An Efficient Route to β-D-Isoxazolidinyl Nucleosides via Diastereoselective Michael Addition of Hydroxylamine to Unsaturated Esters

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Enantioselective syntheses of β-D-isoxazolidinyl pyrimidine and purine nucleosides are described. Michael addition of *N*-methylhydroxylamine to α,β-unsaturated esters was investigated. Both *E*- and *Z*-esters **10*E*** and **10*Z*** produced the same intermediates which were cyclized to isoxazolidin-5-ones **8** with high diastereoselectivity. The major isoxazolidin-5-one **8a** was reduced and acetylated to acetate **11** for the preparation of nucleosides. The coupling reaction of acetate **11** with silylated thymine, uracil, and N^4-benzoylcytosine using TMSOTf as a Lewis acid yielded the corresponding nucleoside derivatives. The related purine analogue was produced by the $BF_3{\cdot}Et_2O$-catalyzed condensation of acetate **11** with silylated 6-chloropurine. The predominant formation of the cis isomers for both pyrimidine and purine analogues was unexpected and the reaction mechanism was investigated. The nucleoside intermediates were converted to the corresponding 1,2-diols, which were latter oxidized and reduced to the desired monoalcohol products such as **14**, **16**, **19,** and **24**.

Introduction

Synthesis of nucleosides as antiviral and anticancer agents has attracted great attention in the past decade.[1] 2′,3′-Dideoxynucleosides are an important class of anti-HIV reverse transcriptase inhibitors. Many of the FDA-approved anti-AIDS drugs such as AZT, ddC, ddI, d4T, and 3TC belong to this class.[2] Their cytotoxicities and drug resistances have been the obstacles in the treatment of AIDS patients, suggesting the need for further research in this field.[3] A general strategy is the development of new classes of modified nucleoside analogues[4] that feature novel analogues of ribose as the possible bases for potent antiviral agents with cross resistances and low cytotoxicities.[5]

In this context, exciting biological results have been achieved from a new generation of nucleoside analogues in which a second heteroatom is inserted in the furanosyl ring.[6,7] 3TC, which contains an oxathiolanyl ring, has shown excellent antiviral (HIV and HBV) activities and no significant drug resistance after 1 year of clinical trials when used in combination with AZT.[6] Interestingly, many other diheteroatom ring analogues such as dioxolanyl and oxathiolanyl nucleosides are being used as antiviral agents while additional ones are undergoing preclinical and clinical trials.[7] The general methods for the synthesis of these substances have involved the insertion of oxygen or sulfur in 1,3-relationship as in five-membered ring **1** (Figure 1). The preparation of the corresponding 1,3-oxazolidine systems (**1**, X = NR) has, however, been difficult because of the unstable properties of aminal moieties.[8]

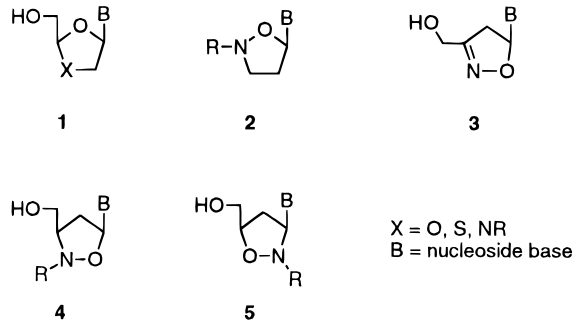

Figure 1.

Isoxazolidine **2** illustrates a structure that allows the stable placement of nitrogen into the furanosyl ring of

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nucleoside analogues (Figure 1). The successful introduction of isoxazolidinyl structures into nucleoside chemistry was achieved by Tronchet and his associates who, in 1992, reported the first synthesis of compounds **2** (R = Me, Ph; B = thymine).[9] Although these compounds do not show anti-HIV activity, their novel structures hold potential for the development of active compounds.[10]

