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Articles

Homochiral α-D- and β-D-Isoxazolidinylthymidines via 1,3-Dipolar Cycloaddition†

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The introduction of chiral auxiliaries at the C- or N-atom in starting nitrones has been investigated as a stereoselective synthetic route to heterocyclic nucleoside analogues. The carbohydrate auxiliary at nitrogen atom gave the best results, thus allowing an easy and enantioselective synthesis of isoxazolidinyl thymine **26**.

Introduction

The synthesis of modified nucleosides has recently received considerable attention in the search for compounds with antiviral and anticancer activity.[1] In this context, exciting biological results have been obtained from a new generation of nucleoside analogues where the ribose moiety has been replaced by alternative heterocyclic rings.[2] In particular, the insertion of a second heteroatom in the furanosyl ring has led to the preparation of dioxolane-T (**1**) and 3TC (**2**), which contain a dioxolane or oxathiolane ring, respectively.[3,4] These compounds have shown excellent antiviral (HIV and HBV) activities with no significant drug resistance after 1 year of clinical trials when used in combination with AZT[5] (Figure 1).

Nucleosides **3** and **4**, containing an isoxazoline or isoxazolidine moiety, are of current interest as potential antiviral agents.[3d,6] As a consequence, following the first report on the synthesis of compound **4**,[7] a series of synthetic efforts have been devoted toward the preparation of suitable isoxazolidinyl nucleosides.[8,9]

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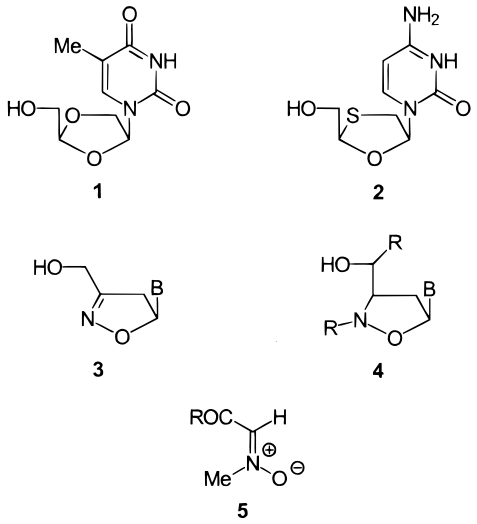

Figure 1.

We have previously reported the synthesis of nucleosides **4**,[10] which bear pyrimidine bases, in a racemic form; the synthetic scheme involves the 1,3-dipolar cycloaddition[11] of C-substituted carbonylnitrones **5** to vinyl acetate, followed by nucleosidation of the resulting 5-acetyloxyisoxazolidine derivatives with persylilated nucleobases.

In this paper, we have turned our attention to the asymmetric version of this route, by the use of chiral dipoles,[12] and we report herein the successful implementation of this strategy directed toward the stereoselective synthesis of isoxazolidinyl nucleosides **4**.

Results and Discussion

In the first approach, we exploited the introduction of a chiral auxiliary, as (−)-menthol, in the starting nitrone. Thus, nitrone **7** (prepared from **6**) through a transesterification reaction with (−)-menthol (1:1.5 ratio) in the presence of $TiCl_4$ as catalyst and molecular sieves reacted with vinyl acetate to give three stereoisomeric compounds (80% global yield), two of them (**8a** and **8b**) with a C_3-C_5 trans configuration (relative ratio 5:1) and one (**9**) with a C_3-C_5 cis configuration (cis/trans ratio 1:8). Structures of the obtained compounds have been assigned on the basis of NMR data and by NOE measurements (Scheme 1).

Flash chromatography of the crude reaction mixture allowed the separation of two trans derivatives from the cis stereoisomer; unfortunately, all the attempts to obtain pure compounds **8a** and **8b** failed.

The obtained results indicate that the reaction proceeds with a good control of cis/trans diastereoselectivity and a satisfactory level of asymmetric induction (5:1).

Nitrone **7** exists as a mixture of *E* and *Z* isomers, with the more reactive *E* isomer predominating (4:1).[13] Both cycloadducts **8a** and **8b** arise from reaction of *E* nitrone through an exo TS; the major stereoisomer was tentatively assigned the stereochemistry indicated in **8a** (3*S*,5*S*), according to PM3 calculations, which show that the *E-exo* transition state (addition of vinyl acetate to *si* face of nitrone) leading to this compound is about 1.1 kcal/mol more stable than *E-exo* transition state (*re* attack) leading to its stereoisomer **8b** (Figure 2).

We have, then, exploited an alternative route directed to the synthesis of homochiral N,O-nucleosides, based on the introduction of a stereocenter in α to the nitrone functionality (Scheme 2).

Nitrone **12** has been prepared starting from (−)-methyl lactate **10**, which has been silylated with *tert*-butyldiphenylsilyl chloride, reduced with DIBALH to the corresponding aldehyde **11**, and finally converted into the expected nitrone by reaction with methyl hydroxylamine hydrochloride. Nitrone **12**, in a *Z* configuration as confirmed by NOE experiments, has been reacted with vinyl acetate to give two epimeric isoxazolidines **13** and **14** (1:1 ratio), in good overall yield (88%).[14]

The mixture of compounds **13** and **14** has been coupled with silylated thymine to give, after deprotection with TBAF, the enantiomerically pure α- and *β*-nucleosides **15** and **16** in a 3:2 ratio, respectively (57% and 38% yield; $[\alpha]_D^{25} = -24.7$ for α-isomer and $[\alpha]_D^{25} = +90.1$ for *β*-isomer).

Nucleosides **15** and **16** have been separated by flash chromatography, and their structures have been mainly established by ^{1}H NOEDS. While, in compound **16**, diagnostic contacts were observed between $H_{3''}$ and H_6 and between $H_{3'}$ and $H_{5'}$, no such effects were detectable in the α anomeric counterpart. In addition, an NOE between $H_{3'}$ and H_6, in compound **15**, clearly indicated a syn relationship for these protons.

The results thus obtained can be rationalized as follows: the formation, in the coupling reaction, of enantiomerically pure α- and *β*-nucleosides **15** and **16** indicates that isoxazolidines **13** and **14** are epimeric only at C_5. Thus, the presence of the chiral center located in position α with respect to the nitrone functionality induces a some degree of asymmetric induction: with respect to the above-reported cycloaddition process, the cycloaddition reaction shows a nearly complete diastereofacial selectivity. In fact, conformations **A** and **B** are the major conformations available to the *Z*-nitrone for asymmetric induction:[15] PM3 calculations confirm that **A** is more stable than **B** by about 3.0 kcal/mol (Figure 3).

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(14) Compounds **13** and **14** have been separated by HPLC, and their configuration have been assigned by NOEDS experiments.

