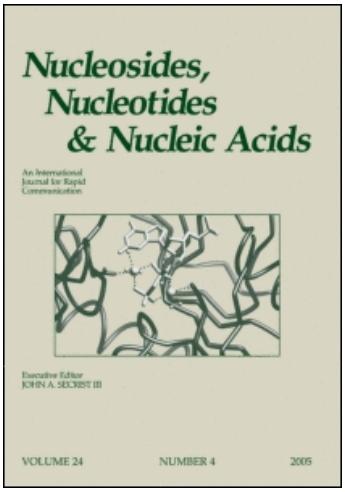

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Asymmetric Synthesis of Oxazolidine Nucleosides and Related Chemistry

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ASYMMETRIC SYNTHESIS OF OXAZOLIDINE NUCLEOSIDES AND RELATED CHEMISTRY

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Abstract: Asymmetric synthesis of *N*-substituted oxazolidinyl nucleosides has been accomplished from *L*-isoserine. *trans*- and *cis*-Oxazolidine intermediates (**4** and **5**) were stereoselectively constructed from *N*-protected *L*-isoserine with a menthoxycarbonyl group by the condensation with benzoyloxy acetaldehyde dimethyl acetal in a ratio of 3.9 to 1 in favor of *trans*-isomer **4**. The major isomer **4** was converted to enantiomerically pure β- and α- *N*-*L*-menthoxycarbonyl oxazolidinyl thymine nucleosides **11** and **12** in 6 steps.

In the search for novel nucleosides as antiviral agents, various modifications of nucleosides on both sugar and heterocyclic moieties have been extensively studied in our laboratory. Among the modifications of sugar moiety of nucleosides, 1,3-dioxolane[1-3] and 1,3-oxathiolane[4-6] nucleosides were found to be the most interesting and successful examples in finding biologically active compounds, in which 3'-carbon has been replaced by an oxygen or a sulfur atom, respectively. Among these modified nucleosides, (-)-(2'*R*,5'*S*)-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)cytosine (3TC),[5] *cis*-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)cytosine (FTC),[6] (-)-β-*L*-dioxolane cytosine [(-)-OddC][2], (-)-(2'*R*,5'*R*)-9-(dioxolan-5-yl)guanine (DG)[3] and (-)-(2'*R*,5'*R*)-9-(dioxolan-5-yl)-2,6-diaminopurine (DAPD)[3] are the most interesting compounds. 3TC has been approved by FDA as anti-HIV drug for combination therapy of AIDS and the others are currently undergoing various stages of preclinical and clinical trials. These promising results of the 3'-modifications prompted us to design and to synthesize the additional novel

** This paper is dedicated to the late professor Tsujiaki Hata.

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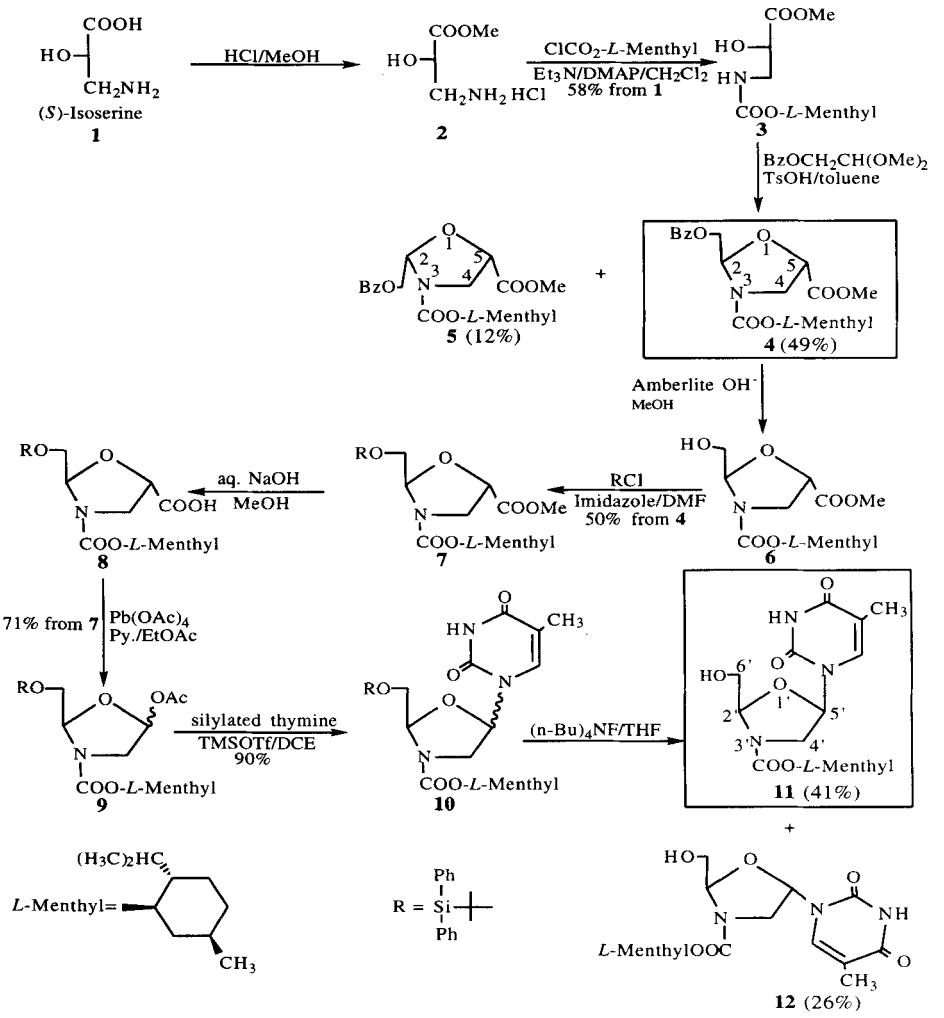
class of nucleosides, in which 3'-carbon is replaced by a nitrogen. In this paper, we report the synthesis of oxazolidine nucleosides and the related chemistry.