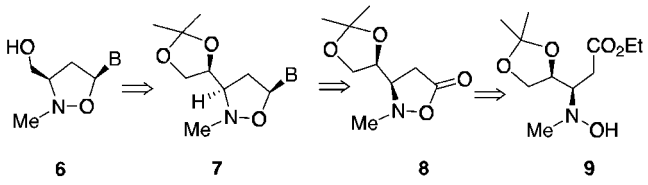
Isoxazolines **3** and isoxazolidines **4**−**5**,[11] which are substituted with a nucleoside base and a *hydroxymethyl* group in a 1,3-relative position, can be suitable models for the study of their antiviral properties. The key structural elements of **3**−**5** are the hydroxymethyl group, the nucleoside base, and the isoxazole core. First, incorporation of the hydroxymethyl group potentially allows enzymatic phosphorylation to triphosphate intermediates which function as RT inhibitors or DNA chain terminators. Second, the nucleoside base should be conveniently coupled to the N−O-containing ring via a glycosidic bond. Third, the connection of oxygen and nitrogen might provide fair structural stability as a result of the reduced basicity caused by the mutual inductive effect of the two heteroatoms.

We have successfully prepared nucleosides **3**−**4** which bear pyrimidine and purine bases.[12] Compound **3**, which exhibits moderate anti-HIV-1 activity, was prepared in a racemic form via a 1,3-dipolar cycloaddtion.[12b,d] The racemic analogues **4** were prepared via a noncycloaddition method[12a] and the related L-isomer was constructed by using an optically active lactone as the starting material.[12c] In this paper, we report the diastereoselective Michael addition of hydroxylamine derivatives to α,β-unsaturated ester for the synthesis of the D-isomers of **4**. The chemistry has been designed so that both D- and L-isomers **4** can be efficiently prepared from readily available starting materials. More interestingly, the availability of **4** and related derivatives provide a great possibility for future construction of the optically active compounds **3**.[13]

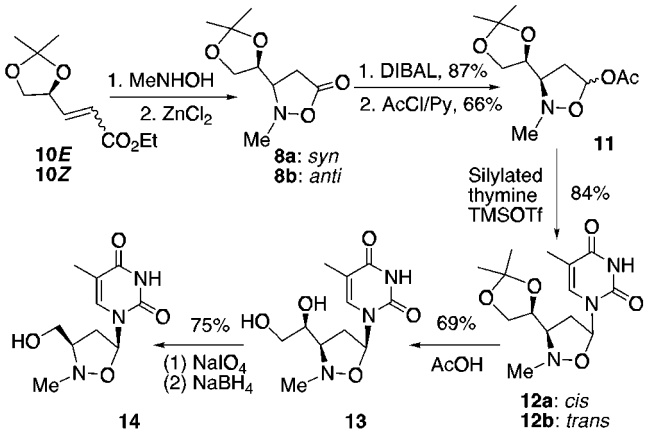
Results and Discussion

Diastereoselective Michael Addition of Hydroxylamine to Unsaturated Esters. We envisioned that the D-isomer **6** could be obtained from **7** which, in turn, could be prepared from compound **8** (Scheme 1). We further imagined that a route to the desired target **8** would be

Scheme 1



Scheme 2



via the synthesis of **9,** which would require the *diastereoselective* Michael addition of *N*-methylhydroxylamine to the required unsaturated esters.[14,15]

With this goal in mind, we investigated the preparation of isoxazolidin-5-one **8** from ester **10** via the Michael addition of hydroxylamine derivatives and the subsequent cyclization reactions (Scheme 2). The trans ester **10*E*** was first treated with *N*-methylhydroxylamine in THF for 12 h and the resultant solution was then allowed to react with zinc chloride, producing two products **8a** and **8b** with a ration of 20:1 in favor of the syn adduct **8a**. The high diastereoselectivity in the Michael addition of *N*-methylhydroxylamine to this *acyclic* conjugated system was of considerable interest. The *Z* olefinic ester **10*Z*** was then used to react with *N*-methylhydroxylamine, and the syn adduct **8a** was produced as the major product (**8a**:**8b**/18:1). Since both olefins **10*E*** and **10*Z*** gave similar results, it can be concluded that the stereochemistry of the unsaturated esters has very little influence on the Michael addition diastereoselectivity. Although the stereoselectivity can be assumed to result from the intramolecular hydrogen bond between the hydroxyl group and a ring oxygen or alternatively in terms of steric hindrance,[15,16] the mechanism remains to be proved. It appears that the dimethyldioxolane derivatives play an important role since these moieties have been frequently used for chiral induction in the processes of nucleophilic additions or dihydroxylation with complete syn or anti selectivity.[16]