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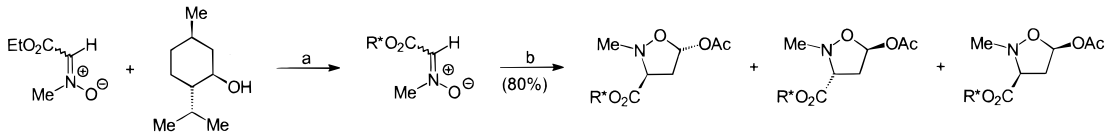
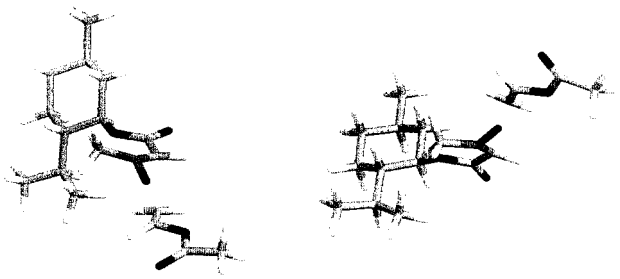
Scheme 1[a]



6 **(–)-Menthol** **7** (95%) **8a** (60%) **8b** (12%) **9** (8%)

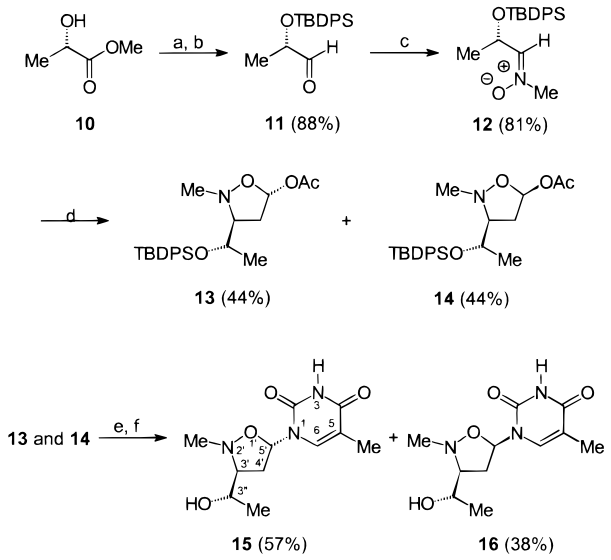
[a] Reaction conditions: (a) $TiCl_4$; (b) vinyl acetate, 70 °C, 48 h.



Si-E-Exo-TS *Re-E-Exo*-TS

Figure 2.

Scheme 2[a]



[a] Reaction conditions: (a) TBDPSCl, imidazole, CH_2Cl_2, 0 °C, 3 h; (b) DIBALH, diethyl ether, −78 °C, 6 h; (c) *N*-methylhydroxylamine hydrochloride, AcONa, EtOH, rt, 3 h; (d) vinyl acetate, 70 °C, 48 h; (e) *O*,*O*′-bis(trimethylsilyl)thymine, $SnCl_4$, CH_2Cl_2, overnight; (f) TBAF, THF, 3 h.

According to this rationale, the dipolarophile approaches the *si* face of nitrone and the cycloaddition proceeds with no preference for an endo or exo TS, in accord with the results reported with similar nitrones.[13,15]

On this basis, the configurational assignment to **15** and **16** has been performed by assuming that C_3 has a *S* configuration controlled by the chiral center present in the starting nitrone, derived from the initial (−)-lactate.

The 1,3-dipolar cycloaddition methodology for the enantioselective synthesis of N,O-nucleosides was extended to the examination of a nitrone containing the chiral center at the nitrogen atom.[16]

N-Glycosylnitrones can serve as versatile building blocks in the preparation of the target modified nucleosides: the chiral auxiliary can be easily introduced before the cycloaddition process and removed subsequently to give an N,O-nucleoside unsubstituted at the nitrogen atom.

Thus, 5-*O*-*tert*-butyldiphenylsilyl-2,3-*O*-isopropylidene-D-ribofuranose (**17**) was reacted with hydroxylamine hydrochloride to give, in a nearly quantitative yield, a *Z*/*E* mixture of the corresponding oxime **18** in equilibrium with the corresponding D-ribosyl hydroxylamine **19** (relative ratio **18**/**19** 50:1). Subsequent treatment of **19** with ethyl glyoxylate and vinyl acetate at 60 °C for 14 h gave, through the intermediate nitrone **20**, a mixture of two homochiral isoxazolidines **21** and **22**, epimeric at C_5, in a relative ratio of trans/cis 1:1. Moreover, the ^1H NMR analysis of the crude reaction mixture shows the presence of another unidentified diastereoisomer (minor) (Scheme 3).

Independent hydrolysis of isoxazolidines **21** and **22**, followed by oxidation with potassium permanganate, led to **23**. This result confirms that the isoxazolidines at hand are epimeric at C_5.[17]

Contrary to the poor cis/trans diastereoselectivity, the diastereofacial selectivity of the cycloaddition process is high. The results obtained in this cycloaddition may be interpreted in terms of the "O-endo" transition-state model[18] as shown in **C**, by involving, according to MNDO-MM$^+$ calculations,[19] which take in account the anomeric effect,[20] the *E* isomer as the more reactive form of nonisolated nitrone **20**: thus, two isomers **21** and **22** arise from the exo and endo attack on the *re* face of **20**, respectively (Figure 4).

Subsequent coupling of **21** or **22** with silylated thymine afforded the N,O-nucleosides **24** (β) and **25** (α) (1:2.5 relative ratio) in enantiomerically pure form (Scheme 3).

Configurational assignments have been performed on the basis of NOE experiments. Irradiation of the $H_{5'}$ signal in **24** induces a positive NOE effect on the downfield resonance of methylene protons at $C_{4'}$; in turn, irradiation of this proton gives rise to enhancement of the $H_{3'}$ resonance, so indicating that these protons are in a topological cis arrangement. Analogously, α-nucleoside **25** shows a NOE correlation between $H_{5'}$ and the downfield resonance at $C_{4'}$, but only a negligible NOE effect between this last resonance and $H_{3'}$.

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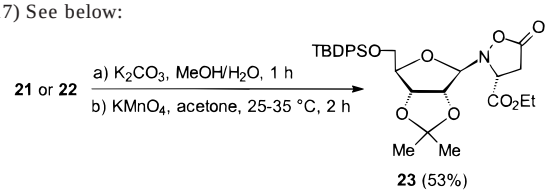
(17) See below:



23 (53%)

(18) Kasahara, K.; Iida, H.; Kibasyashi, C. *J. Org. Chem.* **1989**, *54*, 2225.

