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De Novo Synthesis of 4′-Ethoxy Nucleoside Analogues

Louis S. Hegedus,* Lisa Geisler, Andrew G. Riches, Sarri S. Salman, and Gisela Umbricht

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

hegedus@lamar.colostate.edu

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Butenolides **5a** and **13** were used as optically active templates in the de novo synthesis of 4′-disubstituted nucleoside analogues. The butenolides were reduced and acylated in situ to give acetates **10** and **14**. Vorbrüggen coupling gave the protected nucleoside analogues **11** and **15**. Reduction of **11** gave 4′-ethoxy-2′,3′-dideoxythymidine (**6**) and deprotection of **15** gave 4′-ethoxy-2′,3′-dideoxydidehydrothymidine (**7**). The *cis*-dihydroxylation of a variety of butenolides occurred with the major product formed from oxidation of the β-face.

Introduction

Since the initial discovery of nucleocidin, a 4′-fluororibonucleoside having potent antibiotic activity,[1] members of this unusual class of compounds have been shown to have anticancer activity,[2] agonistic activity toward adenosine receptors,[3] and more recently, anti-HIV activity.[4] In contrast to other nucleoside analogues having anti-HIV activity, which must lack the 3′-hydroxy group, the anti-HIV active 4′-azidonucleosides required a 3′-hydroxy group for activity,[5] indicating a fundamentally different mode of action for this class.

Many syntheses of 4′-disubstituted nucleosides involve functionalization of existing nucleosides.[1b,2,5a,6] Control of stereochemistry is often the difficult aspect of these syntheses, and this approach is restricted to the naturally occurring D-nucleosides.[7] 4′-Disubstituted nucleosides have also been synthesized from carbohydrates, converting the 4′-hydroxymethyl group to an aldehyde and using enolate chemistry to introduce the other 4′(carbon)-substitution,[8] or from open-chain, ribose-derived 4′-keto carbohydrates.[9] The recent availability of L-ribose from L-xylose[7] should provide access to the unnatural L-series of nucleosides, of current interest both as antivirals having reduced toxicity,[10] and precursors to stable L-RNA building blocks.[11]

De novo syntheses of 4′-disubstituted nucleoside analogues provide the most flexibility, both with respect to functionality and stereochemistry.[12] An efficient synthesis of an optically active template for nucleoside analogue synthesis has recently been reported from these laboratories.[13] The conversion of this key intermediate into 4′-disubstituted nucleoside analogues is reported below.

Results and Discussion

The starting point for these synthetic studies was the synthesis of optically active butenolides via chromium carbene photochemistry (Scheme 1).[13] Photolysis of optically active ene carbamates **2** with chromium carbene complex **1** produced optically active cyclobutanones **3** in good yield. The absolute configuration of the two new stereogenic centers was determined by the absolute configuration of the chiral auxiliary, making both enantiomers of **3** equally available. Baeyer−Villiger oxidation proceeded with retention of configuration of the migrating group, and in high yield giving lactones **4**. Treatment

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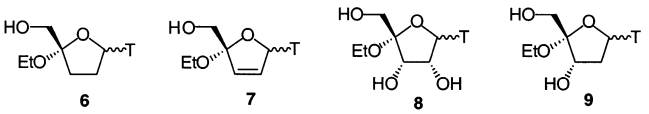
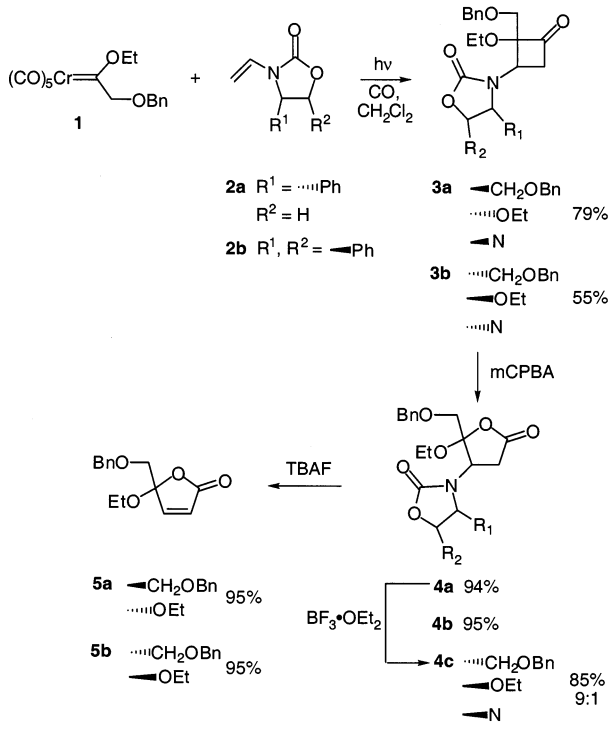


