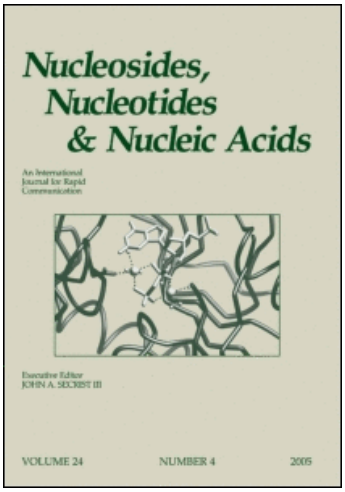

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SYNTHESIS OF (±)-*cis*-1-[2-(HYDROXYMETHYL)-1,3-OXATHIOLAN-5-YL]CYTOSINE AND ITS (±)-*trans* ISOMER

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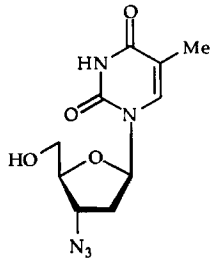
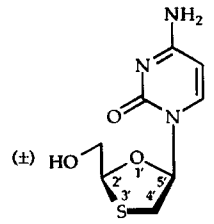
Abstract: The title compounds were synthesized by the formation of 2-[(benzyloxy)methyl]-1,3-oxathiolan-5-one and subsequent DIBALH reduction, acetylation, coupling with N-(1,2-dihydro-2-oxo-4-pyrimidinyl)-2-ethylhexanamide and deprotection.

Interest in nucleoside chemistry has been intensified since the discovery that the triphosphate of 3'-azido-3'-deoxythymidine (AZT) is an inhibitor of the reverse transcriptase (RT) of HIV (human immunodeficiency virus), the virus that causes AIDS.[1] A variety of 2',3'-dideoxynucleosides and their analogues (e.g., ddI,[2] ddC,[3] d4C,[4] d4T,[5] AZDU,[6] and AZG[7]) were subsequently synthesized and found to show similar inhibitory activity against HIV-1. These nucleosides are metabolized to their corresponding triphosphates, which then inhibit HIV-1 RT. Incorporation of the 5'-monophosphate terminates nascent viral DNA.[8]



AZT



1

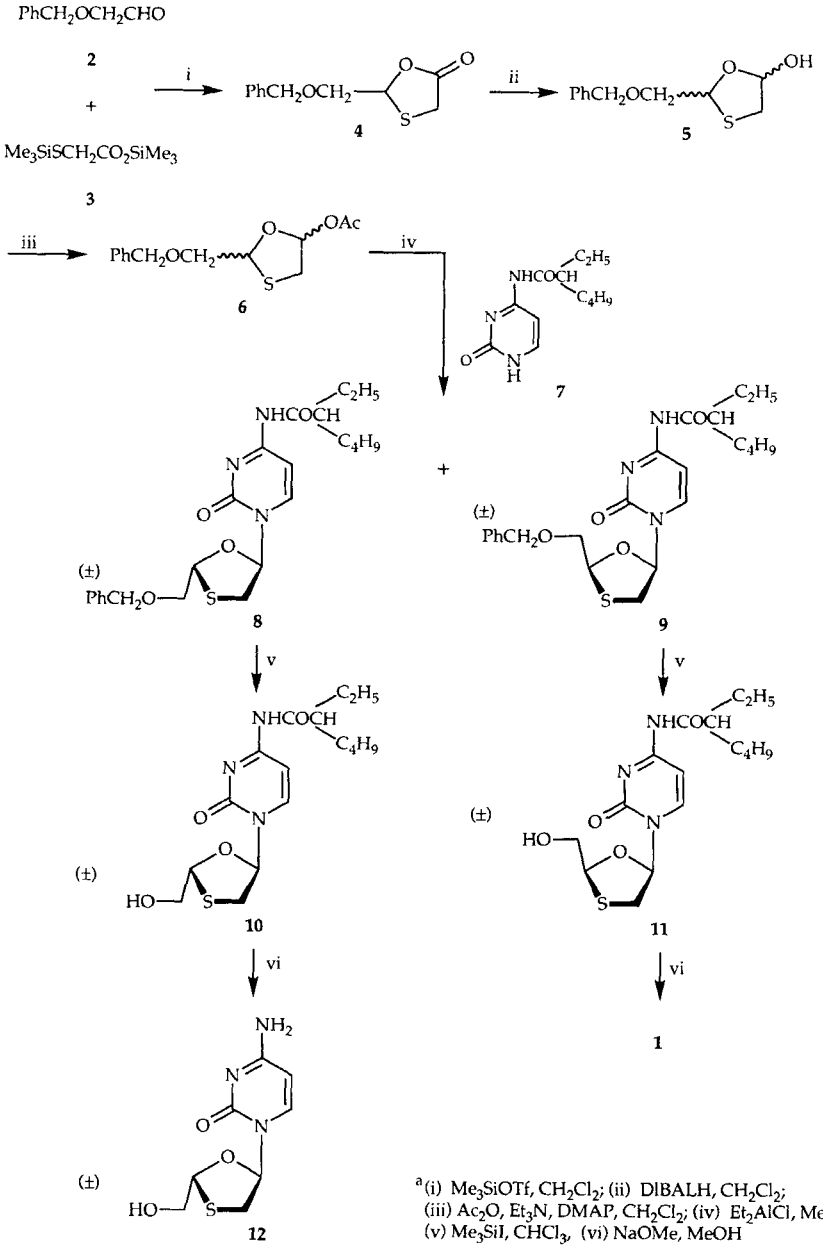
Synthetic modifications of nucleosides have included changes in substituents on the heterocyclic base and sugar moieties, most notably carbovir.[9] Four-membered oxetane[10] and cyclobutane[11] systems have also been reported. Nucleosides or carbocyclic