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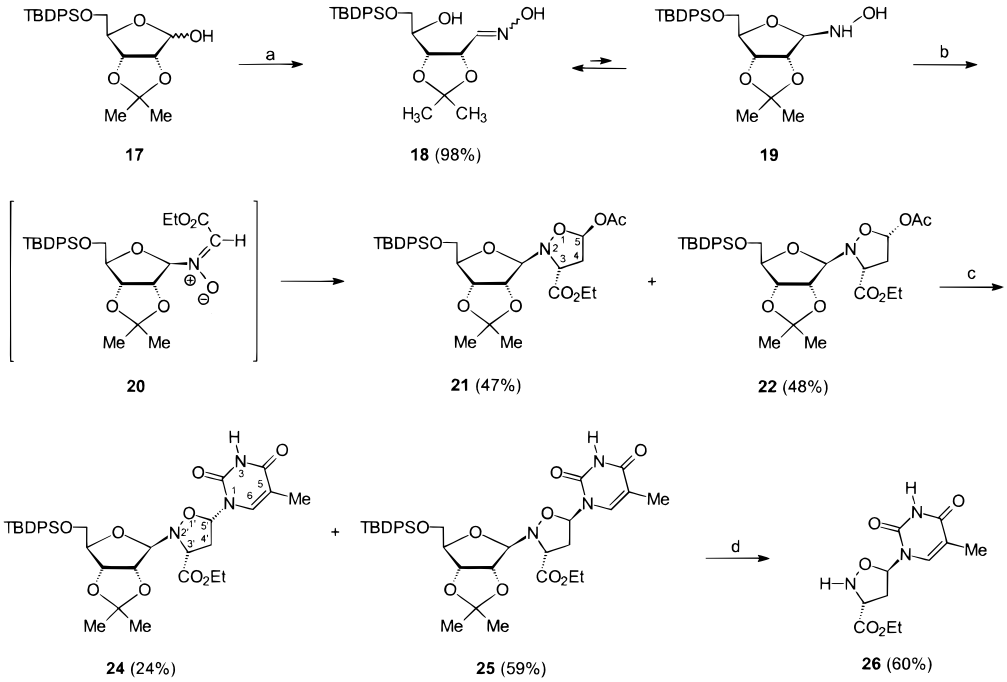
Scheme 3[a]



[a] Reaction conditions: (a) hydroxylamine hydrochloride, pyridine, rt, 1 h; (b) vinyl acetate, ethyl glyoxalate, 60 °C, 14 h; (c) BSA, thymine, Me_3SiOTf, MeCN, reflux, 1 h; (d) reaction of **25** with 3.7% HCl in EtOH, rt, 3 h.

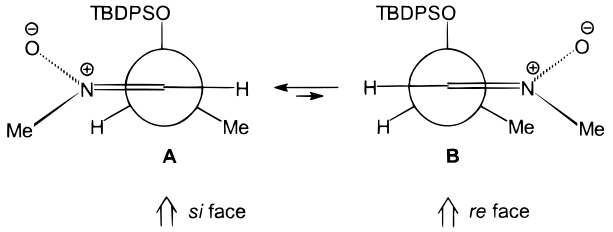


Figure 3.

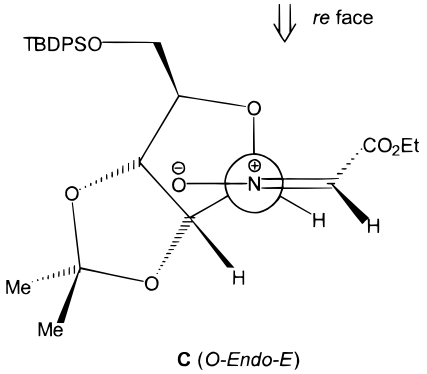


Figure 4.

Finally, the synthetic scheme devoted toward the synthesis of homochiral N,O-nucleosides has been completed by the selective cleavage of the sugar moiety, performed by treatment with 3.7% aqueous HCl. Thus, **25**, as the selected model, furnishes the N-unsubstituted nucleoside **26** in 60% yield (Scheme 3).

In conclusion, the 1,3-dipolar cycloaddition methodology, using nitrones carrying the carbohydrate-derived chiral auxiliaries developed by Vasella,[16] provides the basis for an enantioselective synthesis of modified N,O-nucleosides. Moreover, the mixture of isoxazolidines **21** and **22** can be directly converted into nucleosides **24**, and **25** without any tedious HPLC purification, because they are epimeric at C_5. The synthetic pattern here described shows its versatility in the potential construction of other nucleosides with different purine and pyrimidine bases. Furthermore, the process allows an easy entry to enantiomerically pure N-unsubstituted compounds that have already shown interesting biological activity in vitro.[21]

Experimental Section

General Procedures. Melting points are uncorrected. NMR spectra were recorded at 200 and 500 MHz (^{1}H) and at 50 and 125 MHz (^{13}C) and are reported in ppm downfield from TMS. Thin-layer chromatography was done on plates coated with Merck 60 F_{254} silica gel. Silica gel chromatography was done with Macherey-Nagel 60 M (0.040−0.063 mm). Preparative radial chromatography was done on glass rotors coated with Merck 60 PF_{254} silica gel (1−4 mm layer). All reactions involving air-sensitive agents were conducted under a nitrogen atmosphere. All reagents were purchased from Aldrich or Acros Chimica and were used without further purification. Solvents for chromatography were distilled at atmospheric pressure prior to use and dried using standard procedures. HPLC purifications were made with a semipreparative column (Partisil-10 Magnum 9, 9.4 × 250 mm). The purity of all homochiral compounds has been tested with a Nucleosil Chiral-2, 4 × 250 mm column with mixtures of *n*-hexane−2-propanol as eluent.

(3*S*,5*S*)-, (3*R*,5*R*)-, and (3*S*,5*R*)-5-Acetyloxy-3-[(1′*R*,2′*S*,-5′*R*)-menthoxycarbonyl]-2-methylisoxazolidine (8a,b and 9). $TiCl_4$ (0.1 M solution in 1,2-dichloroethane, 10 mL, 1 mmol) and (−)-menthol (2.81 g, 18 mmol) were added successively to a stirred suspension of molecular sieves 4A (20 g) and nitrone **6** (1.57 g, 12 mmol) in dry 1,2-dichloroethane (300 mL) at room temperature under a nitrogen atmosphere. After the mixture was stirred for 24 h, a small amount of water and Celite were added to the mixture, and the mixture was filtered through a pad of Celite. The filtrate was diluted with water, extracted

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with dichloromethane, dried over sodium sulfate, and concentrated in vacuo. The residue, purified by column flash chromatography on silica gel (cyclohexane/ethyl acetate 1:4), gave an *E*/*Z* mixture (4:1) of *C*-[(1*R*,2*S*,5*R*)-menthoxycarbonyl]-*N*-methylnitrone (**7**)[22] (2.75 g, 95%) as a light yellow oil: $[\alpha]_D^{25} = -63.9$ (*c* 1.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) *E*-isomer δ 0.85 (d, 3H, $J = 7.0$ Hz), 0.88 (d, 3H, $J = 6.9$ Hz), 0.91 (d, 3H, $J = 6.9$ Hz), 1.65 (m, 2H), 1.81−1.95 (m, 4H), 2.43 (m, 3H), 4.18 (s, 3H), 4.71 (ddd, 1H, $J = 4.5$, 10.8, 10.8 Hz), 7.04 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.6, 19.5, 22.3, 23.2, 26.2, 31.7, 34.1, 40.9, 48.3, 50.5, 76.1, 128.6, 165.1. Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.57; H, 9.62; N, 5.80.