Synthesis of Isoxazolidine Nucleosides. The conversion of **8** to D-nucleoside **14** has been accomplished as in the reported procedure for the corresponding L-compounds.[12c] Compound **8a** was reduced by DIBAL to give the corresponding lactols, which were acetylated

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(13) Compound **3** was produced in low ee by using the dipolar cycloaddition of various chiral synthons to vinylthymine. A method for the oxidative conversion of the optically active isoxazolidines to isoxazoline derivatives such as **3** has, however, been developed: Pan, L.; Gi, H.; Zhao, K. *J. Org. Chem.* Submitted for publication.

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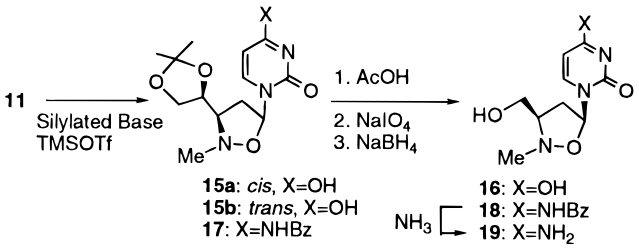
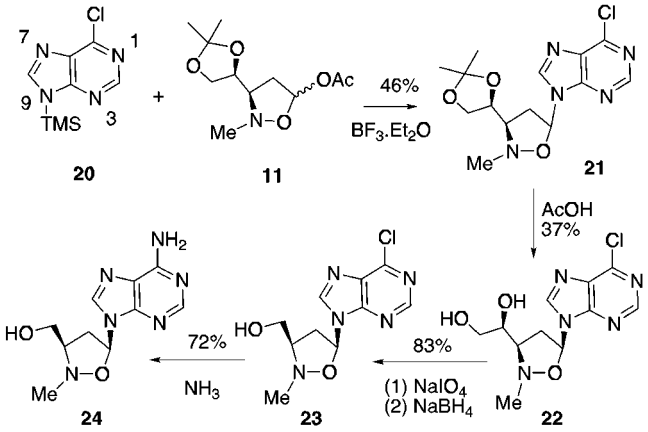
Scheme 3



Scheme 4



by a mixture of acetyl chloride (1.1 equiv), pyridine (1.0 equiv), and methylene chloride at 0 °C to afford the cyclic compounds **11** as the major products in 66% yield (Scheme 2). Condensation of acetate **11** with silylated thymine in acetonitrile using TMSOTf as a Lewis acid afforded the cis compound **12a** (79%) and the corresponding trans isomer **12b** in 4.6% yield. Compound **12a** was deprotected by 60% aqueous acetic acid at 72 °C to give diol nucleoside **13** (69%), which was oxidized by sodium periodate and then reduced by sodium borohydride to the desired compound **14** (75% overall yield). The configuration of **14** followed from its identical ^{1}H NMR spectroscopy with its racemic cis isomer.[17]

It was remarkable that the coupling reaction of acetate **11** with thymine formed the cis isomer as the major compound. The silylated uracil was then used to further investigate this coupling by varying reaction catalyst and temperature (Scheme 3). The TMSOTf-promoted condensation at room temperature gave uracil derivatives **15a**,**b** (cis:trans) with a stereoselectivity of 47:1. The use of $Et_2O{\cdot}BF_3$, however, allowed the isolation of the same products in a ratio of 4:1 (43% total yield) by intercepting the reaction after 2 h at room temperature. Alternatively, heating at 80 °C for an additional 3 h increased the ratio (81:1) and yield (58%). It appears that the cis isomer **15a** was predominately formed under both kinetic and thermodynamic conditions. We have also observed that the trans isomer **15b** is not very stable under acid conditions. In fact, compound **15b** decomposed to uracil in 60% acetic acid at 72 °C in 30 min. Under the same condition, however, compound **15a** afforded a diol (76% yield) which was converted to the desired compound **16** in 92% yield.[17]