nucleosides in which a ring methylene of the sugar moiety is substituted by an oxygen,[12] sulfur[12b,13] or nitrogen[14] have recently been synthesized. Of particular interest, racemic *cis*-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (**1**) shows significant anti-HIV activity and low toxicity.[12b] The more active and less toxic enantiomer has been identified and corresponds to the unnatural L-form. Other synthetic approaches to this compound have since been developed.[15] Although attention has been on the *cis* isomer, the *trans* isomer remains of interest for biological explorations. This paper describes a synthetic method for the *cis* and *trans* racemates[16] (Scheme 1) and, where appropriate, comparison is made with methods in the literature. It should be noted that the current work had been in fact developed and completed before the literature reports[15] were published.

As shown in Scheme 1, the key intermediate for the synthesis of **1** is 2-[(benzyloxy)methyl]-1,3-oxathiolan-5-one (**4**) which was derived from the condensation reaction of 2-(benzyloxy)acetaldehyde (**2**)[17] with trimethylsilyl 2-[(trimethylsilyl)thio]acetate (**3**)[18] in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf).[19] Other protected forms of the 1,3-oxathiolan-5-one ring have also been analogously prepared as a *tert*-butyldiphenylsilyl ether[15a,c,d,f,g] or an ester (benzoate,[15b,e,h,i] acetate, proprionate, or butyrate[15j]). The advantage of the use of the persilylated form **3** over the free mercaptoacetic acid being used in all other publications[15] is to allow ring formation under milder reaction conditions (0 °C versus reflux in toluene). The OH group was protected, in the current work, as a benzyl ether for the reasons of: (1) providing methylene protons as a useful marker in ^{1}H NMR spectral analysis; (2) introduction of a UV chromophore for TLC monitoring of reactions; and (3) stability under both acidic and basic conditions to offer flexibility in the choice of reaction sequences.

Thia-lactone **4** was then reduced with diisobutylaluminum hydride (DIBALH) to afford, as determined by NMR spectroscopy,[20] a 2:1 mixture of racemic diastereomeric lactols **5**, the *cis* isomer presumably being the major component.[21] The crude lactols **5** were acetylated by acetic anhydride in the presence of triethylamine and a catalytic amount of 4-(dimethylamino)pyridine to give the corresponding acetates **6**.