A solution of nitrone **7** (2.7 g, 11.2 mmol) in vinyl acetate (40 mL) was heated at 70 °C, in a sealed tube, for 24 h. The reaction mixture was evaporated and the residue subjected to flash chromatography (cyclohexane/ethyl acetate 9:1). First eluted fractions gave an inseparable mixture of **8a**,**b** (5:1) (2.11 g, 72%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.76 (d, 3H, $J = 7.0$ Hz), 0.90 (d, 3H, $J = 6.9$ Hz), 0.91 (d, 3H, $J = 6.9$ Hz), 1.02 (sept, 1H, $J = 6.9$ Hz), 1.48 (m, 3H), 1.72 (m, 3H), 1.82 (m, 1H), 2.05 (m, 1H), 2.08 (s, 3H), 2.64 (m, 1H), 2.84 (m, 1H), 2.94 (s, 3H), 3.72 (dd, 1H, $J = 7.6$, 7.8 Hz), 4.75 (ddd, 1H, $J = 4.4$, 10.8, 10.8 Hz), 6.37 (d, 1H, $J = 4.8$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.17, 16.22, 20.70, 20.73, 20.76, 21.26, 21.28, 21.90, 21.92, 23.33, 23.36, 26.24, 26.30, 31.4, 34.1, 39.9, 40.1, 40.4, 40.7, 46.9, 67.1, 67.3, 75.7, 75.8, 96.7, 169.0, 169.1, 169.8. Anal. Calcd for $C_{17}H_{29}NO_5$: C, 62.36; H, 8.93; N, 4.28. Found: C, 62.28; H, 8.91; N, 4.29.

(3′*S*,5′*S*)- and (3′*S*,5′*R*)-1-(3′-[(1*S*)-1-(Hydroxyethyl)]-2′-methyl-1′,2′-isoxazolidinyl)thymine (15 and 16). To a stirred solution of **10** (2.08 g, 2.0 mmol) and imidazole (3.24 g, 4.8 mmol) in dry dichloromethane (60 mL) at 0 °C was dropwise added a solution of *tert*-butyldiphenylsilyl chloride (6.2 mL, 2.4 mmol) in dry dichloromethane (20 mL), and the reaction mixture was stirred at room temperature until TLC showed the disappearance of the starting material (3 h). The solution was then evaporated, and the residue was purified by flash chromatography (cyclohexane/ethyl acetate 95:5) to afford methyl (2*S*)-2-*tert*-butyldiphenylsilyloxypropanoate (5.75 g 84%) as a colorless oil: $[\alpha]_D^{25} = -34.7$ (*c* 1.18, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.09 (s, 9H), 1.37 (d, 3H, $J = 6.7$ Hz), 3.55 (s, 3H), 4.28 (q, 1H, $J = 6.7$ Hz), 7.33−7.71 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.2, 21.2, 26.8, 51.5, 68.9, 127.5, 127.6, 129.7, 133.1, 133.5, 135.7, 135.8, 174.1. Anal. Calcd for $C_{20}H_{26}O_3Si$: C, 70.14; H, 7.65. Found: C, 69.98; H, 7.66.

To a stirred solution of the above protected lactate (2.74 g, 8.0 mmol) in anhydrous diethyl ether (70 mL) at −78 °C, under nitrogen, was slowly added via cannula DIBALH (15 mL, 1.0 M solution in toluene) with stirring. After 6 h, the reaction was then quenched with ethyl acetate (2 mL). The mixture was left to warm to room temperature, water (2 mL) was added, and and the mixture was stirred for 3 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (cyclohexane/ethyl acetate 95:5) to afford (2*S*)-2-*tert*-butyldiphenylsilyloxypropanal (2.20 g, 88%) as a colorless oil: $[\alpha]_D^{25} = -15.0$ (*c* 1.07, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.11 (s, 9H), 1.22 (d, 3H, $J = 6.8$ Hz), 4.09 (dq, 1H, $J = 1.0$, 6.8), 7.32−7.70 (m, 10H), 9.64 (d, 1H, $J = 1.0$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.4, 19.2, 26.8, 74.4, 127.7, 127.8, 129.9, 130.0, 133.2, 133.4, 135.7, 135.8, 203.7. Anal. Calcd for $C_{19}H_{24}O_2Si$: C, 73.03; H, 7.74. Found: C, 72.83; H, 7.75.

Nitrone **12**, prepared following the literature method,[11] was obtained exclusively as *Z* isomer in 81% yield as a white solid: mp 131−133 °C; $[\alpha]_D^{25} = +65.0$ (*c* 2.18, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.08 (s, 9H), 1.35 (d, 3H, $J = 6.4$ Hz), 3.40 (s, 3H), 5.03 (dq, 1H, $J = 5.7$, 6.4 Hz), 6.57 (d, 1H, $J = 5.7$ Hz), 7.30−7.68 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.0, 19.6, 26.8, 52.0, 65.5, 127.6, 129.7, 133.3, 133.6, 133.7, 135.5, 143.8. Anal. Calcd for $C_{20}H_{27}NO_2Si$: C, 70.34; H, 7.97; N, 4.10. Found: C, 70.60; H, 7.99; N, 4.10.