RESULTS AND DISCUSSION

1. SYNTHESIS

Retrosynthetic analysis of the target compounds suggested that the key step for the synthesis of enantiomeric oxazolidine nucleosides is to construct the oxazolidine ring system. Thus, (*S*)-isoserine (**1**), which was synthesized by the modified method of Maeda *et al.*[7] in three steps, was esterified in refluxing methanol in the presence of hydrogen chloride followed by selective protection[8] of the amino group with *L*-menthyl chloroformate and triethylamine in methylene chloride to give (*S*)-isoserine derivative **3** (Scheme 1). It is expected that a bulky chiral *L*-menthyl group may provide a good stereoselectivity in the ring closure reaction.[9-11] The reaction of compound **3** with 2-*O*-benzoyloxy acetaldehyde dimethyl acetal catalyzed by *p*-toluenesulfonic acid gave a mixture of *trans*-**4** and *cis*-**5** isomers with a ratio of 3.9 to 1 in favor of the *trans*-isomer **4** which were separated by silica gel column chromatography. The structures and stereochemistry of **4** and **5** were confirmed by NMR spectroscopy including 2D NOESY. The stereochemistry was assigned on the basis of a correlation between H-2 and H-5 in **5** (*cis*-isomer) which was absent in compound **4** (*trans*-isomer) in 2D NOESY spectra (FIGURE 1). The major isomer **4** was selectively debenzoylated in methanol catalyzed by Amberlite IRA-400 (OH^- form) followed by silylation with *t*-butylchlorodiphenylsilane in DMF in the presence of imidazole to give compound **7**. The crude carboxylic acid **8**, obtained by hydrolysis of **7** with NaOH in methanol, was treated with $Pb(OAc)_4$ in ethyl acetate in the presence of pyridine to give the key intermediate **9**. Condensation of **9** with silylated thymine in 1,2-dichloroethane in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) gave an inseparable α- and β- mixture (**10**). Deprotection of the mixture **10** with *tetra*-n-butylammonium fluoride in THF yielded a mixture of β-**11** and α-**12**, which were separated by silica gel column chromatography. The structures of these compounds were confirmed by UV, ^1H, ^{13}C and Distortionless Enhancement by Polarization Transfer (DEPT) NMR experiment. The ^{13}C and DEPT NMR experiments suggested that compound **11** consists of twenty carbons, including four methyl, five methylene, seven methine, a quarternary carbon and three carbonyl carbons, which is in agreement with the designed compound **11**. The assignment of the anomeric configuration was based on the 2D NOESY experiments, in which the β-isomer **11** exhibited a correlation between signals of 5'-H (6.28 ppm) and 2'-H (5.30 ppm) while no correlation between signals of 5'-H (6.37 ppm) and 2'-H (5.70 ppm) of the α-isomer **12** was observed. Additionally, we also



Scheme 1

observed a correlation between 6-H (7.00 ppm) and 2'-H (5.70 ppm) of the α-isomer **12** while no such correlation exibited in the β-isomer **11**. The fact that 2'-H of β-isomer **11** had an upfield chemical shift (5.30 ppm) compared to that of the α-isomer **12** (5.70 ppm) which is deshielded by the heterocyclic ring additionally supports the above stereochemical assignment.

In an attempt to obtain the free nucleosides, several different *N*-deprotection conditions were tried, including conc NH_4OH, NH_2NH_2,[12] NaOMe,[9] *p*-TsOH,[13] $LiAlH_4$ and

