Preparation of 4-Substituted Thymidines by Substitution of the Thymidine 5′-Esters

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ter-butyl thymidylate 3 was prepared from thymidine 1 in six steps and 67% overall yield. When the lithium trianion of 3 (prepared by treatment of 3 with excess LDA and then excess tert-butyl lithium) is reacted with electrophiles, trapping occurs stereoselectively from either the α- or β-face depending on the electrophile (Scheme 1). Deuterioacetic acid in deuteriomethanol affords mainly the α-deuterated product (4a/4b = 2.4:1) while all other electrophiles, e.g., phenylselenenyl chloride, allyl bromide, and N-fluorobenzensulfonylimide (NFSI), give predominately (or completely) the products of attack from the β-face (5bcd/4bcd = 3.7:1 to 100:0). The structures of the products were determined by coupling constant analysis of both the initial compounds and the diols 6bcd prepared by ester reduction and by formation of the acetonides 7bc. The methyl ester of the 3'-epimer of thymidylic acid 9 was also prepared from thymidine 1 in nine steps and 74% overall yield. When the lithium trianion of 9 (prepared by treatment of 9 with excess LDA and then excess tert-butyl lithium) is reacted with electrophiles, trapping also occurs stereoselectively with attack on either the α- or β-face depending on the electrophile (Scheme 2). Again, deuterioacetic acid in deuteriomethanol affords mainly the β-deuterated product (11a/10a = 1.6:1) while all other electrophiles, e.g., phenylselenenyl chloride, methyl iodide, allyl bromide, and NFSI, gave predominately (or completely) the product of attack from the α-face (8.7:1 to 100:0). Again, the structures of the products were determined by coupling constant analysis of both the initial compounds, and the diols 12b-e were prepared by reduction of the ester and by formation of the acetonides 13bcd. A rationale has been developed using molecular mechanics calculations to explain the diastereoselectivity that involves staggered axial attack on the sp2 carbon opposite to the pseudooxial alkoxy group in the most stable half-chair conformation of the enolates, as shown in Schemes 3–5.

Introduction and Background

Modified nucleosides have become useful agents for the treatment of cancer and viral diseases due to their good antitumor and antiviral activity.1 In particular, several nucleosides with substituents at the 4'-position are good candidates as antiviral agents.2 For example, 4'-azidothymidine demonstrated very potent anti-HIV activity, but its high toxicity rendered it ineffective as an antiviral drug.3 Other 4'-substitutions, such as fluoro,4 cyano,5 and even an unusual oxetane,6 have also afforded nucleosides with strong activity, including anti-HIV activity. Recent, in connection with biological studies of the mechanism of synthetic nucleases, we published a synthesis of 4'-deuterothymidine,6 which proceeded via deuteration of the anion of the corresponding 5'-ester. We now report the use of such anions of the 5'-esters of 2'-deoxy nucleosides and their analogues. Most syntheses of 4'-carbon-branched nucleosides usually involve reactions of various 5'-oxo nucleoside derivatives, e.g., 4'-formyl and 4'-acyl nucleosides. Thus, 4'-carbon-substituted nucleosides were prepared years ago by the Syntex group via an aldol condensation–Cannizzaro reaction process to give the 4',4'-bis-hydroxymethyl derivatives.7 These diols could then be converted into other compounds since the α-hydroxymethyl group is generally more reactive than the β-hydroxymethyl group,8 an approach that has since been successfully applied often to the synthesis of more complex derivatives.9 Another very interesting route employs dimethyl...
Results and Discussion

Although several methods exist for the preparation of thymidylic acid and its derivatives directly from thymidine,\(^1\) we opted for a longer approach to guarantee the purity of the starting materials. Thus we prepared the tert-butyl ester of thymidylic acid \(^{3}\) from thymidine \(^1\) by a multistep route which gave very pure product. We protected first the 5'-hydroxyl group as the mono-tert-butyl ester with EDCI\(^{10}\) followed by addition of electrophiles to the anions of the 5'-esters of thymidine\(^6\) to determine if other electrophiles could also be added. Herein we report the results of our study of the stereochemistry of the addition of electrophiles to the anions of the 5'-esters of thymidine.

In our earlier study of the triple deprotonation of the trianion in order to produce the more reactive unchelated lithium salt. Thus, we routinely added a full equivalent of n- or tert-butyl lithium to reform the LDA and thereby remove it from the trianion complex, a procedure first discovered by Seebach and co-workers and since often used.\(^{13}\) Thus, deprotonation of the ester \(^3\) using excess LDA (normally about 5–5.6 equiv) followed by reformation of the LDA with tert-butyl lithium and deuteration gave mainly the \(\alpha\)-deuterio thymidylate \(^4\) (43%), along with a smaller amount of the \(\beta\)-isomer \(^5\) (18%). This is in agreement with our earlier reported results, although we were unable at the time to isolate any of the minor \(\beta\)-isomer \(^5\). Thus, as we reported, deuteration occurs primarily, but not exclusively, from the \(\alpha\)-face.

However, when the lithium trianion of \(^3\) was trapped with other electrophiles, the product of the reaction from the \(\beta\)-face was the major isomer isolated. For example, phenylselenenylation gave mainly \(^5\) (57%) along with a small amount of the \(\alpha\)-isomer \(^4\) (5%) and allyl bromide gave mostly the \(\beta\)-isomer \(^5\) (34%) with 9% of the \(\alpha\)-isomer \(^4\) being produced.\(^{14}\) Using the strong, commercially available fluorinating agent N-fluorobenzensulfonyl fluoride (NFSI) as the electrophile afforded mainly the \(\beta\)-fluoro 3'-sulfonate \(^5\) in 48% yield (under different conditions, one can isolate the free alcohol \(5e\))


Table 1. Stereoselectivity of Addition of Electrophiles (E\textsuperscript{+}) to Ester Enolates

<table>
<thead>
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<th>ester</th>
<th>E</th>
<th>α-product</th>
<th>β-product</th>
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<tr>
<td>3</td>
<td>D</td>
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<td>3</td>
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<td>allyl</td>
<td>1.0</td>
<td>3.8</td>
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<tr>
<td>3</td>
<td>F</td>
<td>0.0</td>
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<td>9</td>
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<td>1.0</td>
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in 21% yield along with 19% of 5d). The structures of the products 5bc were proven by reduction of the esters to the corresponding primary alcohols 6bc with lithium borohydride followed by formation of the acetonides 7bc with acidic dimethoxypropane.\textsuperscript{15} Control experiments showed that the trans-oriented diol did not form an acetonide under these conditions therefore proving that the ester group in 5 was cis to the hydroxyl group. The results of the addition of electrophiles to the trianion derived from 3 are shown in Table 1.