A solution of nitrone **12** (0.92 g, 2.7 mmol) in vinyl acetate (40 mL) was heated at 70 °C, in a sealed tube, for 24 h. The reaction mixture was evaporated, and the residue was purified by column chromatography (cyclohexane/ethyl acetate 3:1) and then by HPLC with a linear gradient of 2-propanol (2−2.5%, 0−6 min, flow 3.5 mL/min) in *n*-hexane. The first eluted product was (3*S*,5*R*)-5-acetyloxy-3-[(1*S*)-1-(*tert*-butyldiphenylsilyloxy)ethyl]-2-methylisoxazolidine **14** (t_R 5.6 min, 0.5 g, 44%) as a colorless oil: $[\alpha]_D^{25} = +76.4$ (*c* 0.14, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.05 (d, 3H, $J = 6.3$ Hz), 1.07 (s, 9H), 2.01 (s, 3H), 2.45 (ddd, 1H, $J = 1.8$, 5.9, 11.2 Hz, H_{4a}), 2.61 (ddd, 1H, $J = 6.0$, 8.8, 11.2 Hz, H_{4b}), 2.62 (ddd, 1H, $J = 3.0$, 5.9, 8.8 Hz, H_3), 2.68 (s, 3H), 3.91 (dq, 1H, $J = 3.0$, 6.3 Hz, $H_{3'}$), 6.23 (dd, 1H, $J = 1.8$, 6.0 Hz, H_5) 7.36−7.44 (m, 6H), 7.66−7.74 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.3, 21.3, 26.9, 29.7, 38.5, 45.4, 68.0, 73.4, 95.3, 127.5, 127.6, 129.6, 129.7, 133.4, 134.4, 135.9, 136.1, 170.6. Anal. Calcd for $C_{24}H_{33}NO_4Si$: C, 67.41; H, 7.78; N, 3.28. Found: C, 67.30; H, 7.79; N, 3.28. Further elution gave (3*S*,5*S*)-5-acetyloxy-3-[(1*S*)-1-(*tert*-butyldiphenylsilyloxy)ethyl]-2-methylisoxazolidine **13** (t_R 5.9 min, 0.5 g, 44%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.08 (s, 9H), 1.09 (d, 3H, $J = 6.2$ Hz), 2.06 (s, 3H), 2.45 (ddd, 1H, $J = 1.8$, 5.5, 11.6 Hz, H_{4a}), 2.65 (ddd, 1H, $J = 6.1$, 9.2, 11.6 Hz, H_{4b}), 2.97 (ddd, 1H, $J = 5.5$, 5.8, 9.2 Hz, H_3), 2.81 (s, 3H), 3.79 (dq, 1H, $J = 5.8$, 6.2 Hz, $H_{3'}$), 6.22 (dd, 1H, $J = 1.8$, 6.1 Hz, H_5) 7.36−7.44 (m, 6H), 7.66−7.72 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.3, 20.3, 26.8, 29.7, 38.4, 45.2, 69.0, 75.6, 97.7, 127.4, 127.6, 129.6, 129.7, 133.3, 134.4, 135.8, 136.1, 170.6. Anal. Calcd for $C_{24}H_{33}NO_4Si$: C, 67.41; H, 7.78; N, 3.28. Found: C, 67.55; H, 7.76; N, 3.29.

The crude epimeric mixture of isoxazolidines **13** and **14** (950 mg, 2.22 mmol) and *O*,*O*′-bis(trimethylsilyl)thymine (0.82 g, 3.0 mmol) were dissolved in anhydrous CH_2Cl_2 (10 mL) under a nitrogen atmosphere. This solution was cooled to 0 °C, and $SnCl_4$ (0.5 mmol) was added. The reaction mixture was then warmed to room temperature, left to stir overnight, and finally, poured slowly into a mixture of cold saturated aqueous $NaHCO_3$ (5 mL) and $CHCl_3$ (10 mL). The resulting emulsion was separated by filtration through Celite, the aqueous layer was further extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The residue, obtained as a light yellow oil, was characterized as an anomeric mixture (α:β 3:2) of (3′*S*,5′*S*)- and (3′*S*,5′*R*)-1-(5′-acetyloxy-3′-[(1*S*)-1-(*tert*-butyldiphenylsilyloxy)ethyl]-2′-methyl-1′,2′-isoxazolidinyl)-thymine (0.943 g, 86%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.04 (s, 9H), 1.05 (s, 9H), 1.81 (d, 3H, $J = 1.1$ Hz), 1.92 (d, 3H, $J = 1.1$ Hz), 2.02 (s, 3H), 2.05 (s, 3H), 2.45−3.02 (m, 6H), 2.62 (s, 6H), 3.90 (m, 2H), 6.08 (m, 2H, H_5) 7.30−7.78 (m, 22H).

To a THF solution (20 mL) of the above protected nucleosides (0.943 g, 1.91 mmol) was added a TBAF solution (2.13 mL, 2.1 mmol, 1 M solution in THF), and the mixture was stirred at room temperature for 3 h. At that time, the solvent was removed and the residue was subjected to silica gel column chromatography (chloroform/methanol 95:5). The first eluted product was the α-anomer **15** (0.277 g, 57%) as a sticky oil: $[\alpha]_D^{25} = -24.7$ (*c* 1.70, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.19 (d, 3H, $J = 6.3$ Hz), 1.91 (d, 3H, $J = 1.2$ Hz), 2.48 (bs, 1H, OH), 2.56 (m, 1H), 2.69 (m, 1H), 2.81 (s, 3H), 2.88 (m, 1H), 3.96 (dq, 1H, $J = 6.3$, 6.8 Hz), 6.15 (dd, 1H, $J = 4.0$, 6.8 Hz), 7.60 (bs, 1H, NH), 7.68 (q, 1H, $J = 1.2$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.6, 19.6, 36.8, 43.6, 63.8, 73.1, 82.8, 110.2, 135.9, 150.7, 164.2. Anal. Calcd for $C_{11}H_{17}N_3O_4$: C, 51.76; H, 6.71; N, 16.46. Found: C, 51.88; H, 6.72; N, 16.45. Further elution afforded β-anomer **16** (0.185 g, 38%) as a sticky oil: $[\alpha]_D^{25} = +90.1$ (*c* 1.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.22 (d, 3H, $J = 6.3$ Hz), 1.94 (d, 3H, $J = 1.2$ Hz), 2.09 (m, 1H), 2.43 (bs, 1H, OH), 2.78 (m, 1H), 2.92 (s, 3H), 3.02 (m, 1H), 3.78 (dq, 1H, $J = 6.3$, 6.8 Hz), 6.14 (dd, 1H, $J = 4.2$, 7.3 Hz), 7.64 (q, 1H, $J = 1.2$ Hz), 9.00 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.6, 21.0, 41.1, 46.6, 69.2, 73.0, 83.2, 110.6, 135.7, 150.6, 164.1. Anal. Calcd for $C_{11}H_{17}N_3O_4$: C, 51.76; H, 6.71; N, 16.46. Found: C, 51.68; H, 6.71; N, 16.47.

