Synthesis of Purine and Pyrimidine Isodideoxynucleosides from (*S*)-Glycydol Using Iodoetherification as Key Step. Synthesis of (*S,S*)-iso-ddA[1]

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Analogues of natural nucleosides have proved to be efficient antiviral agents. The chemistry of nucleosides is a field that is being actively investigated in the search for new antiviral drugs with improved biological properties and minimun toxic effects. Consequently, many different families of nucleoside analogues have been synthesized. Of these, 2′,3′-dideoxynucleosides have been extensively studied,[2] and some of them have been approved for treating AIDS. Nevertheless, dideoxynucleosides degrade rapidly because the glycosidic link hydrolyzes under acidic conditions, such as those in the gastric environment, and becasuse of the action of enzymes.[3] To overcome these limitations, several modifications have been made to the structure of nucleosides (fluoronucleosides, C-nucleosides and carbocyclic analogues, etc). Isonucleosides constitute a novel class of nucleosides that have attracted great interest.[4] They are highly stable toward acids and enzymatic deamination and show strong and selective anti-HIV and anti-HSV activity. Iso-ddA[4a,c] is a good example (Figure 1); its anti-HIV activity is similar to that of ddA, and it has no apparent toxicity. Likewise, some isopyranosyl nucleosides also have potent antiviral activity[4e] (Figure 1).

Isonucleosides are usually prepared from carbohydrates through multistep sequences. The most common strategy reduces methyl glycosides by treating them with triethylsilane in the presence of a Lewis acid (Scheme 1).[4f] The tetrahydrofurans are also synthesized through protocols of ring opening−ring closing of sugar precursors[4a] or through asymmetric synthesis from prochiral starting materials[5] (Scheme 1). Furthermore, the discovery that some L-nucleosides are anti-AIDS agents refutes the idea that the D-configuration is a requirement for biological activity. Thus, the antiviral activities of nucleosides such as L-3TC[6] and L-FTC[6a,7] are similar to, or better than, the activities of D-enantiomers and also have a more favorable toxicity profile.

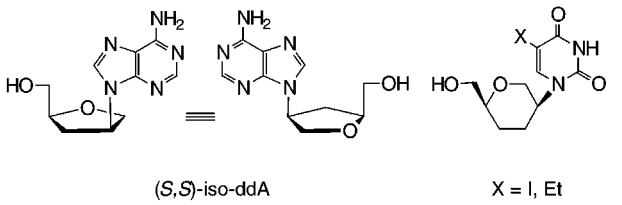
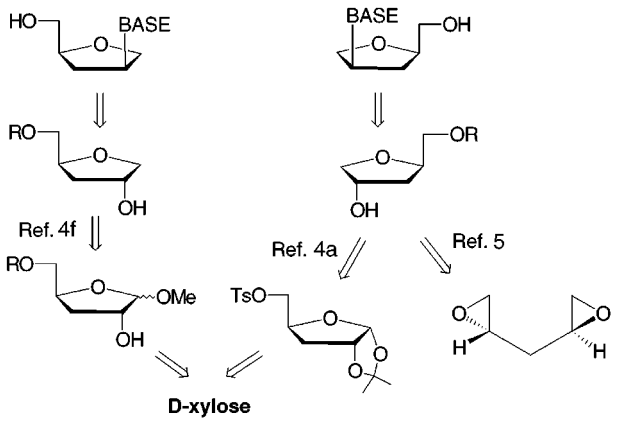
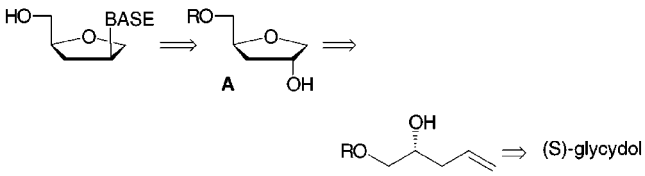


Figure 1.