The cytosine analogue **19** was also synthesized by a similar method (Scheme 3). Condensation of silylated N^4-benzoylcytosine with acetate **11** using TMSOTf as a Lewis acid gave the desired trans isomer **17** as a single product (74% yield). The final compound **19** was obtained by acetic acid hydrolysis, oxidative cleavage, subsequent reduction, and debenzoylation with 47% overall yield.[17]

Synthesis of Purine Nucleosides. The preparation of purine analogues is generally difficult due to the potential production of diastereoisomers (α or β) and regioisomers (N-3, N-7, and N-9) (**20**, Scheme 4).[18,19] The coupling of isoxazolidine acetate **11** and silylated 6-chloropurine **20** was studied since this nucleoside base requires no other protection and can be easily converted to its amino derivative. Moreover, the undesired regioisomers may be isomerizable to the desired N-9 isomers upon treatment with a Lewis acid at high temperature.[19] The initial use of TMSOTf and acetonitrile gave the desired compound **21** in very low yield at either room temperature or 80 °C. The condensation of acetate **11** with base **20**, promoted by $Et_2O{\cdot}BF_3$ at room temperature, gave one of the undesired regioisomers. Fortunately, this isomer could be directly converted to compound **21** (46% yield) at 80 °C by $Et_2O{\cdot}BF_3$.

The hydrolysis of acetonide **21** presented us with a challenge. Several deprotection conditions such as catalytic Dowex 50 (H^+) in water, *p*-toluenesulfonic acid, and PPTs in methanol cleaved the glycosidic bond of **21**, resulting in the release of 6-chloropurine. The use of 40% aqueous acetic acid at room temperature overnight, however, afforded the desired compound **22** in 37% yield together with recovered starting material **21** (33% yield), which could be recycled. Although the yield of **22** could not be improved by varying the reaction time, acetic acid concentration, and reaction temperature, it was very gratifying to be able to achieve the removal of the isopropylidene group in the presence of the purine glycosidic bond. The subsequent steps of oxidation and reduction converted diol **22** to alcohol **23** (83% yield), which was then converted to the final product **24** in 72% yield.[17]

Conclusion

High stereoselectivity was observed in the Michael addition of hydroxylamine derivatives with chiral *acyclic* α,β-unsaturated esters. The Michael adducts were subsequently cyclized under mild conditions to afford, as a single isomer, isoxazolidin-5-ones, which were easily converted to acetate-protected isoxazolidin-5-ols. The coupling of these intermediates and nucleoside bases gave β-D-isoxazolidinyl nucleosides with high cis selectivity.

Experimental Section

General details are as previously described.[12d]

(3*R*,4′*S*)-2-*N*-Methyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-1,2-isoxazolidin-5-one (8a) and Its (3*S*,4′*S*)-Isomer (8b).

(17) The structure of the racemic cis isomer was assigned by the analysis of its 2D NOE spectrum.[12c] It should be noted that the chemical shift of the methylenye protons in the isoxazolidine ring can also be used to determine the cis or trans structure. The chemical shifts of the *gem*-hydrogens are broadly separated (2.98 and 2.29 ppm) in cis compound **14**, while the *gem*-hydrogens in the corresponding trans compound have the same chemical shifts (2.39 ppm).[12a] Broadly separated chemical shifts were also observed in the methylene groups of the cis isoxazolidines such as **16**, **19,** and **24**.