(3*R*,5*R*)- and (3*R*,5*S*)-5-Acetyloxy-2-(5′-*O*-*tert*-butyldiphenylsilyl-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-

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3-ethoxycarbonylisoxazolidines (21 and 22). To a stirred solution of ribofuranose 2,3-acetonide[23] (3.44 g, 18.09 mmol) and imidazole (2.71 g, 39.8 mmol) in dry dichloromethane (60 mL) at 0 °C was dropwise added a solution of *tert*-butyldiphenylsilyl chloride (5.47 g, 19.9 mmol) in dry dichloromethane (20 mL), and the reaction mixture was stirred at room temperature until TLC showed the disappearance of the starting material (3 h). The solution was then evaporated, and the residue purified by flash chromatography (cyclohexane/ethyl acetate 9:1) gave an oil that was identified as an anomeric mixture (α:β = 1:5) of 5-*O*-*tert*-butyldiphenylsilyl-2,3-*O*-isopropilidene-D-ribofuranose (**17**) (6.05 g, 78%) as a colorless oil: $[\alpha]_D^{25} = -19.7$ (*c* 25.95, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ α-anomer 1.07 (s, 9H), 1.39 (s, 3H), 1.55 (s, 3H), 3.63 (dd, 1H, *J* = 2.5, 11.0 Hz, H_{5a}), 3.80 (dd, 1H, *J* = 3.0, 11.0 Hz, H_{5b}), 3.98 (d, 1H, *J* = 11.0 Hz, OH), 4.15 (dd, 1H, *J* = 2.5, 3.0 Hz, H_4), 4.66 (dd, 1H, *J* = 4.0, 6.0 Hz, H_2), 4.78 (d, 1H, *J* = 6.0 Hz, H_3), 5.62 (dd, 1H, *J* = 4.0, 11.0 Hz, H_1); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.9, 24.6, 26.4, 29.6, 65.9 67.9, 81.2, 81.8, 97.9, 112.9, 127.8, 127.9, 129.8, 129.9, 132.4, 132.6, 135.4, 135.6. ^{1}H NMR ($CDCl_3$, 500 MHz) δ β-anomer 1.09 (s, 9H), 1.31 (s, 3H), 1.46 (s, 3H), 3.66 (dd, 1H, *J* = 3.0, 11.5 Hz, H_{5a}), 3.81 (dd, 1H, *J* = 3.5, 11.5 Hz, H_{5b}), 4.28 (dd, 1H, *J* = 3.0, 3.5 Hz, H_4), 4.50 (d, 1H, *J* = 10.0 Hz, OH), 4.60 (d, 1H, *J* = 6.0 Hz, H_2), 4.73 (d, 1H, *J* = 5.5 Hz, H_3), 5.35 (d, 1H, *J* = 10.0 Hz, H_1); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.0, 24.9, 26.5, 26.8, 65.5, 81.7, 87.0, 87.1, 103.2, 112.0, 127.9, 128.0, 130.0, 130.2, 131.7, 131.8, 135.5, 135.6. Anal. Calcd for $C_{24}H_{32}O_5Si$: C, 67.26; H, 7.53. Found: C, 67.13; H, 7.54.

To a solution of **17** (5.76 g, 13.44 mmol) in dry pyridine (100 mL) was added hydroxylamine hydrochloride (11.2 g, 161.28 mmol), and the reaction mixture was stirred for 1 h at room temperature. At the end of this time, water (240 mL) was added, and the mixture was extracted with dichloromethane (4 × 150 mL); the combined organic layers were washed with brine (200 mL), dried over sodium sulfate, and evaporated under reduced pressure to afford a residue that was subjected to flash chromatography (cyclohexane/ethyl acetate 3:1) to give an *E*/*Z* mixture (2.9:1) of (4*S*,5*R*)-5-[(1*R*)-2-[[1-(*tert*-butyl)-1,1-diphenylsilyl]oxy]-1-hydroxyethyl]-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde oxime (**18**) (5.84 g, 98%) as a light yellow oil: $[\alpha]_D^{25} = +8.5$ (*c* 10.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ *E* isomer 1.07 (s, 9H), 1.33 (s, 3H), 1.34 (s, 3H), 3.53 (bs, 1H, OH), 3.76 (dd, 1H, *J* = 2.9, 9.0 Hz, $H_{5'}$), 3.80 (d, 1H, *J* = 10.4 Hz, $H_{5''a}$), 3.88 (dd, 1H, *J* = 2.9, 10.4 Hz, $H_{5''b}$), 4.25 (dd, 1H, *J* = 6.3, 9.0 Hz, H_5), 4.82 (dd, 1H, *J* = 6.3, 7.5 Hz, H_4), 7.52 (d, 1H, *J* = 7.5 Hz, $H_{4'}$), 7.35−7.72 (m, 10H), 9.88 (bs, 1H, N−OH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.2, 25.2, 26.85, 27.6, 65.24, 69.6, 75.23, 77.1, 109.7, 127.65, 127.7, 129.71, 129.75, 132.8, 132.9, 135.4, 135.5, 148.2; ^{1}H NMR ($CDCl_3$, 500 MHz) δ *Z* isomer 1.08 (s, 9H), 1.34 (s, 3H), 1.35 (s, 3H), 3.18 (bs, 1H, OH), 3.72 (dd, 1H, *J* = 2.9, 8.2 Hz, $H_{5'}$), 3.81 (d, 1H, *J* = 10.6 Hz, $H_{5''b}$), 3.84 (dd, 1H, *J* = 2.9, 10.6 Hz, $H_{5''b}$), 4.43 (dd, 1H, *J* = 6.2, 8.2 Hz, H_5), 5.41 (dd, 1H, *J* = 6.2, 6.3 Hz, H_4), 6.88 (d, 1H, *J* = 6.3 Hz, $H_{4'}$), 7.34−7.72 (m, 10H), 9.47 (bs, 1H, N−OH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.1, 25.1, 26.78, 27.4, 65.12, 70.7, 75.20, 77.5, 109.4, 127.5, 127.61, 129.61, 129.67, 135.55, 135.57, 150.2. Anal. Calcd for $C_{24}H_{33}NO_5Si$: C, 64.98; H, 7.50; N, 3.16. Found: C, 65.03; H, 7.49; N, 3.17.