FIGURE 1.

SCHEME 1

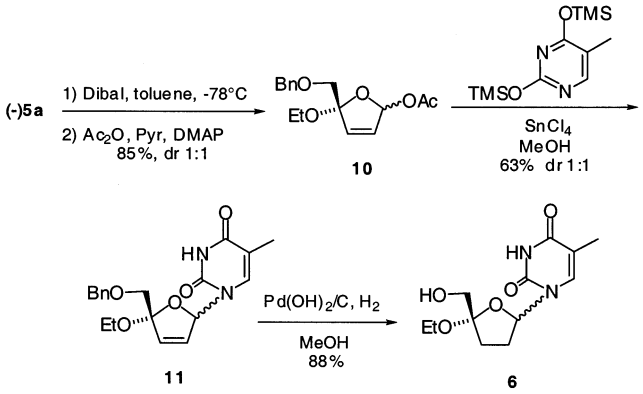


with TBAF eliminated the oxazolidinone giving butenolides **5** in excellent yield.

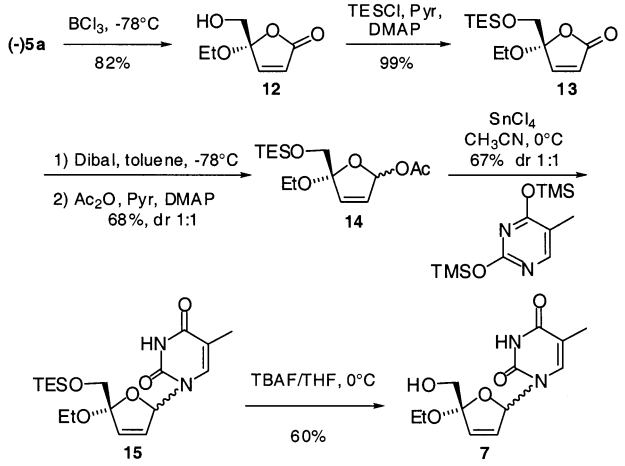
The photochemical step produces the thermodynamically less-stable cyclobutanone, with the two large groups syn, and this relationship carries through to the lactones **4**. Surprisingly, treatment of less-stable lactone **4a** with Lewis acids such as $BF_3{\cdot}OEt_2$ resulted in equilibration to a 9:1 mixture of epimers, favoring the more stable anti epimer. Replacement of the *O*-benzyl group by the larger *O*-TBS group at the cyclobutanone stage resulted in production of the corresponding lactone which epimerized completely to the more stable anti isomer when treated with stannic chloride. This facile epimerization makes both enantiomers of butenolide **5** available from a single enantiomer of the chosen chiral auxiliary. Conversion of butenolide **5a** to 4′-ethoxy nucleoside analogues (**6**−**9**) was next addressed.