Scheme 1



Scheme 2



In this paper, we describe the asymmetric synthesis of purine and pyrimidine isodideoxynucleosides with *S,S* absolute stereochemistry, which may be regarded as L-related dideoxynucleosides[4g] (Figure 1). It is based on the synthesis of the key intermediate A (Scheme 2) from a 4-pentene-1,2-diol through iodine-induced cyclization. The intermediate A can be coupled to the base under

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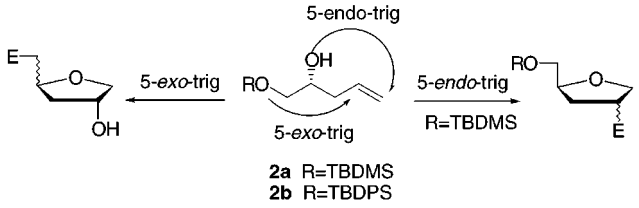
Scheme 3



Mitsunobu conditions or by nucleophilic displacement from the corresponding sulfonates.

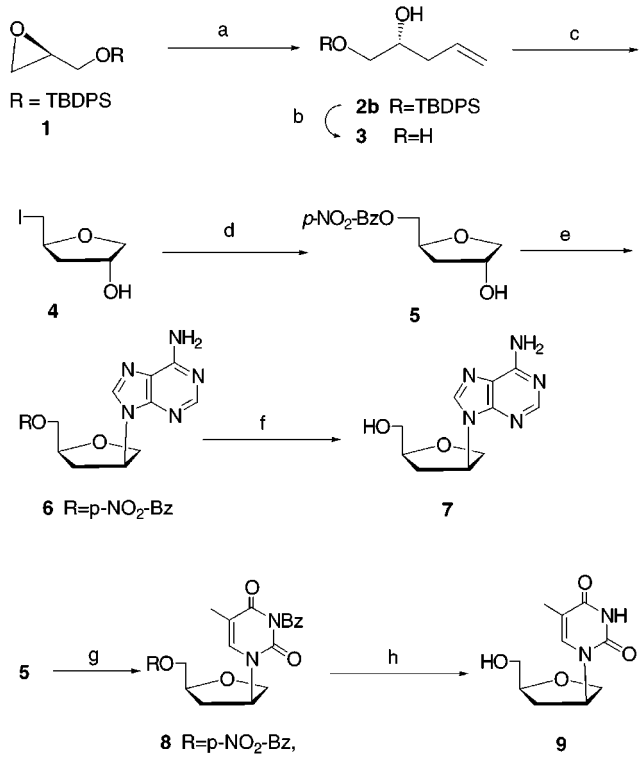
Results and Discussion

Tetrahydrofuran synthesis based on electrophilically induced cyclization has been extensively discussed in the literature.[8] According to Baldwin's rules,[9] the *exo* mode of cyclization is often preferred for small rings, but exceptions to these rules are common, particularly when the *endo* product is preferred for electronic factors.[10] Previous reports on the cyclization of related systems show that cyclization is often in the *exo* mode,[11] even when the alcohol is protected.[12] In particular, Jung observed this in a recently reported synthesis of branched isonucleosides.[13] However, it has been described that the iodine-induced cyclization of compound **2a**, whose primary hydroxyl group is protected, proportionates the 5-*endo-trig* product.[14] Because both 5-*exo-trig* and 5-*endo-trig* products are appropriate starting materials for the synthesis of isonucleosides (see Scheme 3), we decided to explore first the iodoetherification of alkenol **2b** (Schemes 3 and 4) using the more stable TBDPS as the protecting group.

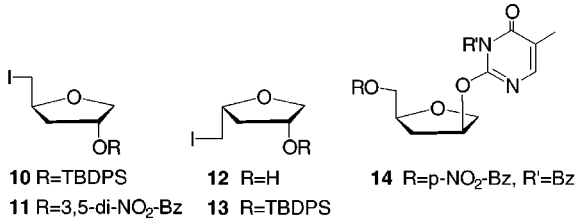
(*S*)-Glycydol (**1**) was treated with an ethereal solution of the higher-order organocuprate reagent $(CH_2CH)_2Cu(CN)(MgCl)_2$ to afford the key homoallyl alcohol **2b** in a 98% yield (Scheme 4).