Attempted purification of the lactols **5** or acetates **6** by silica gel chromatography resulted in decomposition.[22] In the case of the lactols, the only characterizable component was 1,4-dithiane-2,5-diol, which presumably is the result of dimerization of the decomposed mercaptoacetaldehyde.[23] It is conceivable that the crude acetates **6** were contaminated with the corresponding glycal as a result of the elimination of acetic acid. The observation of a doublet at δ 6.50 (J = 4 Hz) and an MH^+ of m/z 209 in the spectral analysis of the crude acetates **6** suggests the presence of up to 15% of the glycal. Without purification, the crude acetates **6** were used to couple with an appropriately protected cytosine in the presence of an acid catalyst. Rather than a persilylated cytosine, an N^4-



Scheme 1 [a]

acylcytosine was selected with the expectation that it would react with both **6** and the glycal.[24] A branched-chain acylcytosine, N-(1,2-dihydro-2-oxo-4-pyrimidinyl)-2-ethylhexanamide (**7**)[25] was then chosen because of its enhanced solubility over other commonly employed N^4-acylcytosines (such as N^4-acetyl and benzoyl) in organic solvents. Using cytosine **7** also provides an additional advantage since the racemic *cis* and *trans* products of the coupling reaction can be separarted by silica gel chromatography, whereas persilylated cytosine gives only inseparable products[12b] which require acetylation prior to *cis/trans* separation. Et_2AlCl was chosen as the catalyst in the coupling reaction for it would also serve as a scavenger of acid generated in the reaction.[26]

Examination of the ^1H NMR spectrum of the coupling reaction mixture revealed a 1:1 ratio of the racemic *cis/trans* diastereomers. It is conceivable that the nonstereoselective reaction at the anomeric center resulted from the lack of neighboring group participation. The fact that the 1:2 composition of diastereomeric **5** did not dictate the outcome of the product distribution of the coupling reaction implies the intermediacy of oxonium ions of **6**.

Silica gel chromatography of the coupling reaction mixture afforded the racemic diastereomeric nucleosides **8** and **9**. (The presence of the chiral center at the 2-ethylhexanamide group did not, in a practical sense, create additional diastereomers.) To determine their structures, COSY and HMQC (proton-detected heteronuclear chemical shift correlation)[27] experiments were undertaken for NMR spectral assignments (see Experimental).[28] The relative stereochemistry of these compounds was assigned by NOE studies (FIGURE 1). The *cis* orientation (stereoisomerism of C-2' with reference to C-5') of the more polar component **9** was established as follows: Irradiation of the 5'-proton (at δ 6.23) gave a 3.8% NOE to the 4'-proton resonating at δ 3.59 and a 0.5% NOE to the other 4'-proton resonating at δ 3.24. Further irradiation of H-2' (at δ 5.42) gave 0.5% NOE to the 4'-proton resonating at δ 3.59. Based on the observed NOE's from H-2' and H-5' to the same 4'-proton resonating at δ 3.59, H-2' and H-5' were located on the same side of the oxathiolane ring.

After the stereochemistry of **9** had been established, the *trans* configuration was assigned to the less polar isomer **8**. In the NOESY spectrum of **8**, H-5' (at δ 6.36) was observed to give an NOE to H-4'β resonating at δ 3.56. H-2' (at δ 5.88) also gave NOE's to both protons of the $PhCH_2\,OCH_2$ (one proton at δ 3.68, dd, J = 11.2 Hz, 6.2 Hz and the other at δ 3.58, dd, J = 10.9 Hz, 4.7 Hz). However, because of overlap of the proton at δ 3.58 with the downfield H-4' at δ 3.56, it was difficult to determine whether there was an NOE between H-2' and H-4' to establish the relative stereochemistry of C-2' to C-5' of racemic **8**. A one-dimensional NOE difference spectrum was therefore acquired with H-2' irradiated; there was no evidence of an NOE between H-2' and H-5', consistent with the *trans* stereochemistry proposed for **8**.