We also investigated deprotonations and functionalizations of the 3'-epimer of thyminic esters, namely the methyl ester 9.\textsuperscript{16} This substrate was prepared as follows. First, inversion of the 3'-hydroxyl of 1 was carried out by a four-step sequence involving initial MMTr protection of the 5'-hydroxyl of 1 followed by mesylation, formation of the anhydro nucleoside, and hydrolysis to give 8 in 86% overall yield. Silylation of the 3'-hydroxyl, removal of the MMTr group, TEMPO-BAIB oxidation as before, formation of the methyl ester with trimethylsilyldiazomethane, and final desilylation with TBAF afforded the desired substrate 9 in 86% overall yield.

Deprotonation of the ester 9 under the same conditions as for 3, namely excess LDA (5.4 equiv) followed by reformation of the LDA with tert-butyllithium (to give the more reactive unchelated lithium salt) and deuteration, gave mainly the β-deuterio thymidylate 11a (53%) along with a smaller amount of the α-isomer 10a (21%). This is again in general agreement with our earlier results in which the deuterium atom is introduced mostly cis to the existing hydroxyl group. However, when the lithium anion of 9 was trapped with other electrophiles, the α product was the major isomer isolated, e.g., phenylselenenyl chloride gave mainly 10b (56%) along with a small amount of the α-isomer 11b (6%), and methyl iodide gave mostly the α-isomer 10c (44%) and an additional 14% of the O-methyl derivative) with 8% of the β-isomer 11c being produced. Allyl bromide afforded a similar mixture with the β-isomer 10d greatly predominating (52%) over the α-isomer (6%). Again, use of the strong fluorinating agent (NFSI) as the electrophile afforded mainly the β-fluoro 3'-sulfonate 10e in 49% yield (under different conditions, one can isolate the free alcohol 10f in 30% yield along with 15% of 10e). The structures of the products 10bcd were again proven by reduction of the esters to the corresponding primary alcohols 12bcd with LiBH\textsubscript{4} followed by formation of the acetonides 13bcd with acidic dimethoxypropane.\textsuperscript{15} Once more, control experiments showed that the trans-oriented diol did not form an acetonide under these conditions. The results of the addition of electrophiles to the trianion of 9 are shown in Table 1.

Trapping of the anions of nucleosides having carbonyl groups at the 4'-position with the 3'-α-hydroxyl protected with electrophiles are known and generally give mostly the β products.\textsuperscript{14} We believe that the selectivity observed

\textsuperscript{15} The diols derived from the fluoro nucleosides, e.g., 6d and 12e, did not give clean acetonides under these conditions. Their structures were assigned by the pattern of coupling constants in the proton NMR, especially the J\textsubscript{H,F}, and by analogy to the formation of the other derivatives.

\textsuperscript{16} We were unable to prepare the corresponding tert-butyl ester due to steric hindrance caused by the large tert-butyl(diphenylsilyl) (TPS) ether at the 3′β position. Normally the methyl ester is not preferred since side products can arise via attack of some nucleophilic species (the ester endate or LDA itself) on the methyl ester. However, presumably due to the steric hindrance around this methyl ester, we do not observe a significant amount of side products of the sort mentioned above during the formation and reaction of the trianion.
Corresponding 3 kcal/mol), while for the enolate derived from the ester of the trianions of 3 with the alkoxy group on the alkene.

We have analyzed the conformations of the precursor esters 3 and 9 by coupling constant analysis and by molecular mechanics calculations (Macromodel 5.0). These two molecules exist in opposite half-chair conformations, with 3 preferring the 3′-exo conformation and 9 existing in the 3′-endo conformation, as shown in Scheme 3 of the manuscript.

The key coupling constants are as follows: (a) the one between H′3 and H′4′, which is very small (~0 Hz) in 3 and medium (4.2 Hz) in 9; (b) the one between H1′ and H2′/β, which is large (9.3 Hz) in 3 and small (2.6 Hz) in 9. The corresponding calculated values for the minimized structures (both methyl esters) are also given in Scheme 3 for comparison purposes. The overall match is quite good. Thus, both molecules prefer conformations in which the hydroxyl group prefers a pseudoaxial position. We have also determined the preferred conformations of the dimethylketene acetals 1–4a by assuming that the anions adopt conformations similar to those calculated for the dimethylketene acetals 1–4. Thus, we expect the trianion of 3 to adopt the conformation shown in V (analogous to 1) while the trianion of 9 adopts the conformation shown in VI (analogous to 11). The stereochemical course of the reaction can then be explained by assuming that the electrophilic agents approach the carbonionic center from the face opposite the 3′-alkoxide group which is in a pseudoaxial arrangement in both V and VI. Attack of the enolate on the electrophile would occur in the staggered axial arrangement due to torsional strain, e.g., on the top face of V and on the bottom face of VI as shown. This "conformational transmission of chirality" via staggered axial attack on an sp² carbon center has been postulated to account for the high diastereoselectivity seen in additions to other half-chair conformations.¹⁸

The deuterium results can be rationalized by assuming that there is a small amount of net complexation of the deuterium source with the 3′-alkoxide group prior to protonation and this leads to a small preference for protonation cis to the alkoxy group, 2:4:1 and 16:1 for the trianions of 3 and 9 respectively.

We have just begun to examine the further chemistry of these novel 4′-substituted nucleoside derivatives, e.g., the transformation of the products into other useful nucleoside derivatives. The results of those experiments will be reported in due course. The preparation and testing of these and other novel nucleoside analogues is currently underway in our laboratories.

Conclusion

We have shown that electrophilic trapping of the lithium trianion of tert-butyl thymidylate 3 occurs stereoselectively from either the α- or β-face depending on the electrophile (Scheme 1). Deuterioacetic acid in deuteriomethanol affords mainly the α-deuterated product (4a/4b = 2.4:1) while all other electrophiles, e.g., phenylessenyl chloride, allyl bromide, and N-fluorobenzensulfonylimide (NFSI), give predominately (or completely) the products of attack from the β-face (5bcd/4bcd = 3.7:1 to 100:0). The structures of the products were determined by coupling constant analysis of both the initial compounds and the diols 6bcd prepared by ester reduction and by formation of the acetonides 7bc. In similar fashion, electrophilic trapping of the lithium trianion of the methyl ester of the 3′-epimer of thymidyl acid 9 also occurs stereoselectively with attack on either the α- or β-face depending on the electrophile (Scheme 2). Again deuterioacetic acid in deuteriomethanol affords mainly the β-deuterated product (11a/10a = 1.6:1) while all other electrophiles, e.g., phenylessenyl chloride, methyl iodide, allyl bromide, and NFSI, gave predominately (or completely) the product of attack from the

Scheme 3. Observed (Top) and Calculated (Bottom) Values in 1H NMR Spectra of 3 and 9

Scheme 4. Macromodel 5.0 Strain Energy Calculations

Scheme 5. Presumed Transition States for Electrophilic Additions to the Enolates of 3 and 9


α-face (8.7:1 to 100:0). Again, the structures of the products were determined by coupling constant analysis of both the initial compounds and the diols 12b–e were prepared by reduction of the ester and by formation of the acetones 13bcd. A rationale has been developed using molecular mechanics calculations to explain the diastereoselectivity, which involves staggered axial attack on the sp² carbon opposite to the pseudoaxial alkyl group in the most stable half-chair conformation of the enolates, as shown in Schemes 3–5.