Previous studies had shown that attempts to reduce 5-ethoxylactones to free lactols resulted in facile ring opening with ejection of ethoxide to give the corresponding 4-keto-aldehyde. To prevent this, the lactol aluminate was trapped in situ with acetic anhydride in the presence of pyridine and DMAP,[14] giving acetate **10** in excellent yield as a 1:1 mixture of C-1 anomers (Scheme 2). Vorbrüggen coupling[15] with silylated thymine produced protected 4′-ethoxy-2′,3′-dideoxydidehydrothymidine derivative **11** in good yield, but with no stereoselectivity, as expected for Vorbrüggen couplings of 2′-deoxyribose

SCHEME 2



SCHEME 3



systems. Reduction (Pearlman's catalyst/H_2) both debenzylated the 5′ position and reduced the double bond, giving 4′-ethoxy-2′,3′-dideoxythymidine (**6**) in excellent yield, again as an inseparable 1:1 mixture of C-1 anomers.

Synthesis of 4′-ethoxy-2′,3′-dideoxydidehydrothymidine (**7**) from **11** proved to be difficult. All attempts to remove the benzyl group from **11** while keeping the double bond intact failed. Oxidative methods, dissolving metals, and Lewis acidic conditions gave no reaction or caused decomposition.

The benzyl group can be removed from butenolide **5a** with BCl_3 to give alcohol **12** and other protecting groups were surveyed. TES-protected alcohol **13** could withstand the reduction/acylation conditions to give acetate **14** as a 1:1 mixture of diastereomers. Vorbrüggen coupling gave the protected 4′-ethoxy-2′,3′-dideoxydidehydrothymidine **15** in good yields. The TES group was removed with TBAF at 0 °C to give 4′-ethoxy-2′,3′-dideoxydidehydrothymidine (**7**) in 60% yield, as a 1:1 mixture of C-1 anomers, which could be separated by preparative TLC (Scheme 3).

Synthesis of 4′-ethoxy- and 4′-ethoxy-2′-deoxythymidine (**8** and **9**) would require the cis-dihydroxylation of butenolide **5a** from the α-face of the butenolide, the same face as the ethoxy substituent. Studies directed toward the total synthesis of neplanocin A[16] revealed that the oxidation with $RuCl_3/NaIO_4$[17] or OsO_4 produced **16**-*β* as

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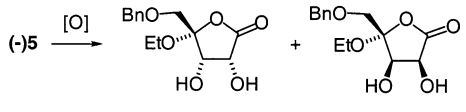
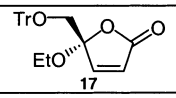
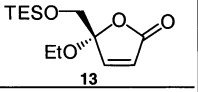
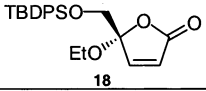
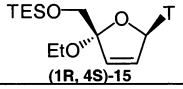
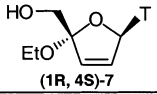
TABLE 1. Cis-dihydroxylation of Butenolide (−)-5



	16-α	16-β
$KMnO_4$	0%	50%
$NaIO_4/RuCl_3$	12%	40%
OsO_4/NMO	5%	9%

TABLE 2. Cis-dihydroxylation Studies

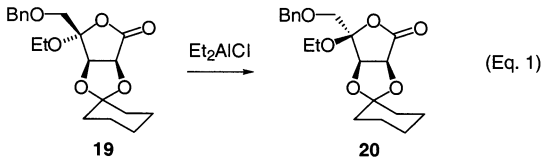
	KMnO4	OsO_4, NMO	$RuCl_3$, $NaIO_4$
5a	50% β	14% 70%[a] 2:1 β:α	52% 3:1 β:α
 17	10% 18%[a]	Low conversion	Low conversion 1:1 β:α
 13	-	1% 75%[a]	39% 67%[a] 1.5:1 mixture
 18	-	-	54% 84%[a] 1.3:1 mixture
 (1R, 4S)-15	SM Decomp.	SM	<30% 1:1 mixture
 (1R, 4S)-7	-	SM Decomp.	-

[a] Percent yield based on recovered starting material.

the major diol, and with $KMnO_4$, **16-**β was the only diol formed (Table 1).