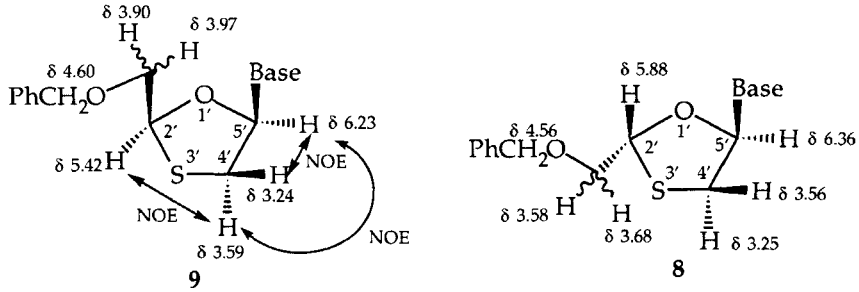


FIGURE 1. ^{1}H NMR of **9** and **8**.

Et_2AlCl was found to be more effctive than TMSOTf or $SnCl_4$ in catalyzing this coupling reaction. It is noteworthy that in the literature, $SnCl_4$ catalyzes persilylated cytosine and a silylated oxathiolane to give exclusively the *cis* product while Et_2AlCl gives no product,[15a] but a 1:1 *cis:trans* mixture is obtained even in the presence of $SnCl_4$ when benzoyloxy-oxathiolane is used.[15i] Based on these inconsistent results, it can be concluded that the effectiveness of a catalyst is dependent upon the nature of both reactants.

Debenzylation of the racemic *cis* nucleoside **9** was achieved with iodotrimethylsilane[29] to afford **11**, which was further treated with methanolic sodium methoxide to yield the target compound **1**[30] (2.1% overall yield starting with aldehyde **2** and silylated acid **3**). In a similar manner, the racemic *trans* nucleoside **8**, was treated with iodotrimethylsilane to produce **10**, which subsequently was converted to the racemic *trans* nucleoside **12** (2.6% overall yield) .

This work provides a mixture of the racemic *cis* nucleoside **1** and the *trans* analogue **12** in low yield. However, as a result of the continued promising anti-HIV activities of **1** and also its 5-fluoro derivative,[15f,g,i,j] more recent advancements in the preparation of **1** have included stereoselective synthesis of the racemate[15a] and enantiomers,[15c-g] and enzymatic resolution by enantiospecific hydrolysis of the monophosphate using 5'-ribonucleotide phosphohydrolase frm *Crotalus atrox* venom,[15h] hydrolysis of esters of **1** with pig liver esterase[15j] and deamination with cytidine deaminase from *Escherichia coli*.[15k] The most practical process of preparation of the desired L-form of **1** in large scale appears to be the one using a chiral auxiliary *d*- or *l*-menthol as the protecting group for the 2-carboxylate derivative of **1** or its precursor and the separation requires simple fractional crystallization.[31]

EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. NMR spectra were recorded on Varian XL-200, -300, or VXR 500S spectrometers and chemical shifts are reported as δ (ppm) downfield from Me_4Si. Chemical ionization mass spectroscopy (using methane as initiator) was performed by Oneida Research Services, Inc., Whitesboro, N.Y. Ultraviolet spectra were obtained on a Beckman DU-70 spectrophotometer. Chromatography (flash chromatography) was performed on 230-400 mesh silica gel (purchased from EM Science). Commercial reagents were purchased form Aldrich Chemical Co. and were used without purification unless otherwise stated.

Trimethylsilyl 2-[(trimethylsilyl)thio]acetate (3). The following procedure is considered an improvement over the literature procedure.[18] To a mixture of freshly distilled mercaptoacetic acid (5 g, 54 mmol) and a catalytic amount of ammonium sulfate (0.1 g, 0.8 mmol) was added hexamethyldisilazane (50 mL). A solid gradually formed with evolution of heat. The resulting mixture was heated at reflux under a nitrogen atmosphere. The white solid dissolved completely in 2 h and heating was continued overnight. Distillation *in vacuo* gave 11 g (84%) of **3** as a colorless liquid: bp 81 °C/0.5 torr (lit.[18] 108 °C/11.5 torr); ^1H NMR ($CDCl_3$) δ 0.30 (s, 9H, $SiMe_3$), 0.34 (s, 9H, $SiMe_3$), 3.19 (s, 2H, CH_2).