Experimental Section

General Methods. ¹H and ¹³C NMR spectra were recorded on Bruker spectrometers at 200 or 400 MHz for proton and at 50 or 100 MHz for carbon and are so indicated. ¹H NMR and ¹³C NMR data are reported in parts per million (δ) downfield from tetramethylsilane. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Infrared spectra were recorded on a Nicolet 510 infrared spectrophotometer as a liquid film or as a thin crystalline film. All IR data are reported in wave numbers (cm⁻¹).

Thin-layer chromatography (TLC) was performed using Merck silica gel 60 F 254 0.25 mm plates. Visualization was accomplished using ultraviolet light or one of the following reagents: Anisaldehyde (2 mL), acetic acid (1 mL), or sulfuric acid (2 mL) in 95% ethanol (85 mL). Flash chromatography was carried out using Merck Biomedicals silica gel 60 (230–400 mesh). Solvent systems are reported as volume percent mixtures. Concentration or evaporation of solvent refers to removal at reduced pressure using a Büchi rotary evaporator and a Büchi aspirator pump. All inorganic solutions are prepared by slow addition of solid to a warm solution of the appropriate solvent. Removal of solvent from the final mixture was accomplished using ultraviolet light or one of the following reagents: tert-butyl ether from sodium benzenophenone ketyl; dichloromethane and triethylamine from calcium hydride. All reactions were performed under an argon atmosphere unless otherwise noted.

1-[2R,4S,5R]-5-[bis(4-methoxyphenyl)phenylmethoxymethyl]-4-hydroxytetrahydrofuran-2-yl]-5-methyl-1H-pyrimidine-2,4-dione. To a solution of thymidine (157 mg, 0.648 mmol) in DMF (1.5 mL) were added triethylamine from calcium hydride. All reactions were performed under an argon atmosphere unless otherwise noted.

1-[2R,4S,5R]-5-[bis(4-methoxyphenyl)phenylmethoxymethyl]-4-hydroxytetrahydrofuran-2-yl]-5-methyl-1H-pyrimidine-2,4-dione (330 mg, 99%) as a colorless foam: [α]₂⁰D +10° (c = 0.33, CHCl₃); IR (neat) 3440, 3071, 2932, 2859, 1690, 1472, 1428, 1364, 1275, 1198, 1105, 1061, 1032, 960, 754, 716, 702, 612 cm⁻¹; 400 MHz ¹H NMR (CDCl₃) δ 1.09 (9H, s), 1.82 (3H, s), 2.14 (1H, ddd, J = 13.5, 6, 8 Hz), 2.26 (1H, ddd, J = 13.5, 6, 3 Hz), 2.45 (1H, br, J = 3.2, 2.5 Hz), 3.63 (1H, dd, J = 12, 2.5 Hz), 3.98 (1H, dt, J = 3, 2.5 Hz), 4.45 (1H, ddd, J = 6, 3 Hz), 6.26 (1H, dd, J = 8, 6 Hz), 7.37 (1H, s), 7.45 (1H, s), 7.52 (1H, ddd, J = 10.5, 2.2 Hz), 7.66 (4H, m), 9.20 (1H, br), 100 MHz ¹³C NMR (CDCl₃) δ 124.7 (C₅-Me), 19.04 (CMe), 26.91 (CMe), 40.27 (C₂), 72.21 (C₃), 73.01 (C₃), 86.67 (C₄), 87.72 (C₁), 110.95 (C₅), 127.92 (4C of MeOAr), 130.11 (1C of Ph), 130.15 (1C of Ph), 133.10 (1C of Ph), 133.19 (1C of Ph), 137.52 (4C), 143.75 (m-C of MeOAr), 148.34 (m-C of MeOAr), 150.46 (C₆), 158.72 (C-O-Me), 163.98 (C₂).

1-[2R,4S,5R]-4-[tertbutyldiphenylsilanyloxy]-5-hydroxymethyltetrahydrofuran-2-yl]-5-methyl-1H-pyrimidine-2,4-dione. A rationale has been developed using ultraviolet light or one of the following reagents: tert-butyl ether from sodium benzenophenone ketyl; dichloromethane and triethylamine from calcium hydride. All reactions were performed under an argon atmosphere unless otherwise noted.

1-[2R,4S,5R]-5-[bis(4-methoxyphenyl)phenylmethoxymethyl]-4-hydroxytetrahydrofuran-2-yl]-5-methyl-1H-pyrimidine-2,4-dione (726 mg, 100%) as a colorless foam: [α]₂⁰D +41° (c = 0.58, CHCl₃); IR (neat) 3056, 2955, 2932, 1692, 1510, 1472, 1428, 1273, 1252, 1181, 1113, 1065, 1034, 999, 856, 756, 702, 613 cm⁻¹; 400 MHz ¹H NMR (CDCl₃) δ 1.06 (9H, s), 1.38 (3H, s), 2.09 (1H, ddd, J = 13.5, 7.5, 6.3 Hz), 2.45 (1H, ddd, J = 10.5, 2.2 Hz), 3.24 (1H, dd, J = 10.5, 2.2 Hz), 3.79 (3H, s), 4.09 (1H, s), 4.57 (1H, m, 6.52 (1H, dd, J = 7.5, 5.5 Hz), 6.77 (2H, d, J = 8.5 Hz), 7.15 (2H, d, J = 8.5 Hz), 7.2–7.3 (12H, m), 7.35–7.47 (4H, m), 7.50 (1H, s), 7.56 (2H, d, J = 7.4 Hz), 7.63 (2H, d, J = 7.4 Hz), 9.09 (1H, br s); 100 MHz ¹³C NMR (CDCl₃) δ 11.72 (C₅-Me), 19.03 (CMe), 26.89 (CMe), 41.16 (C₂), 55.27 (OCH₃), 73.36 (C₃), 88.67 (C₄), 89.62 (C₁), 87.07 (C₆), 111.15 (C₅), 113.23 (C₄), 127.16 (1C of Ph), 127.20 (1C of Ph), 127.67 (2C of Ph), 129.71 (2C of Ph), 129.76 (2C of Ph), 129.82 (2C of Ph), 128.35 (2C of Ph), 130.00 (1C of Ph), 130.06 (1C of Ph), 130.35 (2C of Ph), 133.06 (1C of Ph), 133.09 (1C of Ph), 134.79 (p-C of MeOAr), 135.67 (2C of Ph), 135.72 (2C of Ph), 135.72 (2C of Ph), 143.75 (m-C of MeOAr), 148.34 (m-C of MeOAr), 150.46 (C₆), 158.72 (C-O-Me), 163.98 (C₂).
Preparation of 4′-Substituted Thymidines