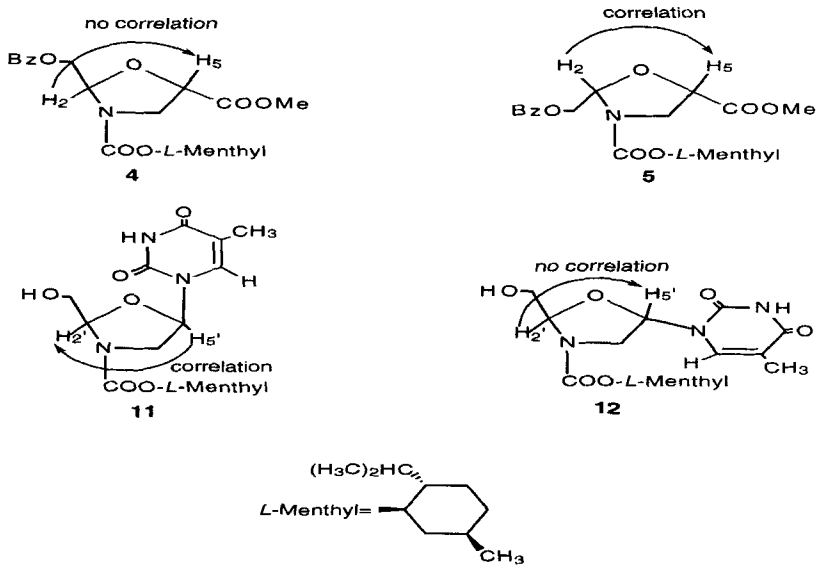
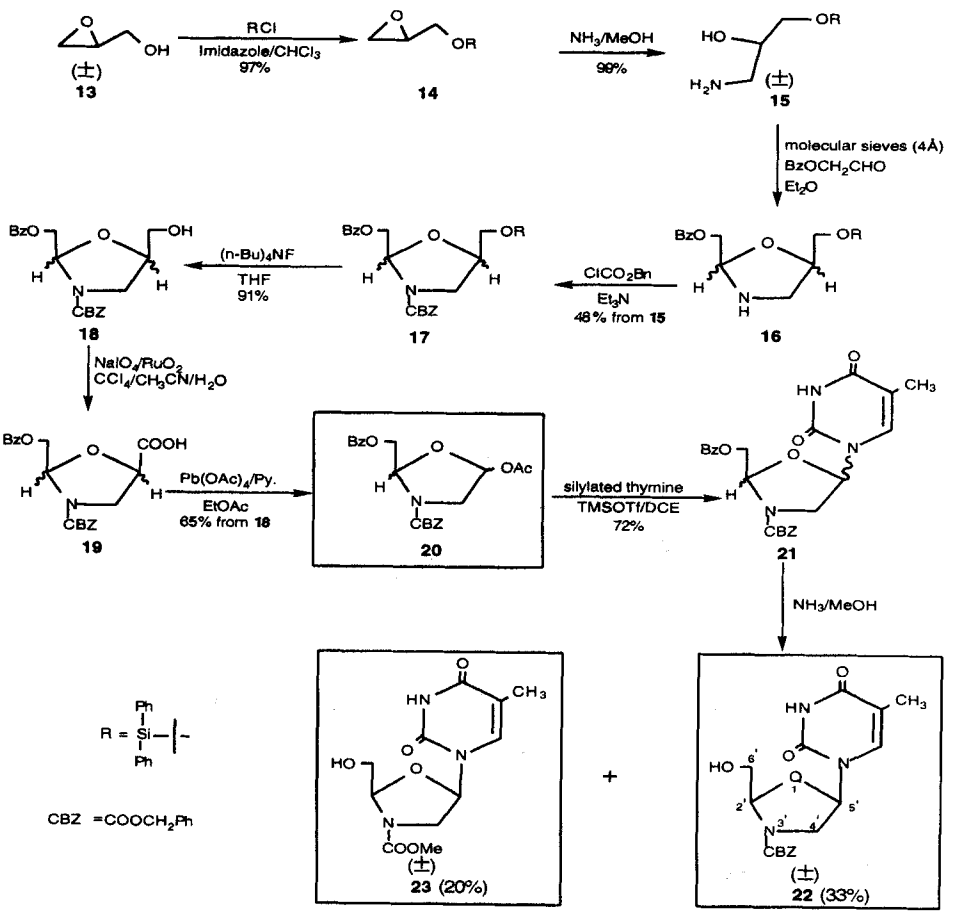


FIGURE 1. The results of 2D NOESY experiments

diisobutylaluminum hydride (DIBAL). All these conditions resulted either in the decomposition of the starting material to thymine or no reaction.

Due to the difficulties in *N*-deprotection of the menthoxycarbonyl group in compounds **11** and **12**, another synthetic method with *N*-benzyloxycarbonyl (CBZ) protecting group was explored, which normally can be removed under mild and neutral hydrogenolysis[14] conditions. In order to find out whether the CBZ group could be removed by the proposed hydrogenolysis, we initially explored the synthesis (Scheme 2) with less expensive (±)-glycidol (**13**). Compound **13** was protected by *t*-butylchlorodiphenylsilane followed by an epoxide opening by methanolic ammonia at rt to give aminoalcohol **15**. Compound **15** was reacted with 2-*O*-benzoyloxy acetaldehyde in diethyl ether in the presence of molecular sieves (4Å)[15] followed by *N*-protection with benzyl chloroformate *in situ* to give a mixture of *cis*- and *trans*-oxazolidine derivative **17** in a ratio of 2:1 determined by a ^{1}H NMR spectrum. Desilylation of **17** with *tetra*-n-butylammonium fluoride in THF yielded an alcohol **18**. The key intermediate **20**, which was prepared from **18** by oxidation with $RuO_2/NaIO_4$ followed by oxidative decarboxylation with $Pb(OAc)_4$, was condensed with silylated thymine in the presence of TMSOTf in 1,2-dichloroethane to give an inseparable α- and β- mixture **21** in a ratio of 3:1 by a ^{1}H NMR spectrum. Individual compounds **22** (β-form) and **23** (β-form) were obtained after debenzoylation of the mixture **21** by



Scheme 2

methanolic ammonia. The structures of **22** and **23** were also confirmed by ^1H and ^{13}C NMR as well as by the comparison of the ^1H NMR spectra with those of **11** and **12**. 2'-H of **22** and **23** had similar chemical shifts (5.33 and 5.31 ppm) as that of **11** (5.30 ppm) (TABLE 1). We could not isolate the α-isomers from the mixture. It was interesting to discover from NMR studies that the nucleoside **23** possesses a methoxy group instead of the expected benzyloxyl group. The unexpected product **23** was probably formed during the deprotection with methanolic ammonia by a transesterification reaction. We did not observe it in Scheme 1, probably due to the bulkiness of the menthoxycarbonyl group of **11** and **12**. For the *N*-deprotection, the *N*-CBZ nucleoside **22** was subjected to hydrogenolysis[14] in ethyl acetate in the presence of Pd/C. After hydrogenation at rt for 24

TABLE 1. Characteristic ^{1}H NMR Data of Nucleosides (ppm)

Compound	Anomer	6-H	5'-H	2'-H
11	β	7.58	6.28	5.30
12	α	7.00	6.37	5.70
22	β	7.58	6.25	5.33
23	β	7.58	6.26	5.31

h, TLC showed that about 10 % of the starting material was converted to thymine (identified by ^{1}H NMR) which probably was resulted from the decomposition of the free oxazolidine nucleoside. Therefore, it appears that free oxazolidine nucleosides are too unstable to be isolated. Literature search indicated that although *N*-methyl substituted oxazolidine ring is more stable than the free oxazolidine, it is also readily decomposed by silica gel or alumina[16].