Iodoetherification was initially tested with compound **2b** in the conditions previously reported,[14] and a diastereoisomeric mixture of 3,5-*trans*-tetrahydrofuran **4** and 3,5-*cis*-tetrahydrofuran **12** was obtained in an 83% yield, after a 5-*exo-trig* cyclization. No silylated products were obtained. However, when the reaction was left to stand for longer reaction times, the silyl derivatives **10** and **13** were isolated alongside the unprotected products **4** and **12**. This may be due to the in situ silylation of products **4** and **12** that initially formed with the *tert*-butyldiphenylsilyl iodide present in the reaction medium. No traces of 5-*endo-trig* products were recovered in any of the conditions tested.

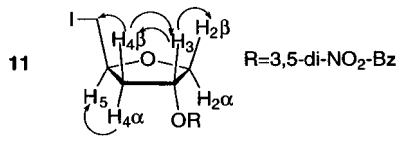
Scheme 4



a) $Cu(CH=CH_2)(CN)(MgCl)_2$, ether, 98%. b) Bu_4NF, THF, 98%. c) I_2, $NaHCO_3$, CH_3CN, 71%. d) KOBz*p*-NO_2, 18-crown-6, DMSO, 73%. e) Adenine/ PPh_3 / DEAD, DMF, 62 %. f) NaMeO, MeOH, 99%. g) N^3-Bz-Thymine/ PPh_3 / DEAD, dioxane, 63 %. h) NH_3, MeOH, 65%.



Compounds **4** and **12** were subjected to NOE experiments to determine their configuration, but the results were unclear, probably because of their conformational mobility. Therefore, compound **4** was transformed into the 3,5-dinitrobenzoate **11**, and NOE experiments in this case enabled the stereochemistry to be determined:



After these results we decided to explore the reaction of the fully deprotected **3** with iodine in dry acetonitrile under the kinetic conditions described by Bartlett.[8a] The reaction proceeded readily to give compound **4** in a 71% yield, together with a minor amount of the 3,5-*cis*-tetrahydrofuran **12**, as a result of a 5-*exo-trig* cyclization.

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It was the gauche effect between both hydroxyls that determined the stereoselectivity.[15]

It has been observed in compounds related to **4** that acetate displaces iodine only with difficulty.[13] We used potassium *p*-nitrobenzoate to reduce the basicity of the reagent. The reaction of compound **4** with potassium *p*-nitrobenzoate in DMF at 60 °C was unsuccessful. However, when the reaction was carried out in DMSO at 90 °C using 18-crown-6, compound **5** was obtained in a 73% yield.

To synthesize iso-ddA, compound **5** was transformed into the tosyl derivative, which was then treated with adenine, potassium carbonate, and 18-crown-6, according to the reported procedure,[4f] to give 42% of compound **6** and a mixture of the unprotected product **7** and crown ether potassium salt. This mixture proved to be inseparable.

Treatment of **5** with adenine in dioxane under Mitsunobu[16] conditions led to a complex inseparable mixture. However, when DMF was used as the solvent, compound **6** was obtained in a 62% yield, without deprotection. The treatment of compound **6** with sodium methoxide in methanol led to compound **7**[4a,c] in quantitative yield. Thus, isonucleoside **7** was obtained in 6 steps from **1** in an overall yield of 31%.

Alcohol **5** was also coupled with N^3-benzoylthymine[17] under Mitsunobu conditions (Scheme 4). The reaction was carried out in dioxane[18] to give the isonucleoside **8** in a 63% yield, together with 15% of the O^2-derivative **14**. Isonucleoside **8** was fully deprotected by treatment with NH_3/MeOH to give **9**[4f] in a 65% yield.

In summary, isodideoxynucleosides with *S,S* absolute stereochemistry were synthesized from the readily avalaible glycydol **1** using a 5-*exo*-*trig* iodocyclization as the key step. The method enables both enantiomeric isonucleosides to be prepared.

Experimental Section

General Procedures. Melting points are uncorrected. Optical rotations were measured at 25 °C in 10 cm cells. ^{1}H and ^{13}C NMR spectra were recorded in a 300 MHz (300 and 75.4 MHz, respectively) apparatus with $CDCl_3$ as solvent, unless otherwise specified. Coupling constants are given in hertz (Hz). Elemental analyses were determined at the Servei de Recursos Cientifics (Universitat Rovira i Virgili). Flash column chromatography was performed using silica gel 60 A CC (40−63 microns). Radial chromatography was performed on 1, 2, or 4 mm plates of silica gel, depending on the amount of product. Medium-pressure chromatography (MPLC) was performed using silica gel 60 A CC (6−35 microns). Band separation was monitored by UV. TLC plates were prepared by using Kieselgel 60 PF_{254}. Solvents for chromatography were distilled at atmospheric pressure prior to use. Reaction solvents were purified and dried by using standard procedures.