1472, 1428, 1279, 1227, 1107, 1084, 741, 702, 610 cm⁻¹; 200 MHz ¹H NMR (CDCl₃) δ 10.10 (1H, s), 1.67 (1H, ddd, J = 13.5, 9.5, 4.4 Hz), 1.78 (3H, s), 2.13 (1H, dd, J = 13.5, 5 Hz), 4.48 (1H, s), 4.52 (1H, d, J = 4.4 Hz), 6.53 (1H, dd, J = 9.5, 5 Hz), 7.29 (6H, m). ¹C NMR (CDCl₃–CD₂OD = 10:1) δ 16.21 (C₅-Me), 31.88 (C₆), 76.73 (C₃), 87.69 (C₄), 89.25 (C₅), 110.55 (C₁'), 114.81 (C₅), 140.53 (C₁), 154.74 (C₂'), 164.14 (C₁), 174.30 (C₅').

(25,35,5R,3′-3′-Tert-Butylidiphenylsilyloxy)-5-(3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)tetrahydrofuran-2-carboxylic Acid tert-Butyl Ester (4a). A solution of 11.5 mg of 2,4-dimethoxy-2,4-dihydrofuran (0.06 mmol) in THF (0.1 mL) was added TBAF (1.0 mL, 0.6 mol/L) at 0 °C, and the mixture was stirred at the same temperature for 1.5 h. After being quenched with water, the mixture was extracted with CH₂Cl₂ and dried over MgSO₄. After removal of the solvent, the residue was purified by flash chromatography (hexane/ethyl acetate = 2:3 to 1:2) to give a 7:1 mixture of 4a and 3 (14 mg, 50%) and a 7:1 mixture of 5a and the C4′-stereoisomer of 3 (5.2 mg, 18%).

(25,35,5R,3′-3′-Tert-Butylidiphenylsilyloxy)-5-(3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)tetrahydrofuran-2-carboxylic Acid tert-butyl ester (4a) (colorless foam): [α]₂⁰D +27° (c = 0.29, CHCl₃–MeOH = 20:1); IR (neat) 3386, 3214, 1732, 1715, 1673, 1457, 1429, 1324, 1084 cm⁻¹; 400 MHz ¹H NMR (CDCl₃–CD₂OD = 20:1) δ 1.45 (9H, s), 1.90 (1H, dd, J = 13.5, 9.2, 4.3 Hz), 1.90 (3H, d, J = 1.2 Hz), 2.33 (1H, dd, J = 13.5, 5.1, 1 Hz), 4.43 (1H, d, J = 4.3 Hz), 6.43 (1H, dd, J = 9.2, 5.1 Hz), 8.11 (1H, d, J = 1.2 Hz); ¹C NMR (CDCl₃–CD₂OD = 20:1) δ 16.21 (C₅-Me), 31.88 (C₆), 42.92 (C₇'), 76.73 (C₃), 87.69 (C₄), 89.25 (C₅), 90.38 (C₁'), 110.55 (C₁'), 114.81 (C₅), 140.53 (C₁), 154.74 (C₂'), 164.14 (C₁), 174.30 (C₅').
THF (0.8 mL) was added LiBH$_4$ (2 mg, 0.092 mmol) at room temperature, and the mixture was stirred for 1 h. After the reaction was quenched with EtOH (0.25 mL) for 0.5 h and neutralized with AcOH (0.01 mL) for 0.5 h, the solvent was evaporated in vacuo. The residue was purified by flash chromatography (hexane/ethyl acetate = 1:2 to ethyl acetate) to give 1-(2R,4S,5S)-4-hydroxy-5-hydroxymethyl-5-(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidine-1-yl)tetrahydrafuran-2-yl-5-methyl-1H-pyrimidine-2,4-dione (7c). To a solution of 6b (9 mg, 0.023 mmol) in 2,2-dimethoxypropane (0.33 mL)—DMF (0.08 mL) was added pyridinium p-toluenesulfonate (<1 mg) at room temperature, and the mixture was stirred for 48 h. After removal of the solvent, the residue was purified by preparative thin-layer chromatography (ethyl acetate) to give 1-(2R,4R,5R)-7a (6.5 mg, 65%), as a colorless foam: [α]$_D^{22}$ = $-57°$ (c = 0.15, CHCl$_3$); IR (neat) 3187, 2928, 2964, 1694, 1470, 1275, 1078, 989, 866 cm$^{-1}$; 400 MHz $^1$H NMR (CDCl$_3$) δ 1.23 (3H, s), 1.35 (3H, s), 1.96 (3H, s), 2.51 (2H, m), 3.94 (1H, $d$, $J$ = 12.9 Hz), 4.23 (2H, $d$, $J$ = 12.9 Hz), 4.61 (1H, br, s), 6.77 (1H, $dd$, $J$ = 8, 7 Hz), 7.35 (2H, $dd$, $J$ = 7.5, 7.5 Hz), 7.87 (1H, $d$, $J$ = 7.3 Hz), 7.86 (1H, $s$), 8.34 (1H, br, s); $^{13}$C NMR (CDCl$_3$) δ 12.60 (CS-Me), 19.45 and 27.91 (MeC), 37.92 (C2), 66.31 (C3), 75.00 (C3), 87.61 (C1), 88.88 (MeC, 98.35 (C4), 117.44 (C5), 125.80 (p-C of Ph), 129.47 (C-Se), 129.59 (2C of Ph), 136.11 (C4), 136.47 (2C of Ph), 150.23 (C6), 163.29 (C2).

(2R,3S,5R)-3-Hydroxy-2-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)tetrahydrafuran-2-carboxylic Acid tert-Butyl Ester (5c). The ester (3 mg) was coevaporated with benzene, dried in vacuo, dissolved in THF (1.0 mL)—HMPA (0.13 mL), and dried under molecular sieves 4A (3 pieces) with stirring for 1 h. To the solution of 3 (7.5 mg, 0.024 mmol) was added lithium diisopropylamide (7.5 mg, 0.024 mmol) was added lithium diisopropylamide (0.1 mL) at $-78 \degree$C for 30 min. tert-Butylium (1.7 M in pentane, 0.065 mL) was added to the solution at $-78 \degree$C, and the mixture was stirred at $-78 \degree$C for 1 h. To the solution was added allyl bromide (0.035 mL, 0.14 mmol) at $-78 \degree$C, and the mixture was stirred at $-78 \degree$C for 1 h and at $0 \degree$C for 40 min. After the reaction was quenched with MeOH (0.09 mL)—AcOH (0.03 mL), the solvent was evaporated in vacuo. The residue was purified by flash chromatography (hexane/ethyl acetate = 1:1.2 to ethyl acetate) to give (2R,3S,5R)-3-hydroxy-2-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)tetrahydrafuran-2-carboxylic acid tert-butyl ester 5c (2.9 mg, 34%), and (25,3S,5R)-3-hydroxy-2-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)tetrahydrafuran-2-carboxylic acid tert-butyl ester 4c (0.8 mg, 9%).