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A mixture of **10*E*** (4.0 g, 20 mmol), HONHMe·HCl (1.67 g, 20 mmol), Et_3N (2.80 mL, 20 mmol), and THF (100 mL) was stirred at rt overnight. Zinc chloride (2.68 g, 20 mmol) was then added and the reaction mixture was stirred for 12 h. After workup (H_2O, 50 mL; EtOAc, 3 × 100 mL) and purification (SiO_2, 50% EtOAc/petroleum ether), compounds **8a** (3.0 g, 75%) and **8b** (0.15 g, 3.8%) were isolated as clear oils. **8a**: ^{1}H NMR ($CDCl_3$) δ 4.15 (dt, J = 6.4 Hz, J = 6.4 Hz, 1H), 4.01 (dd, J = 6.4 Hz, J = 8.4 Hz, 1H), 3.67 (dd, J = 6.4 Hz, J = 8.4 Hz, 1H), 3.23 (dt, J = 7.3 Hz, J = 10.2 Hz, 1H), 2.95 (s, 3H), 2.65 (m, 2H), 1.37 (s, 3H), 1.30 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 173.3, 110.8, 76.9, 70.4, 66.7, 47.6, 33.5, 27.0, 25.7. Anal. Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.46; H, 7.54; N, 6.80. **8b**: ^{1}H NMR ($CDCl_3$) δ 4.15 (m, 2H), 3.76 (m, 1H), 3.26 (m, 1H), 2.90 (m, 5H), 1.41 (s, 3H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 175.1, 110.5, 75.3, 68.7, 67.4, 47.3, 31.2, 26.9, 25.4. Anal. Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.70; H, 7.56; N, 6.90.

(3*R*,4′*S*)-5-Acetoxy-2-*N*-methyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-1,2-isoxazolidine (11). To a solution of **8a** (6.6 g, 32.5 mmol) in dry CH_2Cl_2 (100 mL) at −78 °C was added DIBAL (23 mL, 1.5 M in toluene). The reaction mixture was stirred at −78 °C for 1 h, quenched with MeOH (2 mL), and warmed to rt. After workup (saturated $NaHCO_3$, 100 mL; $CHCl_3$, 5 × 100 mL) and purification (SiO_2, EtOAc), a lactol (5.80 g) was isolated in 87% yield.

A mixture of pyridine (2.4 mL, 39 mmol), AcCl (2.21 mL, 31 mmol), and CH_2Cl_2 (100 mL) was stirred at 0 °C for 15 min and a solution of the above-prepared lactol (4.96 g, 24 mmol) in CH_2Cl_2 (10 mL) was then added over 30 min. After it was warmed to rt and stirred for 2 h, the reaction mixture was washed with 1% HCl (50 mL), saturated $NaHCO_3$ (100 mL), and water (100 mL). After purification (SiO_2, 60% EtOAc/petroleum ether), an oil **11** (3.90 g, 66%) was isolated as a mixture of α and β isomers. ^{1}H NMR ($CDCl_3$) δ 6.25 (m, 1H), 4.12 (m, 2H), 3.63 (m, 1H), 3.10 (m, 1H), 2.91 (m, 3H), 2.24 (m, 2H), 2.04 (m, 3H), 1.39 (s, 3H), 1.31 (s, 3H); ^{13}C ($CDCl_3$) δ 170.3, 110.3, 97.2, 77.7, 68.4, 67.1, 49.3, 39.3, 27.2, 25.8, 21.9. Anal. Calcd for $C_{11}H_{17}NO_5$: C, 53.87; H, 7.81; N, 5.71. Found: C, 53.77; H, 7.75; N, 5.66.

Condensation Method for the Coupling of 11 and Nucleoside Bases: (3′*R*,4″*S*,5′*S*)-1-[2-*N*-Methyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-1,2-isoxazolidinyl]uracil (15a) and Its (3′*R*,4″*S*,5′*R*)-Isomer (15b). **Method A**. To a solution of silylated uracil, which was prepared by refluxing the solution of uracil (0.56 g, 5 mmol), hexamethyldisilazane (20 mL), and ammonium sulfate (cat.) for 2 h, in dry CH_3CN (20 mL), was added a solution of **11** (0.37 g, 1.5 mmol), dry CH_3CN (5 mL), and TMSOTf (0.96 mL, 5 mmol). The reaction mixture was stirred at rt overnight. After workup (cooled saturated $NaHCO_3$, 50 mL; EtOAc, 3 × 50 mL) and purification (SiO_2, EtOAc), compounds **15a** (210 mg, 47%) and **15b** (5 mg, 1%) were isolated as white foams.

Method B. A mixture of the silylated uracil (5 mmol), **14** (0.49 g, 2 mmol), $BF_3{\cdot}Et_2O$ (0.48 mL, 4 mmol), and CH_3CN (20 mL) was stirred at rt for 2 h. Compounds **15a** (210 mg, 35%) and **15b** (50 mg, 8.4%) were similarly isolated.