A solution of the oxime **18** (4.23 g, 9.87 mmol), vinyl acetate (18.2 mL, 197.44 mmol), and ethyl glyoxalate (2.54 mL, 12.8 mmol; 50% solution in toluene) was heated at 60 °C, in a sealed tube, for 14 h. The reaction mixture was evaporated, and the residue was purified by column chromatography (cyclohexane/ethyl acetate 4:1) and then by HPLC (*n*-hexane/2-propanol 96.5:3.5). The first eluted product was **21** (t_R 7.1 min, 2.78 g, 47%): white solid; mp 55−58 °C; $[\alpha]_D^{25} = -56.5$ (*c* 1.35, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.93 (t, 3H, *J* = 7.1 Hz), 1.05 (s, 9H), 1.31 (s, 3H), 1.48 (s, 3H), 2.06 (s, 3H), 2.52 (ddd, 1H, *J* = 2.0, 8.3, 13.9 Hz, H_{4a}), 2.91 (ddd, 1H, *J* = 4.3, 6.2, 13.9 Hz, H_{4b}), 3.65 (dd, 1H, *J* = 5.3, 10.5 Hz, $H_{5'a}$), 3.76 (dq, 1H, *J* = 7.1, 10.9 Hz), 3.77 (dd, 1H, *J* = 9.7, 10.5 Hz, $H_{5'b}$), 3.88 (dq, 1H, *J* = 7.1, 10.9 Hz), 4.10 (dd, 1H, *J* = 4.3, 8.3 Hz, H_3), 4.30 (dd, 1H, *J* = 5.3, 9.7 Hz, $H_{4'}$), 4.78 (d, 1H, *J* = 6.2 Hz, $H_{2'}$), 4.78 (s, 1H, $H_{1'}$), 4.82 (d, 1H, *J* = 6.2 Hz, $H_{3'}$), 6.43 (dd, 1H, *J* = 2.0, 6.2 Hz, H_5), 7.36−7.66 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8, 19.2, 21.2, 25.0, 26.6, 26.8, 37.6, 61.4, 62.4, 63.8, 82.9, 83.7, 87.6, 98.1, 100.3, 112.3, 127.69, 127.73, 129.7, 133.4, 135.5, 169.8, 170.6. Anal. Calcd for $C_{32}H_{43}NO_9Si$: C, 62.62; H, 7.06; N, 2.28. Found: C, 62.60; H, 7.06; N, 2.28. Further elution gave **22** (t_R 8.0 min, 2.83 g, 48%): white solid; mp 54−58 °C; $[\alpha]_D^{25} = +59.5$ (*c* 2.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.04 (s, 9H), 1.13 (t, 3H, *J* = 7.1 Hz), 1.32 (s, 3H), 1.49 (s, 3H), 1.97 (s, 3H), 2.61 (ddd, 1H, *J* = 5.0, 9.0, 13.5 Hz, H_{4a}), 2.75 (dd, 1H, *J* = 1.5, 13.5 Hz, H_{4b}), 3.73 (dd, 1H, *J* = 5.8, 10.7 Hz, $H_{5'a}$), 3.85 (dd, 1H, *J* = 7.0, 10.7 Hz, $H_{5'b}$), 4.01 (dq, 1H, *J* = 7.1, 10.9 Hz), 4.04 (dq, 1H, *J* = 7.1, 10.9 Hz), 4.20 (ddd, 1H, *J* = 1.7, 5.8, 7.0 Hz, $H_{4'}$), 4.28 (dd, 1H, *J* = 1.5, 9.0 Hz, H_3), 4.52 (d, 1H, *J* = 1.5 Hz, $H_{1'}$), 4.73 (dd, 1H, *J* = 1.7, 6.2 Hz, $H_{3'}$), 4.86 (dd, 1H, *J* = 1.5, 6.2 Hz, $H_{2'}$), 6.45 (d, 1H, *J* = 5.0 Hz, H_5), 7.36−7.66 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1, 19.2, 21.0, 25.0, 26.7, 26.8, 37.0, 59.4, 61.3, 64.1, 81.5, 83.5, 87.1, 95.8, 98.9, 112.7, 127.72, 127.73, 129.7, 133.23, 133.32, 135.50, 135.53, 169.6, 170.1. Anal. Calcd for $C_{32}H_{43}NO_9Si$: C, 62.62; H, 7.06; N, 2.28. Found: C, 62.51; H, 7.04; N, 2.29.

(3*R*)-2-(5′-*O*-*tert*-Butyldiphenylsilyl-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-3-ethoxycarbonylisoxazolidin-5-one (23). Isoxazolidine **21** or **22** (200 mg, 0.334 mmol) was dissolved in aqueous methanol (10:1 MeOH/H_2O; 4.4 mL) containing potassium carbonate (25 mg, 0.18 mmol), and the resulting solution was stirred at room temperature for 1 h. The solution was brought to pH 6.0 with aqueous 10% HCl; the solvent was removed under reduced pressure, and the residue was dissolved in water (2 mL). The aqueous solution was extracted with ether (3 × 3 mL), and the combined organic layers were dried over sodium sulfate, filtered, and evaporated to give the crude lactol that was further utilized without purification.

To a vigorously stirred solution of the crude lactol (0.180 g, 0.323 mmol) in acetone (3 mL) was added $KMnO_4$ (0.077 g, 0.485 mmol) in portions over a 1 h period. The temperature of the mixture was maintained between 25 and 45 °C (water bath). Stirring was continued at room temperature for 2 h. The mixture was filtered, and the solid was washed with fresh acetone (2 × 5 mL). The combined filtrate was evaporated to yield a residue that was dissolved in Et_2O (10 mL) and washed with water (3 × 2 mL). After the residue was dried over sodium sulfate, the solvent was evaporated, and the residue was then purified by radial chromatography (cyclohexane/ethyl acetate 85:15) to give **23** (100.8 mg, 53% overall yield) as a light yellow oil: $[\alpha]_D^{25} = +16.3$ (*c* 2.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.06 (s, 9H), 1.13 (t, 3H, *J* = 7.1 Hz), 1.33 (s, 3H), 1.51 (s, 3H), 2.91 (dd, 1H, *J* = 7.0, 10.2 Hz, H_{4a}), 2.92 (dd, 1H, *J* = 5.2, 10.2 Hz, H_{4b}), 3.73 (dd, 1H, *J* = 4.8, 10.7 Hz, $H_{5'a}$), 3.82 (dd, 1H, *J* = 6.6, 10.7 Hz, $H_{5'b}$), 4.01 (dq, 1H, *J* = 7.1, 10.9 Hz), 4.10 (dq, 1H, *J* = 7.1, 10.9 Hz), 4.24 (ddd, 1H, *J* = 1.6, 4.8, 6.6 Hz, $H_{4'}$), 4.37 (dd, 1H, *J* = 5.2, 7.0 Hz, H_3), 4.69 (dd, 1H, *J* = 2.4, 6.2 Hz, $H_{2'}$), 4.75 (dd, 1H, *J* = 1.6, 6.2 Hz, $H_{3'}$), 4.84 (d, 1H, *J* = 1.6 Hz, $H_{1'}$), 7.39−7.66 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9, 19.1, 25.1, 26.8, 29.6, 30.5, 59.4, 62.1, 63.7, 80.8, 82.3, 86.1, 99.6, 113.5, 127.8, 127.9, 129.7, 132.8, 132.9, 135.4, 135.5, 169.1, 174.5. Anal. Calcd for $C_{30}H_{39}NO_8Si$: C, 63.25; H, 6.90; N, 2.46. Found: C, 63.20; H, 6.91; N, 2.46.