(2R,3S,5R)-3-Hydroxy-2-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)tetrahydrafuran-2-carboxylic acid tert-butyl ester 5c (colorless foam): [α]$_D^{22}$ = $+33°$ (c = 0.22, CHCl$_3$); IR (neat) 3492, 2930, 1740, 1709, 1476, 1437, 1275, 1235, 1140, 1086 cm$^{-1}$; 400 MHz $^1$H NMR (CDCl$_3$) δ 1.52 (9H, s), 1.92 (3H, s), 2.25 (1H, $d$, $J$ = 13.7, 6.8, 6.5 Hz), 2.47 (1H, $d$, $J$ = 13.5, 6.5, 4.4 Hz), 2.54 (1H, $d$, $J$ = 14, 7 Hz), 2.82 (1H, $d$, $J$ = 14, 7.2 Hz), 4.46 (1H, m), 5.22 (2H, m), 5.83 (1H, m), 6.35 (1H, $d$, $J$ = 6.6, 6.6 Hz), 7.19 (1H, $d$, $J$ = 1 Hz), 8.70 (1H, br s); $^{13}$C NMR (CDCl$_3$) δ 12.60 (CS-Me), 28.11 (CMe), 39.00 (C2), 40.64 (allyl), 75.46 (C3), 83.45 (CMe$_3$), 86.20 (C4), 89.81 (C5), 111.08 (C9), 119.91 and 131.64 (vinyl of allyl), 135.84 (C4), 149.99 (C6), 163.58 (C2), 170.30 (C5).

(2R,3S,5R)-2-Methyl-3-(2-propenyl)oxy-5-(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)tetrahydrafuran-2-carboxylic acid tert-buty ester 5c: colorless foam: 400 MHz $^1$H NMR (CDCl$_3$) δ 13.60 (CH$_3$), 1.91 (3H, $d$, $J$ = 1.2 Hz), 2.18 (2H, $m$), 13.5, 6.8, 6.5 Hz, 2.54 (2H, $d$, $J$ = 13.5, 6.6 Hz), 4.05 (2H, m), 4.15 (1H, m), 5.15–5.35 (4H, m), 5.75–5.95 (2H, m), 6.32 (1H, $d$, $J$ = 6.6, 6.5 Hz), 7.19 (1H, $d$, $J$ = 1.2 Hz), 8.16 (1H, br).
and room temperature for 30 min. tert-Butyl lithium (1.7 M in pentane, 0.13 mL, 0.22 mmol) was added to the solution at −78 °C, and the mixture was stirred at −78 °C for 1 h. To this solution was added N-fluorobenzensulfonylimide (NFSI) (155 mg, 0.490 mmol) in THF (0.42 mL) at −78 °C, and the mixture was stirred at −78 °C for 6 h and then −25 °C for 6 h for 5 min. After the reaction was quenched with MeOH (0.18 mL)−AcOH (0.08 mL), the solvent was evaporated in vacuo. The residue was purified by flash chromatography (hexane/ethyl acetate = 1:1−2:1) to give 25 (25,35,SR)-3-Benzensulfonyloxy-2-fluoro-5-(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-tetrahydrofuran-2-carboxylic acid tert-butyl ester 5d (10.3 mg, 48%) and the 3′-O-Benzensulfonyl derivative of 3 (3.4 mg, 16%).

(25,35,SR)-3-Benzensulfonyloxy-2-fluoro-5-(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-tetrahydrofuran-2-carboxylic Acid tert-Butyl Ester (5e). The residue was purified by flash chromatography (hexane/ethyl acetate = 1:1−2:1) to give 26 (25,35,SR)-2-fluoro-3-hydroxy-5-(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-tetrahydrofuran-2-carboxylic acid tert-butyl ester 5e (10.9 mg, 21%) and 5d (14 mg, 19%).

1-{(2R,4R,5R)-5-Fluoro-4-hydroxy-5-hydroxymethyltetrahydrofuran-2-yl}-5-methyl-1H-pyrimidine-2,4-dione (6d). To a solution of 5d (9.5 mg, 0.029 mmol) in THF (1.0 mL) was added LiBH4 (3 mg, 0.14 mmol) at room temperature, and the mixture was stirred for 2 h. After the reaction was quenched with F3OH (0.5 mL) for 10 min and neutralized with AcOH (0.02 mL) for 10 min, the solvent was evaporated in vacuo. The residue was purified by flash chromatography (ethyl acetate) to give 1-{(2R,4S,5R)-5-fluoro-4-hydroxy-5-hydroxymethyltetrahydrofuran-2-yl}-5-methyl-1H-pyrimidine-2,4-dione (6d) (6.2 mg, 82%) as a colorless foam. αβD 319.00 (c = 0.1, CHCl3−MeOH = 20:1); IR (neat) 3397, 1701, 1473, 1285, 1071 cm−1; 400 MHz 1H NMR (CDCl3−CD2OD = 20:1) δ 1.88 (3H, s), 2.16 (1H, m), 2.43 (1H, dd, J = 14, 6.6 Hz), 3.86 (1H, dd, J = 18, 12.6 Hz), 3.91 (1H, dd, J = 23, 12.6 Hz), 4.48 (1H, dd, J = 3, 3 Hz), 6.69 (1H, dd, J = 8.3, 8.6 Hz), 7.28 (1H, s); 13C NMR (CDCl3−CD2OD = 20:1) δ 16.42 (C5-Me), 41.18 (C2), 64.57 (C5′, d, J = 129 Hz), 77.73 (C3′, d, J = 157 Hz), 90.85 (C3, d, j = 13 Hz), 116.05 (C5), 124.94 (C4′, d, J = 906 Hz), 138.79 (C4, d, J = 24 Hz), 154.60 (C6), 167.86 (C2).