(*R*)-1-*O*-(*tert*-Butyldiphenylsilyl)-4-penten-1,2-diol (2b). CuCN (6.61 g, 73.6·mmol) was placed in a flask under argon and dried by gentle heating with a flame under vacuum. It was then allowed to cool under a positive pressure of argon. This process was repeated three times, and then ether (100 mL) was added. The resulting mixture was stirred to form a slurry and cooled to −78 °C, and then vinylmagnesium chloride (87 mL, 147.2 mmol) was added dropwise over a period of 15 min. The heterogeneous mixture was warmed to −20 °C until the CuCN completely dissolved, and it was then cooled again to −78 °C. A solution of **1** (10 g, 32 mmol) in 100 mL of dry ether was added dropwise. The resulting mixture was warmed to −60 °C and stirred for 5 h. The reaction was monitored by TLC in EtOAc/Hex 1:10, quenched by addition of an aqueous solution (10% concentrated NH_4OH/90% saturated NH_4Cl), and warmed to ambient temperature with vigorous stirring until the solids dissolved. The mixture was extracted with ether, and the combination of extracts was washed with water and then with brine. The ethereal solution was dried, filtered, and concentrated to dryness to afford 10.70 g (98%) of alcohol **2b** as a syrup. $[\alpha]^{25}_D = +3.0$ (*c* 0.986, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.70−7.35 (m, 10H), 5.79 (ddt, 1H, J = 17.1, 10.1, 6.5, 6.5), 5.11−5.02 (m, 2H), 3.79 (dddd, 1H, J = 6.5, 6.0, 6.0, 3.8), 3.67 (dd, 1H, J = 10.1, 3.8), 3.53 (dd, 1H, J = 10.1, 6.0), 2.51 (bs, 1H), 2.24 (tt, 2H, J = 6.5, 6.5, 1.4, 1.4), 1.08 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 135.5, 134.3, 133.0, 129.8, 127.7, 117.4, 71.2, 67.2, 37.5, 26.8, 19.2. Anal. Calcd for $C_{21}H_{28}O_2Si$: C, 74.07; H, 8.29. Found: C, 74.32; H, 8.32.

(*R*)-4-Penten-1,2-diol (3). A solution of 10 g (29.4 mmol) of **2b** in 300 mL of dry THF was treated with 32 mL (32 mmol) of a 1 M tetrabutylammonium fluoride solution in THF at 0 °C under an argon atmosphere. The reaction was monitored by TLC in ethyl ether/petroleum ether 1:1. The mixture was left to warm to room temperature, poured into a water/ice mixture, and extracted with ether. The combination of extracts was concentrated and chromatographed with ethyl ether/petroleum ether 20:1 to give 2.94 g (98%) of **3** as an oil. $[\alpha]^{25}_D$ +3.3 (*c* 0.25, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 5.79 (m, 1H, J = 17.1, 10.2, 5.7, 5.7), 5.10−5.01 (m, 2H), 3.88 (bs, 2H), 3.68 (dddd, 1H, J = 7.5, 6.5, 6.5, 2.8), 3.56 (dd, 1H, J = 11.5, 2.8), 3.37 (dd, 1H, J = 11.5, 7.5), 2.18−2.12 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 134.2, 117.8, 71.4, 66.0, 37.6. Anal. Calcd for $C_5H_{10}O_2$: C, 58.80; H, 9.87. Found: C, 59.15; H, 9.96.