In an attempt to increase the diastereoselectivity to favor the α-diol, studies were performed on a range of butenolides and dideoxydidehydronucleoside analogues (Table 2). The hydroxymethyl group was protected with larger protecting groups in attempts to increase the steric bias for the α-diol. With $KMnO_4$ or OsO_4 as the oxidant, low conversions of the butenolides were obtained. With $RuCl_3$ and $NaIO_4$ as the oxidant, the best diastereoselectivity and conversion (1.3:1 mixture and 54% yield) was obtained with the *tert*-butyldiphenyl silyl ether butenolide **18**. Unfortunately, the *tert*-butyldiphenyl silyl protecting group was not compatible with the remaining synthetic transformations. In an attempt to increase the steric bias even further and change the electronic properties of the alkene, the *cis*-dihydroxylation was attempted on dideoxydidehydronucleoside analogues (**15** and **7**). No reaction was observed with $KMnO_4$ or OsO_4 and $RuCl_3$/$NaIO_4$ gave a very low conversion. Therefore, increasing the steric bulk on the β-face and changing the electronic properties of the butenolide did not improve the diastereoselectivity to favor the α-diol, but inhibited the oxidation reaction. In addition, the use of AD mix α and AD mix β gave no conversion with **5a**.

Epimerization of the 5′-position on the undesired β-diol would lead to the correct relative stereochemistry (diol moiety anti to the CH_2OBn group). Epimerization of the 5′-position was successful with **19** and Et_2AlCl but only to 20% conversion (eq 1). Other protecting groups, such as the boronate ester[18] or benzylidene acetal as well as other Lewis acids ($Sc(OTf)_3$, $SnCl_4$, $TiCl_4$, Et_2OBF_3, $Y(OTf)_3$) did not improve the yield or conversion for the epimerization, making this approach to the desired α-diol impractical.



19 **20**

Since the inability to cis-dihydroxylation from the β-face precluded the syntheses of the "natural" diastereomers of nucleoside analogues **8** and **9**, synthetic approaches to "unnatural" (at C-2 and C-3) diastereomers were examined. Reduction of **16-**β with Dibal/Pyr/DMAP produced lactol triacetate **23** in modest yield, as a 1:1 mixture of C-1 anomers (Scheme 4). The major byproduct of this process was the 2′,3′-diacetate of **16-**β, from acetylation of unreduced **16-**β, and it was formed even when a large excess of Dibal was used. In an attempt to suppress this reaction, **16-**β was protected as acetonide **21**. This completely suppressed formation of the undesired byproduct and gave an excellent yield of the one diastereomer of **22**.

Vorbrüggen coupling of acetates **22** and **23** proved problematic, with most Lewis acids ($SnCl_4$, Me_2AlCl, Et_2AlCl, $Sr(OAc)_3$, TMSOTF) causing extensive ring opening and decomposition. Acetate **22** epimerized completely under the coupling conditions, but no coupled product could be observed.

In an attempt to synthesize the "unnatural" (at C-3) 4′-ethoxy-2′-deoxynucleoside analogue, intermediate **21** was treated with samarium iodide and ethylene glycol[19] to produce α-deoxygenated lactone **24** in good overall yield (Scheme 5). Reduction/acylation as above gave lactol diacetate **25** in fair yield, as a 5:1 mixture of anomers. With this substrate, small amounts of ring opened, reduced material was always observed and easily removed. α-Deoxygenated lactone **24** could also be reduced with Pd/C and H_2 to give a quantitative yield of diol **26**. Conversion to acetonide **27** occurred in an unoptimized 59% yield. Reduction/acylation conditions gave acetate **28** in fair yield, as a 1:1 mixture of diastereomers. Vorbrüggen coupling was unsuccessful with both acetates under a variety of conditions. Starting material was recovered with mild conditions (5 equiv of Lewis acid, 0 °C to rt) or ring opening was seen when a larger excess of the Lewis Acid and higher temperatures were used.