Methanesulfonic Acid (2R,3S,5R)-2-{[4-(4-methoxyphenyl)phenylmethoxymethyl]-5-(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-tetrahydrofuran-2-yl} Ester (7). To a solution of 1-{(2R,4S,5R)-5-[4-(4-methoxyphenyl)phenylmethoxymethyl]-4-hydroxytetrahydrofuran-2-yl}-5-methyl-1H-pyrimidine-2,4-dione (6d) (56 mg, 0.11 mmol) in pyridine (0.3 mL) was added methanesulfonic acid (0.11 mL, 0.14 mmol) at −90 °C as a colorless foam. After removal of the solvent, the residue was purified by flash chromatography (hexane/ethyl acetate = 1:1−2:1) to give methanesulfonic acid (2R,3S,5R)-2-{[4-(4-methoxyphenyl)phenylmethoxymethyl]-5-(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-tetrahydrofuran-2-yl} ester (7) (61 mg, 94%) as a colorless foam: [α]D 22D −1.1° (c = 0.45, CHCl3, CH3OH = 1:1); IR (neat) 3463, 3204, 2466, 1701, 1474, 1285, 1071 cm−1; 1H NMR (CDCl3−CD3OD = 20:1) δ 1.92 (3H, s), 4.09 (1H, s), 4.24 (1H, dd, J = 3, 3 Hz), 6.70 (1H, dd, J = 8.3, 8.6 Hz), 7.24 (1H, s); 13C NMR (CDCl3−CD3OD = 20:1) δ 114.95 (C2), 117.29 (C4′), 122.56 (2C of Ph), 124.79 (2C of Ph), 131.74 (1C of Ph), 134.76 (1C of Ph), 153.82 (C4), 149.92 (C6), 160.17 (C5′, d, J = 130 Hz), 162.92 (C2).

(2R,4R,5R,7S,8R,9R,10R)-10-{[(4-Methoxyphenyl)phenyl]methoxymethyl}-4-methyl-8,11-dioxa-2,6-diazatricyclo[7.2.1.02,7]dodeca-3,6-dien-5-one (8). To a solution of methanesulfonic acid (2R,3S,5R)-2-{[4-(4-methoxyphenyl)phenylmethoxymethyl]-5-(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-tetrahydrofuran-2-yl} ester (7) (1.19 g, 2.81 mmol) was added methane sulfonyl chloride (0.011 mL, 0.14 mmol) at 0 °C, and the mixture was stirred for 6 h at the same temperature and refrigerated for 12 h. After the reaction was quenched with ice−water (5 mL), the mixture was extracted with CH2Cl2 and dried over MgSO4. After removal of the solvent, the residue was purified by flash chromatography (hexane/ethyl acetate = 1:2−3:1) to give methanesulfonic acid (2R,3S,5R)-2-{[4-(4-methoxyphenyl)phenylmethoxymethyl]-5-(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-tetrahydrofuran-2-yl} ester (7) (61 mg, 94%) as a colorless foam: [α]D 22D +1.1° (c = 0.45, CHCl3, CH3OH = 1:1); IR (neat) 3397, 1701, 1474, 1285, 1071 cm−1; 1H NMR (CDCl3−CD3OD = 20:1) δ 1.92 (3H, s), 4.09 (1H, s), 4.24 (1H, dd, J = 3, 3 Hz), 6.70 (1H, dd, J = 8.3, 8.6 Hz), 7.24 (1H, s); 13C NMR (CDCl3−CD3OD = 20:1) δ 114.95 (C2), 117.29 (C4′), 122.56 (2C of Ph), 124.79 (2C of Ph), 131.74 (1C of Ph), 134.76 (1C of Ph), 153.82 (C4), 149.92 (C6), 160.17 (C5′, d, J = 130 Hz), 162.92 (C2).
(2R,4R,5R)-1-[5-(4-methoxyphenyl)phenylmethoxy-4-(tert-butyldiphenylsilanyloxy)-5-hydroxymethyltetrahydrofuran-2-yl]-5-methyl-1H-pyrimidine-2,4-dione. To a solution of (2R,4R,5R)-1-[5-(4-methoxyphenyl)phenylmethoxy-4-(tert-butyldiphenylsilanyloxy)-5-hydroxymethyltetrahydrofuran-2-yl]-5-methyl-1H-pyrimidine-2,4-dione (1.06 g, 2.6 mmol) in DMF (15.4 mL) were added imidazole (1.83 g, 26.9 mmol) and TBDDPSI (2.31 mL, 8.88 mmol) at room temperature, and the mixture was gently refluxed for 1.5 h. After the reaction was quenched with water, the mixture was extracted with EtO and dried over MgSO$_4$. After removal of the solvent, the residue was purified by flash chromatography (hexane/ethyl acetate = 2:1) to give (2R,4R,5R)-1-[5-(4-methoxyphenyl)phenylmethoxy-4-(tert-butyldiphenylsilanyloxy)-5-hydroxymethyltetrahydrofuran-2-yl]-5-methyl-1H-pyrimidine-2,4-dione (1.46 g, 94%) as a colorless foam: $\delta_{\text{H}}$ (300 MHz, CD$_3$OD) 1.08 (9H, s), 1.43 (1H, d, $\text{J} = 1.2$ Hz), 1.45 (1H, m), 1.69 (1H, d, $\text{J} = 7.4$ Hz), 3.75 (6H, m), 5.70 (2H, m), 7.20 (1H, d, $\text{J} = 4.6$ Hz), 7.33 (6H, m), 7.50 (2H, m), 7.70 (2H, m), 7.82 (2H, m), 8.10 (2H, d, $\text{J} = 10.0$ Hz), 10.0 (1H, br s); $\delta_{\text{C}}$ (100 MHz, CD$_3$OD) 102.07 (C5-Me), 16.45 (C5-Me), 22.88 (C5-Me), 30.62 (C5-Me), 44.18 (C2), 76.74 (C3), 87.87 (C4), 90.79 (C1), 113.41 (C5), 131.68 (2C of Ph), 133.98 (1C of Ph), 134.11 (1C of Ph), 135.50 (1C of Ph), 136.55 (1C of Ph), 139.47 (2C of Ph), 139.89 (2C of Ph), 141.67 (C4), 154.13 (C6), 168.70 (C5), 175.13 (C7), 175.48 (C5).