Method C. A mixture of the silylated uracil (5 mmol), **11** (490 mg, 2 mmol), $BF_3{\cdot}Et_2O$ (0.48 mL, 4 mmol), and CH_3CN (20 mL) was stirred at rt for 2 h and then refluxed for another 3 h. Compounds **15a** (340 mg, 57%) and **15b** (4 mg, 0.7%) were similarly isolated.

15a: ^{1}H NMR ($CDCl_3$) δ 10.0 (br s, 1H), 7.81 (d, J = 8.1 Hz, 1H), 6.00 (dd, J = 3.3 Hz, J = 7.3 Hz, 1H), 5.69 (d, J = 8.1 Hz, 1H), 4.03 (m, 2H), 3.59 (m, 1H), 2.98 (m, 5H), 1.96 (m, 1H), 1.38 (s, 3H), 1.30 (s, 3H); ^{13}C δ 164.2, 151.1, 140.6, 110.8, 102.3, 83.7, 77.3, 70.6, 67.5, 45.7, 42.5, 27.2, 26.0. **15b**: ^{1}H NMR ($CDCl_3$) δ 9.72 (br s, 1H), 7.57 (d, J = 8.1 Hz, 1H), 6.03 (dd, J = 3.4 Hz, J = 6.9 Hz, 1H), 5.75 (d, J = 8.1 Hz, 1H), 4.08 (m, 2H), 3.63 (t, J = 7.3 Hz, 1H), 3.03 (m, 1H), 2.93 (s, 3H), 2.49 (m, 1H), 2.37 (m, 1H), 1.96 (m, 1H), 1.38 (s, 3H), 1.30 (s, 3H).

(3′*R*,4″*S*,5′*S*)-1-[2-*N*-Methyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-1,2-isoxazolidinyl]thymine (12a) and Its (3′*R*,4″*S*,5′*R*)-Isomer (12b). Condensation method A was used for converting **11** to thymidine analogues **12a** (79%) and **12b** (4.6%). **12a**: a white foam; ^{1}H NMR ($CDCl_3$) δ 9.65 (s, 1H), 7.63 (d, J = 1.0 Hz, 1H), 6.04 (dd, J = 3.7 Hz, J = 7.4 Hz, 1H), 4.04 (m, 2H), 3.62 (m, 1H), 2.91 (m, 5H), 1.92 (m, 4H), 1.40 (s, 3H), 1.33 (s, 3H); ^{13}C δ 164.7, 151.1, 136.1, 110.8, 83.4, 77.4, 70.8, 67.5, 45.8, 42.3, 27.2, 26.1, 13.3. **12b**: a white foam; ^{1}H NMR ($CDCl_3$) δ 8.81 (br s, 1H), 7.34 (s, 1H), 6.07 (dd, J = 4.0 Hz, J = 7.5 Hz, 1H), 4.20 (dd, J = 6.9 Hz, J = 13.2 Hz, 1H), 4.07 (dd, J = 6.3 Hz, J = 8.2 Hz, 1H), 3.66 (dd, J = 6.5 Hz, J = 8.2 Hz, 1H), 3.11 (m, 1H), 2.96 (s, 3H), 2.47 (m, 2H), 1.95 (s, 3H), 1.43 (s, 3H), 1.36 (s, 3H). Anal. Calcd for $C_{14}H_{21}N_3O_5$: C, 54.01 H, 6.80; N, 13.50. Found: C, 54.17; H, 6.85; N, 13.45.