(3*R*,5*S*)-5-Iodomethyltetrahydrofuran-3-ol (4) and (3*R*,5*R*)-5-Iodomethyltetrahydrofuran-3-ol (12). In a flask fitted with a magnetic bar, 2.05 g (20.07 mmol) of **3** was dissolved in 130 mL of dry acetonitrile under an argon atmosphere, and 5.06 g (60.21 mmol) of $NaHCO_3$ was added. The resulting mixture was stirred at room temperature for 5 min and cooled to 0 °C, and 15.28 g (60.21 mmol) of I_2 was added. The reaction mixture was left to warm to room temperature for 2 h. The evolution of the reaction was monitored by TLC in ether/petroleum ether 1:1. The mixture was diluted with ether and washed with 10% sodium thiosulfate solution until the color disappeared. The aqueous layer was extracted several times with ether. The combination of extracts was dried, filtered, and concentrated. The residue was purified by column chromatography in ether/petroleum ether 1:1 to afford 3.23 g (71%) of **4** (lower R_f) and 1.20 g (26%) of **12**.

(4): $[\alpha]^{25}_D$ −12.6 (*c* 1.005, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 4.57 (dddd, 1H, J = 5.3, 3.9, 1.7, 1.7), 4.22 (dddd, 1H, J = 9.2, 5.6, 5.6, 5.6), 4.08 (dd, 1H, J = 9.9, 3.9), 3.84 (dt, 1H, J = 9.9, 1.3, 1.3), 3.30 (d, 2H, J = 5.6), 2.17 (m, 1H, J = 13.5, 5.6, 1.3, 1.3), 2.06 (bs, 1H), 1.80 (ddd, 1H, J = 13.5, 9.2, 5.3). ^{13}C NMR ($CDCl_3$) δ 77.0, 76.1, 72.8, 41.9, 10.1. Anal. Calcd for $C_5H_9O_2I$: C, 26.34; H, 3.98. Found: C, 26.41; H, 4.03.

(12): $[\alpha]^{25}_D$ +7.2 (*c* 1.349, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 4.53 (dddd, 1H, J = 6.1, 4.1, 1.7, 1.7), 4.06 (dddd, 1H, J = 8.1, 6.4, 5.4, 5.4), 3.98 (dt, 1H, J = 9.9, 1.7, 1.7), 3.81 (dd, 1H, J = 9.9, 3.9), 3.45 (dd, 1H, J = 10.0, 6.4), 3.37 (dd, 1H, J = 10.0, 5.4), 2.36 (ddd, 1H, J = 14.0, 8.1, 6.1), 2.15 (bs, 1H), 1.81 (dddd, 1H, J = 14.0, 5.4, 1.7, 1.7). ^{13}C NMR ($CDCl_3$) δ 78.2, 76.3, 72.2, 40.7, 10.7. Anal. Calcd for $C_5H_9O_2I$: C, 26.34; H, 3.98. Found: C, 26.45; H, 3.93.

[(2*S*,4*R*)-4-Hydroxytetrahydrofuran-2-yl]methyl *p*-Nitrobenzoate (5). Compound **4** (1.1 g, 4.82 mmol) was dissolved in 55 mL of DMSO and 7.9 g (38.54 mmol) of potassium *p*-nitrobenzoate. Then, 0.13 g (0.49 mmol) of 18-crown-6 was added. The heterogeneous mixture was heated to 90 °C for 16 h. The reaction was monitored by TLC in ethyl acetate/hexane 1:1. The reaction mixture was poured into ice/water and stirred for 15 min. The aqueous solution was extracted several times with ether. The combination of extracts was washed with 10% sodium thiosulfate and then with water. The ethereal extracts were dried, filtered, and concentrated. The resulting residue was purified by radial chromatography over aluminum oxide in ethyl

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acetate/hexane 1:1 to furnish 0.94 g (73%) of **5** as crystalline solid. Mp 103−106 °C. $[\alpha]^{25}_D$ +18.7 (*c* 0.910, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 8.37−8.18 (m, 4H), 4.64−4.58 (m, 1H), 4.59 (m, 1H, *J* = 9.8, 6.7, 6.1, 3.1), 4.52 (dd, 1H, *J* = 11.8, 3.1), 4.32 (dd, 1H, *J* = 11.8, 6.7), 4.05 (dd, 1H, *J* = 9.8, 4.0), 3.85 (dt, 1H, *J* = 9.8, 1.3, 1.0), 2.15 (bs, 1H), 2.13 (m, 1H, *J* = 13.3, 6.1, 1.3, 1.3), 1.90 (ddd, 1H, *J* = 13.3, 9.4, 5.1). ^{13}C NMR ($CDCl_3$) δ 164.7, 135.3, 130.9, 123.6, 75.8, 75.5, 72.1, 67.2, 37.6. Anal. Calcd for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.24. Found: C, 53.85; H, 4.89; N, 5.27.