2. BIOLOGICAL STUDIES

The anti-HBV and anti-HIV activities of the synthesized oxazolidine nucleosides were evaluated in 2.2.15 and PBM cells, respectively. No significant activities were observed with concentrations up to 100 μM.

EXPERIMENTAL SECTION

Melting points were determined on a Mel-temp II and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL FX 90Q fourier transform spectrometer for 90 MHz or Bruker 250 AM for 250 MHz, 300 AC for 300 MHz or 400 AMX spectrometer for 400 MHz, with Me_4Si as internal standard. Chemical shifts (δ) are reported in parts per million (ppm), and signals are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or br s (broad singlet). IR Spectra were measured on a Nicolet 510P FT-IR spectrometer. Optical rotations were performed on a Jasco DIP-370 Digital Polarimeter. TLC were performed on Uniplates (silica gel) purchased from Analtech Co. Mass spectra were recorded on a Micromass Quatro II triple quadrupole mass spectrmeter (FAB). Column chromatography was performed using either silica gel-60 (220-440 mesh) for flash chromatography or silica gel G (TLC grade>440 mesh) for vacuum flash column chromatography. UV Spectra were obtained on a Beckman DU-7 or Beckman DU 650 Spectrophotometer. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA. Dry 1,2-dichloroethane (DCE) and methylene chloride were distilled from CaH_2. Dry tetrahydrofuran (THF) was distilled from Na/benzophenone.

Methyl *N*-*L*-menthoxycarbonyl-(*S*)-isoserinate (3). To a solution of HCl in methanol, prepared by bubbling HCl (gas, 6.40 g) into anhydrous methanol (100 mL) at rt, was added compound **1**[7] (6.30 g, 60.0 mmol) at once. The resulting solution was refluxed for 2 h and concentrated to dryness under reduced pressure. To the residue were added methylene chloride (150 mL), Et_3N (14.6 g, 144 mmol), 4-dimethylaminopyridine (DMAP, 50 mg), and *L*-menthyl chloroformate (13.8 g, 63.0 mmol). The solution was refluxed for 3 h and diluted with EtOAc (200 mL). The mixture was washed with brine and dried (Na_2SO_4). The solvent was removed and the residue was purified by silica gel column chromatography eluting with EtOAc in hexanes (0-50 %) to give **3** as a white solid (10.5 g, 58 %): mp 75-77 °C; $[\alpha]^{25}_D$ = +28.0° (*c* 0.10, MeOH); IR (KBr): 3359, 2955, 1742, 1696, 1528, 1273 cm^{-1}; ^1H NMR (DMSO-d_6): δ 6.98 (s, 1H, NH, D_2O exchangeable), 5.52 (d, J = 4.8 Hz, 1H, OH, D_2O exchangeable), 4.40 (m, 1H, CHOOCN), 4.09 (t, J = 6.0 Hz, 1H, 2-H), 3.62 (s, 3H, OCH_3), 3.08 (m, 2H, NCH_2), 0.8-1.90 (m, 18H, menthyl). Anal. Calcd. for $C_{15}H_{27}NO_5$: C, 59.76; H, 9.04; N, 4.56. Found: C, 59.77; H, 8.92; N, 4.56.

(2*R*,5*S*)- and (2*S*,5*S*)-2-Benzoyloxymethyl-5-methoxycarbonyl-3-*L*-menthoxycarbonyl-1,3-oxazolidine (4 and 5). A mixture of **3** (5.16 g, 15.5 mmol) and 2-benzoyloxy acetaldehyde dimethyl acetal (5.38 g, 25.7 mmol) in toluene (300 mL) was refluxed for 8 h in the presence of *p*-toluenesulfonic acid (200 mg) in Dean-Stark apparatus. The solution was neutralized with Et_3N and concentrated to dryness under reduced pressure. The residue was purified by silica gel column chromatography eluting with EtOAc in hexanes (0-35 %) to give (2*R*,5*S*)-isomer **4** (3.42 g, 49 %) and (2*S*,5*S*)-isomer **5** (0.85 g, 12 %) as syrup. The ratio of *trans*/*cis* was 3.9/1.

(2*R*,5*S*)-isomer 4: $[\alpha]^{25}_D$ = +95.95° (*c* 0.10, MeOH); UV (MeOH) λmax 273 nm (ε 900); IR (film) 2955, 2870, 1709, 1410, 1273, 1098 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.03-7.44 (m, 5H, Ph-H), 5.78 (s, 1H, 2-H), 4.78 (dd, J = 3.2, 7.2 Hz, 1H, 5-H), 4.64-4.52 (m, 3H, 2-CH_2, CHOOCN), 4.06 (br s, 1H, 4-H_A), 3.82 (s, 3H, OCH_3), 3.70 (dd, J = 11.2, 7.2 Hz, 1H, 4-H_B), 2.04-0.8 (m, 18H, menthyl); ^{13}C NMR ($CDCl_3$) δ 171.2, 166.4, 157.0, 133.5, 130.0 (2C), 128.8, 87.8, 76.6, 75.2, 64.6, 52.8, 48.3, 47.7, 41.7, 34.6, 31.8, 26.8, 23.8, 22.3, 21.2, 16.7. Anal. Calcd. for $C_{24}H_{33}NO_7$: C, 64.41; H, 7.43; N, 3.13. Found: C, 64.32; H, 7.39; N, 3.10.

