40 wt % solution in H_2O, 5 mL) in MeOH (10 mL) was treated according to the same procedure used for 77 to give 80 (R_f = 0.20, 0.041 g, 70%) as a white solid, which was triturated with hexanes/methylene chloride: UV (H_2O) λ_{max} 265.8 nm (ε 18 840) (pH 7), 262.8 (ε 19 450) (pH 2), 265.8 (ε 20 510) (pH 11).

(−)-(2S,5S)-9-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]hypoxanthine (81). A mixture of 75 (0.07 g, 0.257 mmol), 2-mercaptoethanol (0.07 mL, 1.03 mmol), and NaOMe (0.066 g, 1.03 mmol) in MeOH (10 mL) was treated according to the same procedure used for 78 to give 81 (R_f = 0.14, 0.05 g, 77%) as a white solid: UV (H_2O) λ_{max} 248.9 nm (ε 16 520) (pH 7), 249.0 (ε 15 950) (pH 2), 253.4 (ε 17 010) (pH 11).

(2S,5RS)-2-Fluoro-6-chloro-9-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]purine (82 and 83). A solution of 14 (2.80 g, 6.73 mmol) in dry CH_2Cl_2 (20 mL) was added to a solution of silylated 2-fluoro-6-choropurine, prepared from 2-fluoro-6-choropurine (1.74 g, 10.09 mmol), hexamethyldisilazane (40 mL), and ammonium sulfate (catalytic amount), in dry CH_2Cl_2 (60 mL). TMSOTf (1.95 mL, 10.07 mmol) was added at −10 °C, and the reaction mixture was warmed to room temperature and then refluxed for 4 h, during which time the initially formed N-3 isomer was converted to N-9 isomer. The same workup used in general procedure A and purification by silica gel column chromatography (20% EtOAc in hexanes) afforded a mixture of β-anomer 82 and α-anomer 83 (1.2:1.0; β/α) as a white solid (1.95 g, 55%): UV (MeOH) λ_{max} 269.0 nm.

(−)-(2S,5R)-2-Fluoro-6-amino-9-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]purine (84), (−)-(2S,5S)-2-Fluoro-6-amino-9-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]purine (85), (−)-(2S,5R)-2-Amino-6-chloro-9-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]purine (86), and (+)-(2S,5S)-2-Amino-6-chloro-9-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]purine (87). Dry ammonia gas was bubbled into a stirred solution of 82 and 83 (1.92 g, 3.62 mmol) in DME (50 mL) at room temperature overnight. The salts were removed by filtration and the filtrate evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes–ethyl acetate (5:1)) to give 84 (R_f = 0.29, 0.27 g, 15%) as a white solid [UV (MeOH) λ_{max} 261.0, 268.0 (sh) nm], 85 (R_f = 0.22, 0.22 g, 12%) as a white solid [UV (MeOH) λ_{max} 261.0, 268.0 (sh) nm], and an anomeric mixture of 86 and 87 (R_f = 0.64, 1.27 g, 67%) as a white solid [UV (MeOH) λ_{max} 310.0 nm].

(−)-(2S,5R)-2-Fluoro-6-amino-9-[2-(hydroxymethyl)-1,3-oxathiolan-4-yl]purine (88). General Procedure B. White crystalline solid (0.033 g, 84%) from 2-propanol: UV (H_2O) λ_{max} 260.8 (ε 18 280), 268.5 (sh) nm (ε 14 570) (pH 7), 261.5 (ε 16 710), 269.5 (sh) (ε 13 290) (pH 2), 260.8 (ε 19 570), 269.0 (sh) (ε 15 430) (pH 11).

(−)-(2S,5S)-2-Fluoro-6-amino-9-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]purine (89). General Procedure B. White crystalline solid (0.084 g, 79%) from MeOH: UV (H_2O) λ_{max} 261.3 (ε 15 760), 269.5 (sh) nm (ε 12 280) (pH 7), 261.5 (ε 15 980), 269.0 (sh) (ε 12 930) (pH 2), 261.3 (ε 16 630), 269.5 (sh) (ε 13 590) (pH 11).

(−)-(2S,5R)-2-Amino-6-chloro-9-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]purine (90) and (+)-(2S,5S)-2-Amino-6-chloro-9-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]purine (91). General Procedure B. 90 (R_f = 0.30, 0.12 g, 34%) as a crystalline solid: UV (H_2O) λ_{max} 307.0 nm (ε 8230) (pH 7), 308.0 nm (ε 8230) (pH 2), 307.5 (ε 8480) (pH 11). 91 (R_f = 0.25, 0.15 g, 42%) as a crystalline solid: UV (H_2O) λ_{max} 307.5 nm (ε 6300) (pH 7), 308.0 (ε 5700) (pH 2), 307.5 (ε 6900) (pH 11).

(−)-(2S,5R)-9-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]guanine (92). A mixture of 75 (0.055 g, 0.191 mmol), 2-mercaptoethanol (0.081 mL, 1.13 mmol), and NaOMe (prepared by dissolving 0.078 g in 5 mL of MeOH) in MeOH (10 mL) was treated according to the same procedure used for 78 to give 92 (R_f = 0.030 g, 59%) as a white solid: UV (H_2O) λ_{max} 252.9 nm (ε 14 300) (pH 7), 255.5 (ε 13 500) (pH 2), 263.0 (ε 12 160) (pH 11).

(+)-(2S,5S)-9-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]-guanine (93). A mixture of 91 (0.098 g, 0.34 mmol), 2-mercaptoethanol (0.347 mL, 4.87 mmol), and NaOMe (0.11 g, 2.03 mmol) in MeOH (10 mL) was treated according to the same procedure used in 78 to give 93 (0.065 g, 71%) as a white solid: UV (H_2O) λ_{max} 253.4 nm (ε 6790) (pH 7), 255.0 (ε 5930) (pH 2), 264.8 (ε 5800) (pH 11).

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Supplementary Material Available: ^{1}H NMR data of β-D-(2*S*,5*R*)- and α-D-(2*S*,5*S*)-1,3-oxathiolanylpyrimidines (Table I) and ^{1}H NMR data of β-D-(2*S*,5*R*)- and α-D-(2*S*,5*S*)-1,3-oxathiolanylpurines Table II (10 pages). Ordering information is given on any current masthead page.

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