1-[(3*S*,5*S*)-5-(*p*-Nitrobenzoyloxymethyl)tetrahydrofuran-3-yl]adenine (6). A total of 0.150 g of **5** (0.56 mmol) was dissolved in 10 mL of DMF and added to a flask containing adenine (0.305 g, 2.26 mmol) and triphenylphosphine (0.295 g, 1.12 mmol). Then, DEAD (0.175 mL, 1.13 mmol) diluted in 2 mL of DMF was added dropwise. The reaction mixture was stirred for 5 days at 75 °C, and the reaction was monitored by TLC in dichloromethane/methanol 10:1. The solvent was removed in vacuo, and the residue was purified by MPLC using a linear gradient (dichloromethane to dichloromethane/methanol 20:1) to furnish 0.133 g (62%) of **6**. Mp 190−193 °C (dec). UV ($CHCl_3$) λ_{max} 262 nm. $[\alpha]^{25}_D$ +17.8 (*c* 0.256, $(CHCl_2)_2$). ^1H NMR ($CDCl_3$) δ 8.24 (d, 2H, *J* = 8.6), 8.22 (s, 1H), 8.10 (d, 2H, *J* = 8.6), 8.04 (s, 1H), 5.26 (m, 1H), 4.61 (dd, 1H, *J* = 2.6, 11.8), 4.5−4.4 (m, 2H), 4.32 (d, 1H, *J* = 2.8, 10.4), 4.11 (dd, 1H, *J* = 5.7, 10.4), 3.81 (dt, 1H, *J* = 8.0, 13.9), 2.12 (ddd, 1H, *J* = 4.2, 8.4, 13.9). ^{13}C NMR ($CDCl_3$) δ 152.7, 138.2, 130.7, 123.5, 76.6, 72.2, 65.9, 54.3, 35.2. Anal. Calcd for $C_{17}H_{16}N_6O_5$: C, 53.13; H, 4.20; N, 21.87. Found: C, 53.05; H, 4.30; N, 21.65.

1-[(3*S*,5*S*)-5-(Hydroxymethyl)tetrahydrofuran-3-yl]adenine (7). A suspension of 0.130 g (0.34 mmol) of compound **6** was debenzoylated by treatment with sodium methoxide (0.030 g, 0.56 mmol) in methanol (16 mL). After 30 min the mixture became clear. Then, a few milliliters of methanol were added, and the solvent was evaporated in vacuo. The crude was purified by MPLC using a linear gradient (dichloromethane to dichloromethane/methanol 8:1) to give 0.079 g (99%) of iso-ddA (**7**). UV (H_2O) λ_{max} 262 nm (lit.[4f] 260 nm). $[\alpha]^{25}_D$ −30.3 (*c* 0.840, MeOH) (lit.[4f] −26.6, *c* 1.0; for enantiomer[4b] +31.9, *c* 1.05). ^1H NMR (DMSO) δ 8.26 (s, 1H), 8.14 (s, 1H), 7.24 (bs, 2H), 5.17 (dtd, 1H, *J* = 8.7, 5.3, 5.3, 3.6), 4.98 (t, 1H, *J* = 5.6), 4.01 (dd, 1H, *J* = 9.7, 3.6), 3.99 (m, 1H), 3.95 (dd, 1H, *J* = 9.7, 6.0), 3.62 (ddd, 1H, *J* = 11.8, 4.8, 3.9), 3.52 (ddd, 11.8, 5.6, 4.6), 2.57 (dt, 1H, *J* = 13.2, 8.1, 8.1), 2.08 (ddd, 1H, *J* = 13.2, 8.2, 5.1). ^{13}C NMR (DMSO) δ 156.2, 152.6, 139.1, 118.8, 79.7, 71.9, 62.5, 53.9, 33.9. Anal. Calcd for $C_{10}H_{13}N_5O_2$: C, 51.06; H, 5.57; N, 29.77. Found: C, 50.95; H, 5.63; N, 29.65.