Conclusion

Using chromium carbene chemistry, either enantiomer of butenolide **5** was synthesized and used as an optically

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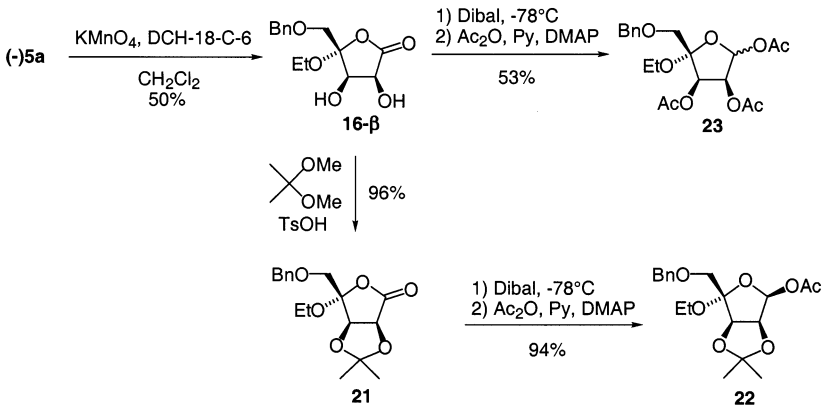
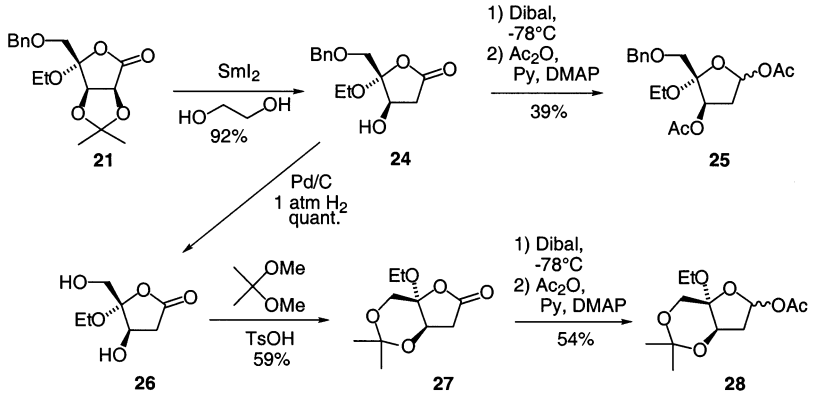
SCHEME 4



SCHEME 5



active template for the de novo synthesis of 4′-disubstituted nucleoside analogues. 4′-Ethoxy-2′,3′-dideoxythymidine (**6**) and 4′-ethoxy-2′,3′-dideoxydidehydrothymidine (**7**) were synthesized. Unfortunately, 4′-ethoxy and 4′-ethoxy-2′-deoxythymidine (**8** and **9**) could not be synthesized by a variety of methods from the butenolide template because of the lack of stereochemical control of the diol formation. In addition, "unnatural" diastereomers could not be synthesized because of the increased instability of the intermediates caused by the 4′-ethoxy substituent.

Experimental Section

General Methods. THF was distilled from sodium−benzophenone ketyl, DMF was distilled from $MgSO_4$, and CH_2Cl_2, benzene, and Et_3N were distilled from CaH_2. Commercially available reagents were used as received except as indicated. ^{1}H NMR, NOE, COSY (300 MHz), ^{13}C NMR (75 MHz), and HSQC (400 ^{1}H MHz) spectra were recorded in $CDCl_3$ unless otherwise noted and chemical shifts are given in ppm relative to $CDCl_3$ (7.27 ppm). Column chromatography was performed with ICN 32−66 nm, 60 Å silica gel using flash column techniques. Elemental analyses were performed by M−H−W Laboratories, Phoenix, AZ. FAB high-resolution mass spectrometry (HRMS) was obtained with a Fisons VG AutoSpec mass spectrometer with a Cs ion gun, *m*-nitrobenzyl alcohol was used for the matrix, and the resolution was set to 10000. All reactions were performed in flame-dried glassware under an atmosphere of Ar unless otherwise noted. Compounds **3a**, **4a**, **5a**, and **5b** were made by published procedures,[13a] as were **3b** and **4b**.[20]

(20) Brown, B.; Hegedus, L. S. *J. Org. Chem.* **2000**, *65*, 1865−1872.