(2*S*,5*S*)-Isomer 5: $[\alpha]^{25}_D$ = -78.6° (*c* 0.09, MeOH); UV (MeOH) λmax 273.5 nm (ε 930); IR (film) 2955, 2870, 1709, 1414, 1273, 1098 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.03-7.42 (m, 5H, Ph-H), 5.66 (t, J = 3.4 Hz, 1H, 2-H), 4.65 (t, J = 7.8 Hz, 1H, 5-H), 4.62-4.55 (m, 3H, 2-CH_2, CHOOCN), 4.24 (br s, 1H, 4-H_A), 3.69 (s, 3H, OCH_3), 3.57 (dd, J = 10.4, 8.1 Hz, 1H, 4-H_B), 2.02-0.74 (m, 18H, menthyl); ^{13}C NMR ($CDCl_3$) δ 170.3, 166.3, 153.3, 133.5, 130.3, 130.2, 128.7, 87.9, 76.7, 75.6, 64.6, 52.9, 47.6, 47.4,

41.6, 34.5, 31.7, 26.9, 24.0, 22.3, 21.1, 16.9. Anal. Calcd. for $C_{24}H_{33}NO_7$: C, 64.41; H, 7.43; N, 3.13. Found: C, 64.51; H, 7.45; N, 3.15.

(2*R*,5*S*)-2-*t*-Butyldiphenylsilyloxymethyl-5-methoxycarbonyl-3-*L*-menthoxycarbonyl-1,3-oxazolidine (7). A mixture of (2*R*,5*S*)-benzoate **4** (2.62 g, 5.86 mmol), and Amberlite IRA-400 (OH^- form, 10.0 g) in methanol (200 mL) was stirred at rt for 24 h, and filtered. The solvent was removed to dryness under reduced pressure to give a crude alcohol **6** which was redissolved in DMF (50 mL). To the solution were added *t*-butylchlorodiphenylsilane (1.93 g, 7.03 mmol), and imidazole (0.80 g, 11.7 mmol). The resulting solution was stirred at rt for 3 h and concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography eluting with EtOAc in hexanes (0-10 %) to give **7** (1.70 g, 50 %) as a syrup: $[\alpha]^{25}_D = +29.5°$ (*c* 0.07, MeOH); UV (MeOH) λmax 264.5 nm (ε 640); IR (film) 2955, 2932, 2859, 1757, 1707, 1414, 1129 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70-7.40 (m, 10H, Ph-H), 5.54 (s, 1H, 2-H), 4.86 (br s, 1H, 5-H), 4.60 (m, 1H, CHOOCN), 4.03-3.73 (m, 7H, OCH_3, 2-CH_2O, 4-H_A, 4-H_B), 2.00-0.78 (m, 27H, menthyl, *t*-butyl). Anal. Calcd. for $C_{33}H_{47}NO_6Si \cdot 0.5H_2O$: C, 67.08; H, 8.18; N, 2.37. Found: C, 66.78; H, 8.10; N, 2.30.

(2*R*)-5-Acetoxy-2-*t*-butyldiphenylsilyloxymethyl-3-*L*-menthoxycarbonyl-1,3-oxazolidine (9). To a solution of methyl ester **7** (1.60 g, 2.75 mmol) in methanol (32 mL) and H_2O (8 mL) was added aqueous NaOH (5.0 N, 0.6 mL 3.0 mmol). The solution was stirred at rt for 4 h and the methanol was removed under reduced pressure. The residue was acidified with AcOH (3 mL) and redissolved in EtOAc (100 mL). The resulting solution was washed with brine, dried ($MgSO_4$), and filtered. The filtrate was concentrated to give crude acid **8** which, without further purification, was dissolved in EtOAc (100 mL). To the solution were added $Pb(AcO)_4$ (1.83 g, 4.13 mmol), and pyridine (0.22 g, 2.75 mmol). The resulting mixture was refluxed for 2 h, cooled to rt, and filtered through silica gel pad. The solvent was removed and the residue was purified by a short silica gel column eluting with EtOAc in hexanes (0-20 %) to give **9** (1.14 g, 71 %) as an oil: ^1H NMR ($CDCl_3$) δ 7.60-7.35 (m, 10H, Ph-H), 6.37 (d, *J* = 3.5 Hz, 1H, 5-H), 5.40 (br s, 1H, 2-H), 4.80-3.30 (m, 5H, 4-H_A, 4-H_B, 6-H_A, 6-H_B CHOOCN), 1.95-0.60 (m, 21H, CH_3CO, menthyl).

(2'*R*,5'*S*)- and (2'*R*,5'*R*)-1-(2-*t*-Butyldiphenylsilyloxymethyl-3-*L*-menthoxycarbonyl-1,3-oxazolidin-5-yl)thymine (10). A suspension of thymine (1.00 g, 8.25 mmol) in 1,1,1,3,3,3-hexamethyldisilazane (HMDS, 50 mL) was refluxed for 6 h in the presence of ammonium sulfate (50 mg) under N_2 until a clear solution was obtained, which was concentrated to dryness under reduce pressure. The residue was dissolved in 1,2-dichloroethane (30 mL). To the solution were added compound **9** (1.60