1-[(3*S*,5*S*)-5-(*p*-Nitrobenzoyloxymethyl)tetrahydrofuran-3-yl]-3-benzoylthymine (8) and 2-[(3*S*,5*S*)-5-(*p*-Nitrobenzoyloxymethyl)tetrahydrofuran-3-yl]-3-benzoylthymine (14). To a solution of **5** (0.2 g, 0.75 mmol), N^3-benzoylthymine (0.344 g, 1.50 mmol), and triphenylphosphine (0.393 g, 1.50 mmol) in dioxane (7 mL) was added DEAD (0.250 mL, 1.50 mmol) dissolved in 4 mL of dioxane over a period of 30 min. The reaction mixture was stirred for 5 days, and the reaction was monitored by TLC in ethyl acetate/hexane 1:1. The solvent was removed in vacuo, and the residue was purified by column chromatography to furnish 0.225 g (63%) of **8** and 0.054 g (15%) of **14**. They were contaminated with impurities which were removed in the next deprotection step.

(8): UV ($CHCl_3$) λ_{max} 268 nm. ^1H NMR ($CDCl_3$) δ 8.28−7.15 (m, 10H), 5.35−5.26 (m, 1H), 4.68 (dd, 1H, *J* = 12.3, 2.8), 4.51 (dd, 1H, *J* =12.3, 6.9), 4.30−4.19 (m, 1H), 4.13 (dd, 1H, *J* = 11.1, 2.0), 3.95 (dd, 1H, *J* = 11.1, 6.9), 2.70 (ddd, 1H, *J* = 13.9, 9.0, 7.3), 1.87−1.76 (m, 1H), 1.82 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 164.0, 163.4, 162.4, 150.2, 137.3, 135.6−128.0, 112.0, 76.9, 71.8, 65.6, 55.1, 35.0, 12.3.

(14): ^1H NMR ($CDCl_3$) δ 8.41−7.43 (m, 10H), 5.61−5.55 (m, 1H), 4.33−4.23 (m, 1H), 4.16 (dd, 1H, *J* = 11.8, 4.0), 4.14 (dd, 1H, *J* = 10.8, 6.9), 3.98 (dd, 1H, *J* = 11.8, 7.5), 3.93 (dd, 1H, *J* = 10.8, 4.0), 2.46 (m, 1H, *J* = 14.7, 8.1, 6.3), 2.23−2.17 (m, 1H), 2.18 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 164.4, 162.8, 161.9, 157.2, 149.5, 135.5−123.6, 119.1, 78.9, 76.0, 73.0, 66.8, 34.5, 12.4.

1-[(3*S*,5*S*)-5-(Hydroxymethyl)tetrahydrofuran-3-yl]-thymine (9). Compound **8** (0.225 g, 0.47 mmol) was treated with 2.5 mL of ammonium hydroxide in 9 mL of methanol at room temperature for 8 h. The course of the reaction was monitored by TLC in ethyl acetate. The solvent was removed in vacuo, and the residue was chromatographed to afford 0.069 g (65%) of **9**. UV (MeOH) λ_{max} 268 nm (lit.[4f] 271). $[\alpha]^{25}_D$ +25.5 (*c* 0.945, MeOH) (lit.[4f] +26.0). ^1H NMR ($CDCl_3$) δ 9.86 (bs, 1H), 7.53 (d, 1H, *J* = 1.2), 5.40−5.31 (m, 1H), 4.06 (dd, 1H, *J* = 10.6, 2.2), 4.06−4.01 (m, 1H), 4.00 (dd, 1H, *J* = 12.6, 2.7), 3.94 (dd, 1H, *J* = 10.6, 6.7), 3.72 (dd, 1H, *J* = 12.6, 4.8), 2.83 (bs, 1H), 2.58−2.43 (m, 1H), 1.98−1.88 (m, 1H), 1.89 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 162.8, 151.3, 137.3, 111.7, 80.1, 72.5, 62.6, 54.7, 33.5, 12.3.