Hydrolysis−Oxidation−Reduction Sequence for Converting Dioxolanes to Hydroxymethyl Derivatives: (3′*R*,5′*S*)-1-[2-*N*-Methyl-3-(hydroxymethyl)-1,2-isoxazolidinyl]thymine (14). A solution of **12a** (200 mg, 0.64 mmol) in 60% AcOH (50 mL) was heated at 72 °C for 30 min and then concentrated. The residue was coevaporated with toluene (2 × 10 mL) and then purified by column chromatography (SiO_2, 10% MeOH/$CHCl_3$) to give diol **13** (120 mg, 0.44 mmol), which was then mixed with MeOH (20 mL), water (5 mL), and $NaIO_4$ (0.17 g, 0.80 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h and $NaBH_4$ (78 mg, 2 mmol) was then added. The reaction mixture was kept at 0 °C for 5 min and then neutralized with AcOH. The mixture was filtered and concentrated. The residue was purified by column chromatography (SiO_2, 15% MeOH/$CHCl_3$), affording compound **14** (80 mg, 75%), which was crystallized from MeOH−Et_2O−petroleum ether: mp 129−130 °C; ^{1}H NMR (CD_3OD) δ 7.93 (d, J = 1.2 Hz, 1H), 6.16 (dd, J = 4.0 Hz, J = 7.8 Hz, 1H), 3.75 (dd, J = 3.4 Hz, J = 11.9 Hz, 1H), 3.63 (dd, J = 3.4 Hz, J = 11.9 Hz, 1H), 2.81 (m, 5H), 2.29 (m, 1H), 1.89 (s, 3H). Anal. Calcd for $C_{10}H_{15}N_3O_4$: C, 49.79; H, 6.27; N, 17.42. Found: C, 49.78; H, 6.26; N, 17.34.

(3′*R*,5′*S*)-1-[2-*N*-Methyl-3-(hydroxymethyl)-1,2-isoxazolidinyl]uracil (16). The hydrolysis−oxidation−reduction sequence was used for converting compound **15** to analogue **16** (70%): mp 148−150 °C; ^{1}H NMR (CD_3OD) δ 8.09 (d, J = 8.1 Hz, 1H), 6.12 (dd, J = 3.7 Hz, J = 7.8 Hz, 1H), 5.68 (d, J = 8.1 Hz, 1H), 3.73 (dd, J = 3.5 Hz, J = 11.9 Hz, 1H), 3.61 (dd, J = 3.5 Hz, J = 11.9 Hz, 1H), 3.00 (dt, J = 7.9 Hz, J = 13.3 Hz, 1H), 2.81 (m, 4H), 2.27 (m, 1H). Anal. Calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.65; H, 5.74; N, 18.59.

(3′*R*,4″*S*,5′*S*)-*N*^{4}-Benzoyl-1-[2-*N*-methyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-1,2-isoxazolidinyl]cytosine (17). Condensation method A was used for converting **11** to analogue **17** (74%). **17**: a white foam; ^{1}H NMR ($CDCl_3$) δ 8.21 (d, J = 7.5 Hz, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.49 (m, 4H), 5.97 (dd, J = 2.9 Hz, J = 7.3 Hz, 1H), 3.98 (m, 2H), 3.56 (m, 1H), 2.93 (m, 5H), 2.00 (m, 1H), 1.37 (s, 3H), 1.29 (s, 3H); ^{13}C ($CDCl_3$) δ 167.0, 162.8, 155.4, 145.1, 133.5, 129.4, 128.1, 110.7, 96.5, 85.5, 77.6, 70.7, 67.5, 45.8, 42.8, 27.2, 26.0. Anal. Calcd for $C_{20}H_{24}N_4O_5{\cdot}0{\cdot}60\ H_2O$: C, 58.41; H, 6.18; N, 13.62. Found: C, 58.56; H, 6.12; N, 13.15.

(3′*R*,5′*S*)-1-[2-*N*-Methyl-3-(hydroxymethyl)-1,2-isoxazolidinyl]cytosine (19). Product **18**, which was obtained from **17** by using the hydrolysis−oxidation−reduction sequence, was dissolved in 20 mL of saturated methanolic ammonia and stirred at rt overnight. The solvent was evaporated and the residue was purified by column chromatography (SiO_2, 35% MeOH/$CHCl_3$) to give **19** (65 mg, 87%) as a white solid which was crystallized from MeOH−EtOAc−petroleum ether: mp 157−158 °C; ^{1}H NMR (CD_3OD) δ 8.03 (d, J = 7.4 Hz, 1H), 6.07 (dd, J = 3.8 Hz, J = 7.5 Hz, 1H), 5.88 (d, J = 7.4 Hz, 1H), 3.70 (dd, J = 3.8 Hz, J = 11.8 Hz, 1H), 3.56 (dd, J = 3.8 Hz, J = 11.8 Hz, 1H), 3.03 (dt, J = 7.6 Hz, J = 13.5 Hz, 1H), 2.83 (m, 4H), 2.15 (m, 1H). Anal. Calcd for $C_9H_{14}N_4O_4{\cdot}\ 0.60H_2O$: C, 45.60; H, 6.46; N, 23.64. Found: C, 45.31; H, 6.45; N, 23.29.