2-[(Benzyloxy)methyl]-1,3-oxathiolan-5-one (4). To a solution of **3** (41 g, 0.17 mol) in anhydrous dichloromethane (600 mL) cooled in an ice-water bath were added 26 g (0.17 mol) of 2-(benzyloxy)acetaldehyde (**2**)[17] and 3.8 g (0.017 mol) of trimethylsilyl trifluoromethanesulfonate. The solution was kept at 0 °C overnight. The solution was then neutralized with aqueous NaOH (pH 7 using pH paper) and filtered through a pad of celite. The organic phase was separated, washed with water, dried over magnesium sulfate, filtered, and evaporated *in vacuo*. The residue was chromatographed on silica gel, eluted with hexane:chloroform/1:1 then chloroform to give 11 g (29%) of **4** as a colorless oil. An analytical sample was obtained by further vacuum distillation: bp 158 °C/0.5 torr; CIMS m/z 225 (MH^+); ^1H NMR ($CDCl_3$) δ 3.54 (d, J = 16 Hz, 1H, H-4a), 3.70 (dd, J = 11 Hz, 4 Hz, 1H, $PhCH_2OCH_2$), 3.72 (d, J = 16 Hz, 1H, H-4b), 3.76 (dd, J = 11 Hz, 4 Hz, 1H, $PhCH_2OCH_2$), 4.59 (s, 2H, $PhCH_2$), 5.56 (t, J = 4 Hz, 1H, H-2), 7.30 (m, 5H, Ph). Anal. Calcd. for $C_{11}H_{12}SO_3$: C, 58.91; H, 5.39; S, 14.30. Found C, 59.04; H, 5.37; S, 14.25.

(±)-*trans*-N-[1-[2-(Benzyloxy)methyl-1,3-oxathiolan-5-yl]-1,2-dihydro-2-oxo-4-pyrimidinyl]-2-ethylhexanamide (8) and (±)-*cis*-N-[1-[2-(Benzyloxy)methyl-1,3-oxathiolan-5-yl]-1,2-dihydro-2-oxo-4-pyrimidinyl]-2-

ethylhexanamide (9). To a solution of lactone **4** (7.25 g, 32.3 mmol) in anhydrous dichloromethane (50 mL) cooled in a dry ice-acetone bath (-76 °C), was added a toluene solution of diisobutylaluminum hydride (1 N, 40 mL, 40 mmol). After 2 h, the reaction was removed from the cooling bath, and while cold a solution of citric acid (7 g) in water (35 mL) was slowly added. Vigorous gas evolution was observed. After 0.5 h, the resulting mixture was filtered through a pad of celite and the filtrate was extracted with dichloromethane. The dichloromethane solution was washed with water and dried over magnesium sulfate. Filtration and evaporation of the solvent gave 6.5 g of a racemic *cis* and *trans* mixture of the corresponding lactols **5**. The entire crude lactols **5** were dissolved in dichloromethane (10 mL). To this solution were added Et_3N (6 g, 59 mmol), acetic anhydride (4.4 g, 43 mmol), and 4-(dimethylamino)pyridine (0.35 g, 2.9 mmol). After stirring at room temperature overnight, the reaction was washed with water and dried over magnesium sulfate. Evaporation of the solvent afforded 7 g of a racemic *cis* and *trans* mixture of the corresponding acetates **6**. The entire crude acetates **6** were dissolved in acetonitrile (90 mL), and to this solution were added N-(1,2-dihydro-2-oxo-4-pyrimidinyl)-2-ethylhexanamide (**7**) (6.2 g, 26 mmol) and a 1.0 M solution of Et_2AlCl in hexanes (50 mL, 50 mmol). Heat was generated. The resulting solution was stirred at room temperature under nitrogen overnight. The solution was cooled in an ice-water bath and cold aqueous K_2CO_3 was added slowly (gas was evolved) until the mixture was basic. Chloroform was added and the mixture was filtered through a pad of celite. The chloroform phase was separated, washed with water, and dried over $MgSO_4$. After evaporation of the solvent *in vacuo,* the residue (*cis:trans*/1:1 based on the ^1H NMR spectral analysis) was chromatographed on silica gel eluted with $CHCl_3$ followed by $CHCl_3$:MeOH/9:1 to give 0.52 g of *trans* **8** as an oil, 2.3 g of a mixture of *cis* and *trans*, and 1.16 g of *cis* **9** as an oil (28% overall yield based on lactone **4**).