g, 2.75 mmol) in 1,2-dichloroethane (30 mL), and TMSOTf (1.20 g, 5.50 mmol). The resulting solution was stirred at rt for 2 h under N_2 and diluted with EtOAc (100 mL). Sat. $NaHCO_3$ solution (50 mL) was added to the solution and the resulting mixture was stirred at rt for 10 min. The organic layer was separated, washed with brine, dried ($MgSO_4$), and filtered through a silica gel pad. The filtrate was concentrated to give an inseparable mixture **10** of α- and β-isomers (1.60 g, 90 %) as a foam: UV (MeOH) λmax 265 nm; IR (film) 2957, 1700, 1464, 1428, 1277, 1115, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.20 (s, 1H, NH, D_2O exchangeable), 7.65-7.45 (m, 10H, Ph-H), 7.60, 7.05 (2 x s, 1H, 6-H), 6.29 (m, 1H, 5'-H), 5.70, 5.39 (2 x s, 1H, 2'-H), 4.60 (m, 1H, CHOOCN), 4.30-3.40 (m, 4H, 4'-H_A, 4'-H_B, 6'-H_A, 6'-H_B), 2.00-0.70 (m, 27H, menthyl, *t*-butyl). Anal. Calcd. for $C_{36}H_{49}N_3O_6Si{\cdot}0.5H_2O$: C, 65.82; H, 7.67; N, 6.40. Found: C, 66.03; H, 7.69; N, 6.34.

(2'*R*,5'*R*)- and (2'*R*,5'*S*)-1-(2-Hydroxymethyl-3-*L*-menthoxycarbonyl-oxazolidin-5-yl)thymine (11 and 12). To a solution of **10** (1.50 g, 2.32 mmol) in THF (100 mL) was added n-Bu_4NF (7.0 mL, 7.0 mmol, 1 M in THF). The solution was stirred at rt for 3 h and concentrated to give a syrup, which was separated by silica gel column chromatography eluting with EtOAc in hexanes (20-70 %) to give the less polar product **11** (0.39 g, 41 %) as a white foam: $[\alpha]^{25}_D$ = -32.2° (*c* 0.15, MeOH); UV (H_2O) λmax 265 (ε 9050, pH 2), 265 (ε 9740, pH 7), 264.5 nm (ε 7400, pH 11); IR (KBr) 3428, 2955, 1694, 1418, 1277, 1107, 961 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.25 (br s, 1H, NH, D_2O exchangeable), 7.58 (s, 1H, 6-H), 6.28 (t, *J* = 6.8 Hz, 1H, 5'-H), 5.30 (d, *J* = 2.0 Hz, 1H, 2'-H), 4.60 (m, 1H, CHOOCN), 4.20-4.05 (m, 2H, 6'-H_A, 6'-H_B), 3.89 (d, *J* = 12.2 Hz, 1H, 4'-H_A), 3.45 (dd, *J* = 6.9, 11.2 Hz, 1H, 4'-H_B), 2.41 (br s, 1H, OH, D_2O exchangeable), 2.10-0.70 (m, 21H, menthyl, 5-CH_3); ^{13}C ($CDCl_3$) δ 163.7, 153.2, 150.5, 135.4, 111.8, 89.3, 81.6, 76.4, 63.0, 49.0, 47.2, 41.3, 34.0, 31.3, 26.3, 23.2, 22.0, 20.9, 16.2, 12.6; MS: m/z 410 (MH^+). Anal. Calcd. for $C_{20}H_{31}N_3O_6$: C, 58.67; H, 7.63; N, 10.26. found: C, 58.41; H, 7.77; N, 10.05;

The more polar compound **12** (0.25 g, 26 %) was obtained by preparative TLC purification (EtOAc/hexanes:1/3) as a foam: $[\alpha]^{25}_D$ = -41.0° (*c* 0.16, MeOH); UV(H_2O) λmax 268.5 (ε 11620, pH 2), 268.5 (ε 11170, pH 7), 267.5 nm (ε 8670, pH 11); IR (KBr) 3422, 2955, 2870, 1694, 1414, 1266, 1107, 768 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.52 (br s, 1H, NH, D_2O exchangeable), 7.00 (s, 1H, 6-H), 6.37 (br s, 1H, 5'-H), 5.70 (m, 1H, 2'-H), 4.65 (m, 1H, CHOOCN), 4.24-3.65 (m, 4H, 4'-H_A, 4'-H_B, 6'-H_A, 6'-H_B), 2.10-0.70 (m, 21H, menthyl, 5-CH_3); ^{13}C ($CDCl_3$) δ 164.2, 153.7, 151.0, 134.5, 112.1, 90.9, 84.3, 77.0, 64.0, 50.7, 47.6, 41.7, 34.5, 31.8, 27.1, 23.8, 22.3, 21.1, 16.8, 13.0; MS: m/z 410 (MH^+). Anal. Calcd. for $C_{20}H_{31}N_3O_6{\cdot}0.4H_2O$: C, 57.65; H, 7.69; N, 10.08. found: C, 57.66; H, 7.69; N, 9.97.

***O*-*t*-Butyldiphenylsilylglycidol (14).** To a solution of glycidol **13** (5.0 g, 67.6 mmol) in $CHCl_3$ (100 mL) were added imidazole (9.2 g, 135 mmol), and *t*-butylchlorodiphenylsilane (19.5 g, 71.0 mmol). The solution was stirred at rt for 1 h, diluted with EtOAc (200 mL), washed with H_2O, and dried ($MgSO_4$). The solvent was removed to give **14** (20.5 g, 97 %), which was used for the next reaction without further purification. Analytical sample was purified by preparative TLC (EtOAc/Hexanes: 2/8): UV (MeOH) λmax 264.5 nm; IR (film): 3071, 3000, 2959, 2932, 2894, 2859, 1472, 1464, 1428, 1113, 741, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65-7.40 (m, 10H, Ph-H), 3.85-3.72 (m, 2H, CH_2OSi), 3.11 (m, 1H, CH), 2.73-2.60 (m, 2H, CH_2), 1.08 (s, 9H, *t*-butyl). Anal. Calcd. for $C_{19}H_{24}O_2Si$: C, 73.04; H, 7.74. Found: C, 72.97; H 7.72.