(3*R*,5*S*)-3-*O*-(*tert*-Butyldiphenylsilyl)-5-iodomethyltetrahydrofuran-3-ol (10) and (3*R*,5*R*)-3-*O*-(*tert*-Butyldiphenylsilyl)-5-iodomethyltetrahydrofuran-3-ol (13). $NaHCO_3$ (0.694 g, 8.28 mmol) was added under argon to a solution of 0.94 g (2.76 mmol) of **2b** in 20 mL of dry acetonitrile. The mixture was stirred at room temperature for 5 min and cooled to 0 °C. Then, 2.10 g (8.28 mmol) of I_2 was added. The resulting mixture was warmed to room temperature and maintained at this temperature for 9 h. The reaction was monitored by TLC in ethyl ether/petroleum ether 1:1. The mixture was diluted with ether and washed with a 10% solution of sodium thiosulfate until the color disappeared. The combination of extracts was dried, filtered, and concentrated. The resulting residue was chromatographed over silica gel in ethyl ether/petroleum ether 1:1 to furnish 0.150 g (12%) of a silyl derivative **10**/**13** mixture and 0.39 g (62%) of a mixture of the alcohols **4** and **12** as syrups. Data for the diastereoisomeric mixture follows. (**10**): ^1H NMR ($CDCl_3$) δ 7.76−7.35 (m, 10H), 4.54−4.46 (m, 1H), 4.24 (m, 1H, *J* = 9.3, 5.7, 5.4, 5.1), 3.88 (dd, 1H, *J* = 9.3, 4.2), 3.80 (ddd, 1H, *J* = 9.3, 2.1, 1.0), 3.27 (dd, 1H, *J* = 10.2, 5.7), 3.23 (dd, 1H, *J* = 10.2, 5.1), 2.15−2.04 (m, 1H), 1.64−1.53 (m, 1H), 1.06 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 135.7, 133.7, 129.9, 127.8, 79.0, 76.4, 74.0, 42.1, 26.7, 18.9, 10.3. (**13**): ^1H NMR ($CDCl_3$) δ 7.76−7.35 (m, 10H), 4.47−4.41 (m, 1H), 4.15 (m, 1H, *J* = 7.6, 7.6, 6.0, 4.9), 3.90 (ddd, 1H, *J* = 9.5, 1.2, 0.9), 3.68 (dd, 1H, *J* = 9.5, 4.8), 3.46 (dd, 1H, *J* = 9.7, 7.6), 3.39 (dd, 1H, *J* = 9.7, 6.0), 2.04−1.94 (m, 1H), 1.64−1.53 (m, 1H), 1.08 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 135.8, 133.4, 129.9, 127.8, 77.3, 76.1, 73.5, 40.3, 26.7, 18.9, 10.1. Anal. Calcd for $C_{21}H_{27}IO_2Si$: C, 54.08; H, 5.83. Found: C, 54.23; H, 5.86.

(3*R*,5*S*)-5-Iodomethyltetrahydrofuran-2-yl 3,5-Dinitrobenzoate (11). A solution of 0.030 g (0.131 mmol) of **4** in 2 mL of pyridine at 0 °C was treated with 0.034 g (0.145 mmol) of 3,5-dinitrobenzoyl chloride for 16 h. The mixture was poured into water/ice and was extracted several times with ethyl acetate. The organic layer was dried, filtered, and concentrated in vacuo. The residue was chromatographed by radial chromatography in ethyl acetate/hexane 1:7 to give 0.047 g (85%) of **11** as a crystalline solid. Mp 91−93 °C. $[\alpha]^{25}_D$ −3.9 (*c* 0.21, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 9.21−9.07 (m, 3H), 5.64 (m, 1H), 4.28 (dd, 1H, *J* = 10.8, 4.8), 4.27−4.18 (m, 1H), 4.04 (dt, 1H, *J* = 10.8, 1.2, 1.2), 3.30 (d, 2H, *J* = 4.5), 2.42 (m, 1H, *J* = 14.2, 5.9, 1.2, 1.2), 2.05 (ddd, 1H, *J* = 14.2, 9.4, 5.9). ^{13}C NMR ($CDCl_3$) δ 162.3, 133.5, 129.5, 122.8, 78.2, 78.0, 73.3, 39.0, 8.9. Anal. Calcd for $C_{12}H_{11}IN_2O_7$: C, 34.14; H, 2.63; N, 6.64. Found: C, 34.16; H, 2.64; N, 6.55.

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