8: CIMS m/z 446 (MH^+); ^1H NMR (DMSO-d_6) δ 0.9-1.6 (m, 14H, NCOCH *(Et)Bu)*, 2.5 (m, 1H, NCOCH, the signal overlapped with the CD_3SOCHD_2 peak, but was evident when CD_3CN was used as solvent), 3.25 (dd, J = 12.2 Hz, 2.0 Hz, 1H, H-4'α), 3.56 (dd, J = 12.2 Hz, 5.2 Hz, 1H, H-4'β), 3.58 (dd, J = 10.9 Hz, 4.7 Hz, 1H, $PhCH_2OCH_2$), 3.68 (dd, J = 11.2 Hz, 6.2 Hz, 1H, $PhCH_2OCH_2$), 4.56 (s, 2H, $PhCH_2$), 5.88 (dd, J = 5.7 Hz, 4.5 Hz, 1H, H-2'), 6.36 (dd, J = 5.1 Hz, 1.9 Hz, 1H, H-5'), 7.27 (d, J = 7.5 Hz, 1H, H-5), 7.33 (m, 5H, Ph), 8.04 (d, J = 7.5 Hz, 1H, H-6), 10.92 (s, 1H, NH); Partial ^{13}C NMR (DMSO-d_6) δ 36.9 (C4'), 72.7 ($PhCH_2$), 73.3 ($PhCH_2OCH_2$,), 85.7 (C2'), 89.4 (C5'); UV (EtOH) λ_{max} 300 nm (ε 8300), 249 (ε 1700), λ_{min} 278 nm (ε 4800), 228 (ε 7000). Anal. Calcd. for $C_{23}H_{31}N_3O_4S$: C, 62.00; H, 7.01; N, 9.43; S, 7.20. Found: C, 61.88; H, 7.01; N, 9.23; S, 7.02.

9: CIMS m/z 446 (MH^+); ^1H NMR (DMSO-d_6) δ 0.9-1.8 (m, 14H, NCOCH*(Et)Bu)*, 2.5 (m, 1H, NCOCH, the signal overlapped with the CD_3SOCHD_2

peak, but was evident when CD_3CN was used as solvent), 3.24 (dd, J = 12.2 Hz, 3.0 Hz, 1H, H-4'β), 3.59 (dd, J = 12.2 Hz, 5.5 Hz, 1H, H-4'α), 3.90 (dd, J = 11.2 Hz, 4.6 Hz, 1H, $PhCH_2OCH_2$), 3.97 (dd, J = 11.3 Hz, 3.9 Hz, 1H, $PhCH_2OCH_2$), 4.60 (s, 2H, $PhCH_2$), 5.42 (t, J = 4.0 Hz, 1H, H-2'), 6.23 (dd, J = 5.2 Hz, 3.0 Hz, 1H, H-5'), 7.18 (d, J = 7.6 Hz, 1H, H-5), 7.35 (m, 5H, Ph), 8.32 (d, J = 7.5 Hz, 1H, H-6), 10.90 (s, 1H, NH); Partial ^{13}C NMR (DMSO-d_6) δ 36.8 (C4'), 69.8 ($PhCH_2OCH_2$), 72.5 ($PhCH_2$), 85.8 (C2'), 87.4 (C5'); UV (EtOH) λ_{max} 300 nm (ε 9600), 249 (ε 17800), λ_{min} 275 nm (ε 5600), 228 (ε 7500). Anal Calcd for $C_{23}H_{31}N_3O_4S$: C, 62.00; H, 7.01; N, 9.43; S, 7.20. Found: C, 61.97; H, 7.04; N, 9.38; S, 7.10.