(25S,3R,5R)-3-(ter-t-Butyldiphenylsilanyloxy)-5-(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)tetrahydrofuran-2-carboxylic Acid Methyl Ester (9). To a solution of (25S,3R,5R)-3-(ter-t-Butyldiphenylsilanyloxy)-5-(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)tetrahydrofuran-2-carboxylic acid methyl ester (800 mg, 1.57 mmol) in THF (17 mL) was added TBAF (1 M in THF, 1.6 mL) at 0 °C. After removal of the solvent, the residue was purified by flash chromatography (hexane/ethyl acetate = 5:1) to give (25S,3R,5R)-3-(ter-t-Butyldiphenylsilanyloxy)-5-(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)tetrahydrofuran-2-carboxylic acid methyl ester (70 mg, 92%) as a colorless foam: $\delta_{\text{H}}$ (300 MHz, CD$_3$OD) 1.08 (9H, s), 1.43 (1H, d, $\text{J} = 1.2$ Hz), 1.45 (1H, m), 1.69 (1H, d, $\text{J} = 7.4$ Hz), 3.75 (6H, m), 5.70 (2H, m), 7.20 (1H, d, $\text{J} = 4.6$ Hz), 7.33 (6H, m), 7.50 (2H, m), 7.70 (2H, m), 7.82 (2H, m), 8.10 (2H, d, $\text{J} = 10.0$ Hz), 10.0 (1H, br s); $\delta_{\text{C}}$ (100 MHz, CD$_3$OD) 102.07 (C5-Me), 16.45 (C5-Me), 22.88 (C5-Me), 30.62 (C5-Me), 44.18 (C2), 76.74 (C3), 87.87 (C4), 90.79 (C1), 113.41 (C5), 131.68 (2C of Ph), 133.98 (1C of Ph), 134.11 (1C of Ph), 135.50 (1C of Ph), 136.55 (1C of Ph), 139.47 (2C of Ph), 139.89 (2C of Ph), 141.67 (C4), 154.13 (C6), 168.70 (C5), 175.13 (C7), 175.48 (C5).
ylid Acid Methyl Ester (11a) and (25,3R,5R)-2-Deutero-3-hydroxy-5-(5-methyl-2,4-dioxo-3,4-di hydro-2H-pyr imidin-1-yl)tetrahydrofuran-2-carboxylic Acid Methyl Ester (10a). The ester 9 (29 mg) was coevaporated with benzene, dried in vacuo, dissolved in THF (4.3 mL)–HMPA (0.52 mL), and dried under molecular sieves 4A (18 pieces) with stirring for 1 h. To the solution of 9 (28.0 mg, 0.104 mmol) was added lithium diisopropylamide (2M in tetrahydrofuran) (LDA) (Aldrich, 1.5 M in cyclohexane, 0.40 mL, 0.60 mmol) at -78 °C (LDA) (Aldrich, 1.5 M in cyclohexane, 0.40 mL, 0.60 mmol) was added to the solution at -78 °C, and the mixture was stirred at -78 °C for 5 min, -78 °C → room temperature for 10 min, and room temperature for 10 min. tert-Butyl lithium (1.7 M in pentane, 0.30 mL, 0.51 mmol) was added to the solution at -78 °C, and the mixture was stirred at -78 °C for 1 h. To the solution were added CD3OD (0.38 mL) and CD3CO2D (0.12 mL) at -78 °C (LDA) (Aldrich, 1.5 M in cyclohexane, 0.40 mL, 0.60 mmol) was added to the solution at -78 °C, and the mixture was stirred at -78 °C for 20 min and at -78 °C for 1 h. To the solution was added LiBH4 (3 mg, 0.14 mmol) at room temperature, and the mixture was stirred for 1 h. After the mixture was neutralized with aq H2SO4 (0.015 mL), the solvent was evaporated in vacuo. The residue was purified by flash chromatography (hexane/ethyl acetate = 1:2) to give 1(2R,3R,5S)-4-Hydroxy-5-hydroxymethyl-5-phenylselenenyltetrahydrofuran-2-yl)-5-methyl-1H-pyrimidine-2,4-dione (12b). To a solution of (2R,3R,5R)-3-hydroxy-5-(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyr imidin-1-yl)tetrahydrofuran-2-carboxylic acid methyl ester 10b (24 mg, 0.056 mmol) in THF (0.75 mL)–EtOH (1.0 mL) was added LiBH4 (3 mg, 0.14 mmol) at room temperature, and the mixture was stirred for 1 h. After the mixture was neutralized with aq H2SO4 (0.015 mL), the solvent was evaporated in vacuo. The residue was purified by flash chromatography (hexane/ethyl acetate = 1:2) to give 1(2R,3R,5S)-4-Hydroxy-5-hydroxymethyl-5-phenylselenenyltetrahydrofuran-2-yl)-5-methyl-1H-pyrimidine-2,4-dione (12b) (14 mg, 63%) as a colorless foam: [α]D 21° = -115° (c = 0.08, CHCl3); IR (neat) 3296, 2926, 1668, 1474, 1279, 1057, 741, 693 cm -1; 400 MHz 1H NMR (CDCl 3) δ 1.81 (3H, s), 2.11 (1H, dm, J 15, 2.2 Hz), 3.08 (1H, ddd, J 15, 8.5, 6 Hz), 4.52 (1H, d, J = 6 Hz), 6.06 (1H, dm, J d = 6 Hz), 8.00 (1H, s); 13C NMR (CDCl 3) δ 12.60 (C1-Me), 39.37 (C2), 73.96 (C3), 110.38 (C4), 141.75 (C5), 165.20 (C6), 174.30 (C7).
44% as a colorless foam: \([\alpha]_D^{22} = -98^\circ\) (c = 0.33, CHCl3); IR (neat) 3399, 1740, 1690, 1476, 1281, 1107 cm\(^{-1}\); 400 MHz \(^1\)H NMR (CDCl3) \(\delta\) 1.48 (3H, s), 1.81 (3H, s), 2.51 (1H, dm, J = 2.7 Hz), 2.72 (1H, dd, \(J = 15, 7, 6\) Hz), 3.86 (3H, s), 4.00 (1H, br s), 4.39 (1H, \(J = 4.4\) Hz), 6.19 (1H, \(J = 7\) Hz), 8.03 (1H, s), 9.86 (1H, br s); \(^13\)C NMR (CDCl3) \(\delta\) 120.32 (C1), 118.50 (C6), 117.12 (C5), 112.05 (C4), 150.97 (C2). To a solution of 10c (11.5 mg, 0.040 mmol) in THF (1 mL) was added LiBH\(_4\) (10 mg, 0.46 mmol) at room temperature, and the mixture was stirred for 1 h. After the reaction was quenched with 20% aqueous MeOH (0.04 mL), the solvent was evaporated in vacuo. The residue was purified by flash chromatography (ethyl acetate) to give 2-(2R,5R,5R)-4-Hydroxy-5-hydroxymethyl-5-methyltetrahydrofuran-2-yl)-5-methyl-1H-pyrimidine-2,4-dione (13d). To a solution of 11d (5 mg, 86%) as a colorless foam: \([\alpha]_D^{22} = 24^\circ\) (c = 0.10, CHCl3); IR (neat) 3403, 1686, 1474, 1277, 1015 cm\(^{-1}\); 400 MHz \(^1\)H NMR (MeOD) \(\delta\) 2.32 (1H, m), 2.67 (2H, m), 3.20 (1H, br s), 4.37 (1H, d, \(J = 5.5, 1.4\) Hz), 6.19 (1H, dd, \(J = 14.7, 7.7, 7\) Hz), 7.03 (1H, br s, OH), 3.89 (2H, s), 4.37 (1H, m), 5.17 (2H, m), 5.81 (1H, m), 6.04 (1H, dd, \(J = 7, 6\) Hz), 7.71 (1H, s), 8.77 (1H, br s); \(^13\)C NMR (CDCl3) \(\delta\) 125.36 (C5-Me), 39.88 (C2), 40.29 (allyl), 65.07 (C5), 75.28 (C3), 85.44 (C4), 88.07 (C1), 111.08 (C5), 119.70 and 131.96 (vinyl of allyl), 137.82 (C4), 150.53 (C6), 163.77 (C2). Methyl-1-[(4aR,6R,7aR)-2,2-dimethyl-4a-(2-propenyl)tetrahydrofuro[3,2-d][1,3]dioxin-6-yl]-1H-pyrimidine-2,4-dione (13d). To a solution of 12c (5 mg, 0.033 mmol) in THF (1 mL) was added lithium diisopropylamide (1.7 M in pentane, 0.095 mL, 0.16 mmol) at 0 °C for 15 min. After the reaction was quenched with 20% aqueous MeOH (0.13 mL, 0.19 mmol) at −78 °C, and the mixture was stirred at −78 °C for 1 h. To a solution of 9 (8.5 mg, 0.031 mmol) was added lithium diisopropylamide mono(tetrahydrofuran) (LDA) (Aldrich, 1.5 M in cyclohexane, 0.12 mL, 0.17 mmol) at −78 °C, and the mixture was stirred at −78 °C for 5 min, −78 °C − room temperature for 5 min, and room temperature for 10 min. tert-Butylthiium (1.7 M in pentane, 0.09 mL, 0.15 mmol) was added to the solution at −78 °C, and the mixture was stirred at −78 °C for 1 h. To the solution was added allyl bromide (0.042 mL, 0.49 mmol) at −78 °C, and the mixture was stirred at −78 °C for 30 min and at −78 °C −−− 15 °C for 1.5 h. After the reaction was quenched with MeOH (0.11 mL)−AcOH (0.036 mL), the solvent was evaporated in vacuo. The residue was purified by flash chromatography (ethanol/ethyl acetate = 2:1) to give 2-(3R,5R,5R)-3-Benzensulfonyloxy-2-fluoro-5-(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrinidin-1-yl)tetrahydrofuran-2-carboxylic Acid Methyl Ester (10e). The ester 9 (9.5 mg) was coevaporated with benzene, dried in vacuo, dissolved in THF (1.4 mL)−HMPA (0.17 mL), and dried under molecular sieves 4A (five pieces) with stirring for 1 h. To the solution of 9 (8.5 mg, 0.031 mmol) was added lithium disoproplamide mono(tetrahydrofuran) (LDA) (Aldrich, 1.5 M in cyclohexane, 0.13 mL, 0.19 mmol) at −78 °C, and the mixture was stirred at −78 °C for 5 min, −78 °C − room temperature for 5 min, and room temperature for 10 min. tert-Butylthiium (1.7 M in pentane, 0.095 mL, 0.16 mmol) was added to the solution at −78 °C, and the mixture was stirred at −78 °C for 1 h. To the solution was added N-fluorobenzenesulfonimide (NFSI) (110 mg, 0.35 mmol) in THF (0.3 mL) at −78 °C, and the mixture was stirred at −78 °C − 30 °C for 1 h and at −30 °C − room temperature for 15 min. After the reaction was cooled to 0 °C, 0.02 mmol of MeOH (0.12 mL)−AcOH (0.04 mL), the solvent was evaporated in vacuo. The residue was purified by flash chromatography (hexane/ethyl acetate = 1:2) to give 2-(3R,5R,5R)-3-benzensulfonyloxy-2-fluoro-5-(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrinidin-1-yl)tetrahydrofuran-2-carboxylic acid methyl ester (10e) (7 mg, 49%) as a colorless foam: \([\alpha]_D^{22} = 16^\circ\) (c = 0.4, CHCl3); IR (neat) 2924, 1771, 1696, 1451, 1377, 1285, 1194, 1115, 743, 586 cm\(^{-1}\); 400 MHz \(^1\)H NMR (CDCl3) \(\delta\) 1.84 (3H, d, \(J = 1.2\) Hz), 2.37 (1H, d, \(J = 16.5\) Hz), 2.90 (1H, d, \(J = 16.5\) Hz), 3.15 (1H, s), 4.26 (2H, m), 7.26 (2H, m), 7.48 (1H, d, \(J = 7.6\) Hz), 7.70 (1H, m), 7.74 (2H, m), 8.90 (1H, br s); \(^13\)C NMR (CDCl3) \(\delta\) 124.63 (C5-Me), 35.98 (C2), 53.75 (ester Me), 79.70 (C3, d, \(J = 165\) Hz), 86.49 (C1, d, \(J = 8\) Hz), 111.95
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(5), 113.28 (C4′, d, J = 939 Hz), 127.73 (2C of Ph), 129.69 (2C of Ph), 134.72 (1C of Ph), 135.45 (C4), 150.04 (C6), 162.25 (C5′, d, J = 129 Hz), 163.30 (C2).