1-Amino-3-*t*-butyldiphenylsilyloxypropan-2-ol (15). A solution of **14** (20.0 g, 638 mmol) in methanolic ammonia (300 mL) was stirred at rt for 48 h and concentrated to dryness under reduced pressure to obtain a crude **15** (20.8 g, 99 %), which was used for the next reaction without further purification. Analytical sample was purified by preparative TLC ($MeOH/CH_2Cl_2$: 1/9): UV (MeOH) λmax 264.5 nm; IR (film) 3366, 3073, 3050, 2932, 2859, 1472, 1428, 1113, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65-7.45 (m, 10H, Ph-H), 3.68 (m, 3H, CH, CH_2OSi), 2.79 (m, 2H, NCH_2), 1.85 (br s, 3H, OH, NH_2, D_2O exchangeable), 1.08 (s, 9H, *t*-butyl). Anal. Calcd. for $C_{19}H_{27}NO_2Si{\cdot}0.1CH_2Cl_2$: C, 67.89; H, 8.11; N, 4.15. Found: C, 67.78; H, 8.15; N, 4.05.

2-Benzoyloxymethyl-5-*t*-butyldiphenylsilyloxymethyl-3-benzyloxycarbonyl-1,3-oxazolidine (17). A solution of aminoalcohol **15** (14.9 g, 45.0 mmol) and 2-*O*-benzoyloxy acetaldehyde (7.38 g, 45.0 mmol) in diethyl ether (200 mL) was stirred at rt for 20 min in the presence of molecular sieves powder (4 Å, 4.50 g). To the mixture were added Et_3N (6.06 g, 60.0 mmol), and benzyl chloroformate (8.53 g, 50.0 mmol). The resulting mixture was stirred at rt for an additional 1h, diluted with EtOAc (200 mL), washed with H_2O, brine, and dried ($MgSO_4$). Solvents were removed and the residue was purified by silica gel column chromatography eluting with EtOAc in hexanes (10 %) to obtain a mixture of *cis*- and *trans*-isomers **17** (13.3 g, 48 %) as a syrup: UV (MeOH) λmax 264.5 nm; IR (film) 3071, 2957, 2992, 2859, 1721, 1418, 1273 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.00-7.35 (m, 20H, Ph-H), 5.65-5.55 (m, 1H, 2-H), 5.20 (m, 2H, $PhCH_2$), 4.47-4.20 (m, 2H, 2-CH_2), 3.90-3.30 (m, 4H, 4-H_A, 4-H_B, 5-CH_2), 0.97 (s, 9H, *t*-butyl). Anal. Calcd. for $C_{36}H_{39}NO_5Si{\cdot}2H_2O$: C, 68.55; H, 6.87; N, 2.22. Found: C, 68.33; H, 6.30; N, 2.19.

2-Benzoyloxymethyl-3-benzyloxycarbonyl-5-hydroxymethyl-1,3-oxazolidine (18). To a solution of **17** (13.0 g, 21.3 mmol) in THF (200 mL) was added n-Bu_4NF (21.3 mmol, 21.3 mL, 1M in THF), and the solution was stirred at rt for

30 min. The solvent was removed and the residue was purified by silica gel column chromatography eluting with MeOH in CH_2Cl_2 (0-10 %) to obtain alcohol **18** (7.16 g, 91 %) as a syrup: UV (MeOH) λmax 273.0 nm; IR (film) 3474, 2955, 1717, 1453, 1420, 1275, 1123 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.04-7.35 (m, 10H, Ph-H), 5.65, 5.54 (2 x s, 1H, 2-H), 5.20 (m, 2H, $PhCH_2$), 4.80-4.21 (m, 3H, 2-CH_2, 2-H), 4.00-3.44 (m, 4H, 4-H_A, 4-H_B, 5-CH_2), 2.57-2.00 (m, 1H, OH, D_2O exchangeable). Anal. Calcd. for $C_{20}H_{21}NO_6$: C, 64.69; H, 5.66; N, 3.73. Found: C, 64.35; H, 5.78; N, 3.72.

5-Acetoxy-2-benzoyloxymethyl-3-benzyloxycarbonyl-1,3-oxazolidine (20). A mixture of **18** (1.86 g, 5.0 mmol), RuO_2 (100 mg), $NaIO_4$ (3.21 g, 15.0 mmol), CCl_4 (30 mL), acetonitrile (30 mL) and H_2O (45 mL) was stirred at rt for 3.5 h. The reaction mixture was extracted with methylene chloride. The organic extracts were combined, washed with brine, and dried ($MgSO_4$). Solvents were removed and coevaporated with benzene to obtain a crude acid **19** which was dissolved in EtOAc (80 mL). To the solution were added $Pb(OAc)_4$ (3.33 g, 7.5 mmol), and pyridine (0.5 mL, 6.10 mmol) . The resulting solution was refluxed for 0.5 h and filtered through a silica gel pad. The filtrate was concentrated to dryness and the residue was purified by silica gel column chromatography eluting with EtOAc in hexanes (20 %) to obtain **20** (1.30 g, 65 %) as a syrup: ^1H NMR ($CDCl_3$) δ 8.08-7.50 (m, 10H, Ph-H), 6.50 (m, 1H, 5-H), 5.75 (m, 1H, 2-H), 5.13 (m, 2H, $PhCH_2$), 4.60-3.15 (m, 4H, 4-H_A, 4-H_B, 6-H_A, 6-H_B), 2.10 (m, 3H, Ac).