(±)-*trans*-N-[1,2-Dihydro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-2-oxo-4-pyrimidinyl]-2-ethylhexanamide (10). To a solution of **8** (1.16 g, 2.6 mmol) in anhydrous chloroform (10 mL) was added iodotrimethylsilane (3 g, 15 mmol) in two portions. After 1 h at room temperature, the reaction was quenched by addition of methanol (10 mL) and the solution was stirred for 10 min followed by evaporation to dryness. Chloroform (10 mL) and 5% aqueous sodium bisulfite were added. The chloroform phase was separated and washed repeatedly with 5% aqueous sodium bicarbonate until the aqueous layer was basic. The separated chloroform solution was then washed with water, dried over magnesium sulfate, filtered and evaporated to dryness. Chromatographic purification of the residue on silica gel eluted with EtOAc:hexane/1:1 then EtOAc gave 0.27 g (30%) of solid **10**: mp 120-130 °C; CIMS m/z 356 (MH^+); ^1H NMR (DMSO-d_6) δ 0.8-1.6 (m, 14H, NCOCH*(Et)Bu*), 2.5 (m, 1H, NCOCH, the signal overlapped with the CD_3SOCHD_2 peak but was evident when CD_3CN was used as solvent.), 3.22 (dd, J = 12 Hz, 2 Hz, 1H, H-4'a), 3.6-3.8 (m, 3H, CH_2OH and H-4'b), 5.21 (t, J = 6 Hz, 1H, OH, D_2O exchangeable), 5.69 (t, J = 5 Hz, 1H, H-2'), 6.36 (dd, J = 5 Hz, 2 Hz, 1H, H-5'), 7.29 (d, J = 7 Hz, 1H, H-5), 8.06 (d, J = 7 Hz, 1H, H-6), 10.92 (s, 1H, NH); UV (EtOH) λ_{max} 299 nm (ε 8600), 248 (ε 16300), λ_{min} 274 nm (ε 4300), 227 (ε 4400); UV (0.1 N HCl) λ_{max} 309 nm (ε 14900), 239 (ε 10000), λ_{min} 269 nm (ε 3000), 226 (ε 8300); UV (0.1 N NaOH) λ_{max} 302 nm (ε 20200); λ_{min} 249 nm (ε 7000). Anal. Calcd. for $C_{16}H_{25}N_3O_4S$ 0.2 H_2O; C, 53.52; H, 7.13; N, 11.70. Found: C, 53.77; H, 7.20; N, 11.41.

(±)-*cis*-N-[1,2-Dihydro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-2-oxo-4-pyrimidinyl]-2-ethyl-hexanamide (11). Compound **9** (1.1 g, 2.4 mmol) was treated with iodotrimethylsilane (3 g, 14.7 mmol) in the same manner as described for **8** to give 0.34 g (40%) of hygroscopic solid **11**: CIMS m/z 356 (MH^+); ^1H NMR (DMSO-d_6) δ 0.8-1.6 (m, 14H, NCOCH*(Et)Bu*), 2.5 (m, 1H, NCOCH, the signal was overlapped with CD_3SOCHD_2 peak but was evident when CD_3CN was used as solvent.), 3.20 (dd, J = 12 Hz, 3Hz, 1H, H-4'a), 3.50 (dd, J = 12 Hz, 5 Hz, 1H, H-4'b), 3.82 (t,

J = 4 Hz, 2H, CH_2OH), 5.25 (t, J = 4 Hz, 1H, H-2'), 5.42 (t, J = 4 Hz, 1H, OH, D_2O exchangeable), 6.20 (dd, J = 5 Hz, 3 Hz, 1H, H-5'), 7.27 (d, J = 8 Hz, 1H, H-5), 8.38 (d, J = 8 Hz, 1H, H-6), 10.91 (s, 1H, NH); UV (EtOH) λ_{max} 299 nm (ε 7900), 249 (ε 15700), λ_{min} 274 nm (ε 4400), 228 (ε 5400); UV (0.1 N HCl) λ_{max} 259 nm (ε 30000), 224 (ε 11400), sh 303 nm (ε 14300); UV (0.1 N NaOH) λ_{max} 268 nm (ε 29200), λ_{min} 234 nm (ε 14000), sh 299 nm (ε 21000). Anal. Calcd. for $C_{16}H_{25}N_3O_4S$ 0.3 H_2O: C, 53.26; H, 7.15; N, 11.64. Found: C, 53.52; H, 7.02; N, 11.31.