(3′*R*,5′*S*)- and (3′*R*,5′*R*)-1-[2′-(5″-*O*-*tert*-Butyldiphenylsilyl-2″,3″-*O*-isopropylidene-β-D-ribofuranosyl)-3′-ethoxycarbonyl-1′,2′-isoxazolidinyl]thymine (24 and 25). A suspension of thymine (78 mg, 0.618 mmol) in dry acetonitrile (3 mL) was treated with bis(trimethylsilyl)acetamide (0.62 mL, 2.54 mmol) and refluxed for 15 min. To the clear solution obtained was added a solution of isoxazolidine **21** or **22** (310 mg, 0.517 mmol) in dry acetonitrile (3 mL). Trimethylsilyltriflate (174 mg, 0.78 mmol) was added dropwise, and the reaction mixture was refluxed for 1 h. After being cooled to 0 °C, the solution was neutralized by careful addition of aqueous

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5% sodium bicarbonate, and then it was concentrated in vacuo. After addition of dichloromethane (8 mL), the organic phase was separated, washed with water (2 × 10 mL), dried over sodium sulfate, filtered, and evaporated to dryness. The residue was purified by radial chromatography (cyclohexane/ethyl acetate 3:2) and then by HPLC with a linear gradient of 2-propanol (6−10%, 0−10 min, flow 3.5 mL/min) in *n*-hexane. The first eluted product was **24** (t_R 11.4 min, 82.6 mg, 24%): white solid; mp 52−56 °C; $[\alpha]_D^{25} = +4.5$ (*c* 1.32, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.06 (s, 9H), 1.13 (t, 3H, $J = 7.1$ Hz), 1.34 (s, 3H), 1.52 (s, 3H), 1.89 (d, 3H, $J = 1.1$ Hz), 2.56 (ddd, 1H, $J = 3.5, 4.5, 13.9$ Hz, $H_{4'a}$), 2.87 (ddd, 1H, $J = 7.8, 9.7, 13.9$ Hz, $H_{4'b}$), 3.73 (dd, 1H, $J = 4.1, 11.0$ Hz, $H_{5''a}$), 3.82 (dd, 1H, $J = 6.3, 11.0$ Hz, $H_{5''b}$), 3.98 (dq, 1H, $J = 7.1, 10.8$ Hz), 4.07 (dq, 1H, $J = 7.1, 10.8$ Hz), 4.12 (dd, 1H, $J = 3.5, 9.7$ Hz, $H_{3'}$), 4.22 (ddd, 1H, $J = 2.0, 4.1, 6.3$ Hz, $H_{4''}$), 4.70 (dd, 1H, $J = 2.9, 6.3$ Hz, $H_{2''}$), 4.75 (dd, 1H, $J = 2.0, 6.3$ Hz, $H_{3''}$), 4.77 (d, 1H, $J = 2.9$ Hz, $H_{1''}$), 6.43 (dd, 1H, $J = 4.0, 7.8$ Hz, $H_{5'}$), 7.38−7.65 (m, 11H), 8.54 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.5, 13.9, 19.2, 25.2, 26.9, 27.0, 29.6, 37.7, 60.8, 61.9, 63.9, 81.0, 82.7, 84.7, 85.7, 100.3, 111.0, 113.5, 127.8, 129.9, 132.8, 133.0, 135.4, 135.5, 150.3, 163.4, 170.9. Anal. Calcd for $C_{35}H_{45}N_3O_9Si$: C, 61.84; H, 6.67; N, 6.18. Found: C, 61.82; H, 6.67; N, 6.17. Further elution gave **25** (t_R 13.2 min, 203.1 mg, 59%): white solid; mp 53−57 °C; $[\alpha]_D^{25} = -36.3$ (*c* 1.04, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.06 (s, 9H), 1.14 (t, 3H, $J = 7.1$ Hz), 1.35 (s, 3H), 1.52 (s, 3H), 1.87 (d, 3H, $J = 1.3$ Hz), 2.41 (ddd, 1H, $J = 6.8, 7.8, 13.5$ Hz, $H_{4'a}$), 2.98 (ddd, 1H, $J = 2.4, 7.0, 13.5$ Hz, $H_{4'b}$), 3.74 (dd, 1H, $J = 4.9, 11.0$ Hz, $H_{5''a}$), 3.77 (dd, 1H, $J = 6.6, 11.0$ Hz, $H_{5''b}$), 4.05 (dq, 1H, $J = 7.1, 10.8$ Hz), 4.09 (dq, 1H, $J = 7.1, 10.8$ Hz), 4.17 (dd, 1H, $J = 2.4, 7.8$ Hz, $H_{3'}$), 4.24 (ddd, 1H, $J = 2.2, 4.9, 6.6$ Hz, $H_{4''}$), 4.72 (dd, 1H, $J = 2.5, 6.4$ Hz, $H_{2''}$), 4.75 (dd, 1H, $J = 2.2, 6.4$ Hz, $H_{3''}$), 4.90 (d, 1H, $J = 2.5$ Hz, $H_{1''}$), 6.23 (dd, 1H, $J = 6.8, 7.0$ Hz, $H_{5'}$), 7.36−7.46 (m, 6H), 7.47 (q, 1H, $J = 1.3$ Hz, H_6), 7.63−7.65 (m, 4H), 8.35 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.5, 13.9, 19.2, 25.2, 26.8, 27.0, 37.9, 61.8, 61.9, 63.6, 81.2, 83.1, 85.9, 99.1, 111.1, 113.5, 127.8, 129.9, 132.9, 133.1, 135.2, 135.5, 135.6, 150.0, 163.3, 169.6. Anal. Calcd for $C_{35}H_{45}N_3O_9Si$: C, 61.84; H, 6.67; N, 6.18. Found: C, 61.89; H, 6.68; N, 6.17.

(3′*R*,5′*R*)-1-(3′-Ethoxycarbonyl-1′,2′-isoxazolidinyl)thymine (26). Compound **25** (100 mg, 0.15 mmol) was dissolved in a 3.7% HCl solution in EtOH (2.5 mL), and the reaction mixture was stirred at room temperature for 3 h. The solution was brought to pH 10 by adding aqueous 10% sodium carbonate and extracted with dichloromethane (2 × 10 mL). The organic phase, dried over sodium sulfate, was filtered and evaporated to dryness. The residue was purified by radial chromatography (chloroform/methanol 9:1) to furnish **26** (19.9 mg, 60%) as a sticky oil: $[\alpha]_D^{25} = +75.0$ (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) 1.25 (t, 3H, $J = 7.1$ Hz), 1.57 (bs, 1H, NH), 1.52 (s, 3H), 1.88 (d, 3H, $J = 1.2$ Hz), 2.71 (dd, 1H, $J = 5.8, 7.8, 13.8$ Hz, $H_{4'a}$), 2.96 (ddd, 1H, $J = 7.6, 8.2, 13.8$ Hz, $H_{4'b}$), 4.18 (q, 2H, $J = 7.1$ Hz), 4.21 (dd, 1H, $J = 5.8, 8.2$ Hz, $H_{3'}$), 5.95 (dd, 1H, $J = 5.2, 7.6$ Hz, $H_{5'}$), 7.64 (q, 1H, $J = 1.2$ Hz, H_6), 8.55 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.7, 14.1, 37.5, 60.7, 62.1, 80.7, 112.5, 134.2, 150.1, 163.3, 171.1. Anal. Calcd for $C_{11}H_{15}N_3O_5$: C, 49.07; H, 5.62; N, 15.61. Found: C, 49.17; H, 5.64; N, 15.57.

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