(2R,3R,5R)-2-Fluoro-3-hydroxy-5-(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)tetrahydrofuran-2-carboxylic Acid Methyl Ester (10f). The ester (13 mg) was coevaporated with benzene, dried in vacuo, dissolved in THF (0.48 mL) at 78 °C for 1 h. To the solution of 10f (12.5 mg, 0.046 mmol) was added lithium diisopropylamide mono-(tetrahydrofuran) (LDA) (Aldrich, 1.5 M in cyclohexane, 0.18 mL, 0.27 mmol) at 78 °C, and the mixture was stirred at 78 °C for 5 min, then 78 °C for 1 h. To the mixture was added MeOH (0.2 mL) and the solvent was evaporated in vacuo. The residue was purified by flash chromatography (hexane/ethyl acetate 93:7) to give 10e (3 mg, 15%) and (2R,3R,5R)-2-fluoro-3-hydroxy-5-(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)tetrahydrofuran-2-carboxylic acid methyl ester 10f (4.6 mg, 30%), both as colorless foams.

(2R,3R,5R)-2-Fluoro-3-hydroxy-5-(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)tetrahydrofuran-2-carboxylic Acid Methyl Ester (10f): [α]23D = −32° (c = 0.2, CHCl3); ν (neat) 2926, 1761, 1694, 1472, 1318, 1285, 756 cm−1; 400 MHz 1H NMR (CDCl3) δ 1.88 (3H, s), 2.39 (1H, dm, J = 15 Hz), 2.87 (1H, ddd, J = 15, 8.5, 6 Hz), 3.94 (3H, s), 4.28 (br s), 4.62 (1H, m), 6.42 (1H, ddd, J = 8.5, 2.5, 2.5 Hz), 7.67 (1H, s), 9.29 (1H, br); 13C NMR (CDCl3) δ: 12.53 (C5-Me), 36.16 (C2′), 53.57 (ester Me), 74.11 (C3′, d, J = 145 Hz), 88.30 (C1′, d, J = 10 Hz), 111.35 (C5), 114.99 (C4′, d, J = 930 Hz), 137.53 (C4), 150.48 (C6), 163.68 (C2), 164.33 (C5′, d, J = 130 Hz).

Supporting Information Available: Proton and carbon NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.