(±)-*cis*-1-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (1). To a solution of **11** (0.3 g, 0.84 mmol) in anhydrous MeOH (10 mL) was added NaOMe (0.15 g, 3 mmol) in MeOH (2 mL). The reaction was heated at reflux for 20 min. The reaction was neutralized with 1 N HCl. The mixture was evaporated to dryness and the residue was chromatographed on silica gel eluted with EtOAC and 10% and 20% MeOH in EtOAc to give 0.15 g (81%) of **1**. An analytical sample was obtained by further recrystallization from MeOH: mp 183-190 °C[30] (lit.[12b] mp 171-173 °C; lit.[15a] mp 189°C); CIMS m/z 230 (MH^+); ^1H NMR (DMSO-d_6) δ 3.05 (dd, J = 12 Hz, 5 Hz, 1H, H-4'a), 3.2-3.4 (m, 1H, H-4'b), 3.7-3.8 (m, 2H, CH_2OH), 5.18 (t, J = 5 Hz, 1H, H-2'), 5.33 (t, J = 6 Hz, OH, D_2O exchangeable), 5.74 (d, J = 7 Hz, 1H, H-5), 6.21 (t, J = 5 Hz, 1H, H-5'), 7.2 (b, 1H, NH), 7.3 (b, 1H, NH), 7.83 (d, J = 7 Hz, 1H, H-6); UV (0.1 N HCl) λ_{max} 280 nm (ε 4600), λ_{min} 240 nm (ε 1300); UV (0.1 N NaOH) λ_{max} 270 nm (ε 10700), λ_{min} 248 nm (ε 7300). Anal. Calcd. for $C_8H_{11}N_3O_3S$: C, 41.91; H, 4.84; N, 18.33. Found: C, 42.01; H, 4.86; N, 18.27.

(±)-*trans*-1-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (12). To a solution of **10** (0.2 g, 0.56 mmol) in anhydrous MeOH (8 mL) was added NaOMe (0.14 g, 2.6 mmol) in MeOH (2 mL). After stirring at room temperature overnight, the solution was neutralized with aqueous 1N HCl, evaporated to dryness, and chromatographed on silica gel eluted with EtOAc, followed by 5% and then 10% MeOH in EtOAc to give 0.11 g (86%) of solid **12**: mp >200 °C (lit.[12b] mp >220 °C); CIMS m/z 230 (MH^+); ^1H NMR (DMSO-d_6) δ 3.10 (dd, J = 12 Hz, 3 Hz, 1H, H-4'a), 3.46 (dd, J = 12 Hz, 6 Hz, 1H, H-4'b), 3.56 (m, 1H, CH_2OH), 5.19 (t, J = 6 Hz, 1H, OH, D_2O exchangeable), 5.51 (t, H = 5 Hz, 1H, H-2'), 5.72 (d, J = 7 Hz, 1H, H-5), 6.35 (dd, J = 6 Hz, 3 Hz, 1H, H-5'), 7.2 (b, 2H, NH_2), 7.60 (d, J = 7 Hz, 1H, H-6); UV (EtOH) λ_{max} 271 nm (ε 7300), 235 (ε 6500), λ_{min} 252 nm (ε 5700), 225 (ε 6200); UV (0.1 N HCl) λ_{max} 280 nm (ε 11500), λ_{min} 241 nm (ε 2400); UV (0.1 N NaOH) λ_{max} 270 nm (ε 7800), λ_{min} 249 nm (ε 5300). Anal. Calcd. for $C_8H_{11}N_3O_3S$: C, 41.91; H, 4.84; N, 18.33. Found: C, 42.03; H, 4.81; N, 18.26.

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