(3′*R*,4″*S*,5′*S*)-6-Chloro-9-[2-*N*-methyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-1,2-isoxazolidinyl]purine (21). Condensation method C (reaction conditions: rt, 30 min; reflux, 30 min) was used for converting **11** to analogue **21** (46%). **21**: an oil; ^{1}H NMR ($CDCl_3$) δ 8.65 (s, 1H), 8.55 (s, 1H), 6.41 (dd, J = 6.3 Hz, J = 7.6 Hz, 1H), 4.11 (m, 1H), 3.99 (t, J = 6.3 Hz, 1H), 3.62 (dd, J = 6.3 Hz, J = 8.3 Hz, 1H), 3.09 (dt, J = 7.9 Hz, J = 13.3 Hz, 1H), 2.92 (m, 4H), 2.32 (m, 1H), 1.39 (s, 3H),

1.30 (s, 3H); ^{13}C ($CDCl_3$) δ 152.2, 151.2, 144.2, 132.1, 112.8, 110.9, 82.0, 77.1, 70.7, 67.4, 45.6, 41.7, 27.2, 26.0. Anal. Calcd for $C_{14}H_{18}N_3O_3 \cdot 0.75H_2O$: C, 47.60; H, 5.56; N, 19.82. Found: C, 47.90; H, 5.50; N, 19.69.

(3′*R*,5′*S*)-6-Chloro-9-[2-*N*-methyl-3-(hydroxymethyl)-1,2-isoxazolidinyl]purine (23). Product **23** was similarly prepared in 31% yield from **21** by using the hydrolysis−oxidation−reduction sequence. **23**: a white solid, mp 133−134 °C; ^{1}H NMR (CD_3OD) δ 8.99 (s, 1H), 8.72 (s, 1H), 6.58 (dd, J = 2.5 Hz, J = 8.0 Hz, 1H), 3.84 (dd, J = 2.9 Hz, J = 12.1 Hz, 1H), 3.73 (dd, J = 2.9 Hz, J = 12.1 Hz, 1H), 3.17 (dt, J = 8.1 Hz, J = 12.3 Hz, 1H), 2.82 (m, 5H). Anal. Calcd for $C_{10}H_{12}ClN_5O_2$: C, 44.50; H, 4.48; N, 25.97. Found: C, 44.50; H, 4.54; N, 25.91.

(3′*R*,5′*S*)-9-[2-*N*-Methyl-3-(hydroxymethyl)-1,2-isoxazolidinyl]adenine (24). A mixture of **23** (90 mg, 0.33 mmol) and saturated methanolic ammonia (20 mL) was heated at 100 °C in a steel bomb overnight. After it was cooled, the reaction mixture was concentrated. The residue was purified by column chromatography (SiO_2, 30% MeOH/$CHCl_3$) to give **24** (60 mg, 72%) as a white solid which was crystallized from MeOH−$CHCl_3$−petroleum ether: mp 220−222 °C; ^{1}H NMR (DMSO-d_6) δ 8.44 (s, 1H), 8.17 (s, 1H), 7.30 (br s, 2H), 6.38 (dd, J = 2.6 Hz, J = 8.1 Hz, 1H), 5.08 (t, J = 5.3 Hz, 1H), 3.69 (m, 2H), 3.07 (dt, J = 8.4 Hz, J = 12.5 Hz, 1H), 2.72 (m, 5H). Anal. Calcd for $C_{10}H_{14}ClN_6O_2$: C, 47.99; H, 5.64; N, 33.58. Found: C, 47.77; H, 5.61; N, 33.33.

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