1-(2-Benzoyloxymethyl-3-benzyloxycarbonyl-1,3-oxazolidin-5-yl)thymine (21). Thymine (1.70 g, 13.5 mmol) was refluxed in HMDS (45 mL) in the presence of $(NH_4)_2SO_4$ (100 mg) for 4 h under N_2 and the excess HMDS was removed under reduced pressure to obtain the silylated thymine, which was dissolved in 1,2-dichloroethane (20 mL). To the solution were added compound **20** (1.8 g, 4.5 mmol) in 1,2-dichloroethane (30 mL), and TMSOTf (2.0 g, 9.0 mmol). The resulting solution was stirred at rt for 1 h under N_2. Additional TMSOTf (1.0 g, 4.5 mmol) was added. The solution was stirred for another 1 h, poured in aqueous $NaHCO_3$, filtered, and extracted with methylene chloride. Organic extracts were combined, washed with brine, and dried ($MgSO_4$). The solvent was removed and the residue was purified by silica gel column chromatography eluting with methanol in chloroform (0-5 %) to obtain **21** (1.50 g, 72 %) as a foam: UV (MeOH) λmax 264 nm; IR (KBr) 3065, 1715, 1420, 1277, 1094, 764, 714 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.13 (br s, 1H, NH, D_2O exchangeable), 8.00-7.35 (m, 10H, Ph-H), 7.60, 6.97 (2 x s, 1H, 6-H), 6.36-6.24 (m, 1H, 5'-H), 5.95, 5.65 (2 x s, 1H, 2'-H), 5.20 (m, 2H, $PhCH_2$), 4.80-4.40 (m, 2H, 6'-H_A, 6'-H_B), 3.95-3.35 (m, 2H, 4'-H_A, 4'-H_B), 1.87, 1.56 (2 x s, 3H, 5-CH_3). Anal. Calcd. for $C_{24}H_{23}N_3O_7 \cdot 0.2H_2O$: C, 61.45; H, 4.94; N, 8.96. Found: C, 61.40; H, 5.03; N, 8.64.

***cis*-1-(3-Benzyloxycarbonyl-2-hydroxymethyl-1,3-oxazolidin-5-yl)thymine (22) and *cis*-1-(2-hydroxymethyl-3-methoxycarbonyl-1,3-oxazolidin-5-yl)thymine (23).** A mixture of benzoylated nucleosides **21** (700 mg, 1.51 mmol) was treated with methanolic ammonia (25 mL), stirred at rt for 24 h, and concentrated to dryness under reduced pressure. The residue was purified by preparative TLC (5 % MeOH in $CHCl_3$) to give **22** (180 mg, 33 %) and **23** (85 mg, 20 %) as foam.

Compound 22: UV (H_2O) λmax 264 (ε 10040, pH 2), 264 (ε 10550, pH 7), 264.5 nm (ε 7610, pH 11); IR (KBr) 3422, 3063, 1694, 1424, 1277, 1107, 1067, 758 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.06 (br s, 1H, NH, D_2O exchangeable), 7.58 (s, 1H, 6-H), 7.35 (m, 5H, Ph-H), 6.25 (t, J = 6.8 Hz, 1H, 5'-H), 5.33 (t, J = 2.0 Hz, 1H, 2'-H), 5.18 (m, 2H, $PhCH_2$), 4.22-4.06 (m, 2H, 6'-H_A, 6'-H_B), 3.90 (m, 1H, 4'-H_A), 3.48 (dd, J = 7.2, 11.2 Hz, 1H, 4'-H_B), 2.35 (br s, 1H, OH, D_2O exchangeable), 1.94 (s, 1H, 5-CH_3); ^{13}C ($CDCl_3$) δ 164.2, 153.5, 151.0, 136.0 135.9, 129.0 128.9, 128.5, 112.1, 89.8, 82.2, 68.2, 63.1, 49.4, 12.6; MS: m/z 362 (MH^+). Anal. Calcd. for $C_{17}H_{19}N_3O_6$: C, 56.51; H, 5.26; N, 11.63. Found: C, 56.23; H, 5.14; N, 11.28.

Compound 23: UV (H_2O) λmax 265 (ε 7740, pH 2), 265 (ε 8270, pH 7), 265 nm (ε 6240, pH 11); IR (KBr) 3436, 1694, 1464, 1401, 1277, 1107, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.20 (s, 1H, NH, D_2O exchangeable), 7.58 (s, 1H, 6-H), 6.26 (t, J = 6.8 Hz, 1H, 5'-H), 5.31 (t, J = 2.0 Hz, 1H, 2'-H), 4.20-4.06 (m, 2H, 6'-H_A, 6'-H_B), 3.90, (m, 1H, 4'-H_A), 3.78, (s, 3H, OCH_3), 3.46 (dd, J = 6.8, 11.2 Hz, 1H, 4'-H_B), 2.40 (br s, 1H, OH, D_2O exchangeable), 1.94 (s, 1H, 5-CH_3); ^{13}C ($CDCl_3$) δ 164.2, 153.4, 150.9, 135.7, 111.0, 89.3, 81.3, 61.9, 52.8, 48.9, 12.6; MS: m/z 285 (M^+). Anal. Calcd. for $C_{11}H_{15}N_3O_6$: C, 46.32; H, 5.26; N, 14.74. Found: C, 45.95; H, 4.83; N, 14.36.

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