(4*R*,5*R*)-5-(Benzyloxymethyl)-5-ethoxy-4-(4′*R*-phenyloxazolidin-2′-one)-dihydrofuran-2-one (4c). (4*R*,5*S*)-Lactone **4a** (44 mg, 0.11 mmol) was dissolved in 3 mL of freshly distilled CH_2Cl_2. BF_3OEt_2 (16 μL, 0.13 mmol) was then added, and the reaction was allowed to stir at room temperature for 4 h. The reaction was poured into $NaHCO_3$ (aq) and stirred. Separation of the organic layer followed by concentration in vacuo yielded an oil. Purification by SiO_2 column chromatography using 3:1 hexane:EtOAc as eluent provided a clear oil (30 mg, 0.073 mmol, 68%) containing a 9:1 mixture of **4c**:**4a**. **4c**: ^{1}H NMR δ 7.4−7.25 (m, 10H), 5.19 (dd, J = 9.1 Hz, J = 4.4 Hz, 1H), 5.01 (dd, J = 8.8 Hz, J = 9.8 Hz, 1H), 4.58 (m, 3H), 4.11 (dd, J = 4.4 Hz, J = 8.4 Hz, 1H), 3.77 (d, J = 10.2 Hz, 1H), 3.84−3.7 (m, 2H), 3.71 (d, J = 10.2 Hz, 1H), 2.33 (dd, J = 17.5 Hz, J = 8.7 Hz, 1H), 2.23 (dd, J = 17.5 Hz, J = 8.9 Hz, 1H), 1.28 (t, J = 6.9 Hz, 3H), 1.18 (t, 3H). ^{13}C NMR δ 172.2, 140.4, 137.2, 129.5, 129.1, 128.4, 127.9, 127.8, 126.3, 107.4, 73.9, 70.8, 69.1, 59.9, 58.6, 53.9, 31.4, 15.7. IR (neat) 2978, 2359, 1790, 1753 cm^{-1}.

General Procedure for Dibal Reductions. The starting material was dissolved in CH_2Cl_2 and dried with $MgSO_4$. The mixture is filtered through Celite into a flame-dried flask. The solution was purged with Ar and then cooled to −78 °C. A 1.3 equiv amount of Dibal was added dropwise via syringe. The reaction was stirred at −78 °C for 1 h. The reaction was monitored by TLC and more Dibal was added, as needed, in portions of 0.5 equiv until there is no starting material present by TLC. 3 equiv of pyridine, 2 equiv of DMAP, and 4 equiv of Ac_2O were added, respectively, and the reaction was warmed to 0 °C. The ice bath was allowed to warm to room-temperature overnight, and then the solution was quenched with Rochelle's salt, extracted with CH_2Cl_2, dried, and concentrated. The crude mixture was purified by flash column chromatography (hexane/EtOAc).

(5*S*)-2-Acetoxy-5-(benzyloxymethyl)-5-ethoxy-2,5-dihydrofuran (10). Acetate **10** was prepared by using the general

procedure to give 66 mg (0.23 mmol, 85%) as a 1:1 mixture of diastereomers and as a yellow oil: ^{1}H NMR δ 7.38−7.26 (m, 5H), 6.89 (s, 0.5H), 6.75 (s, 0.5H), 6.23−6.11 (m, 2H), 4.64 (s, 1H), 4.6 (s, 1H), 3.77 (d, J = 12.5 Hz, 0.5H), 3.73 (d, J = 12.3 Hz, 0.5H), 3.56 (d, J = 15.9 Hz, 0.5H), 3.53 (d, J = 16.2 Hz, 0.5H), 3.65−3.3 (m, 2H), 2.1 (s, 1.5H), 2.03 (s, 1.5H), 1.19 (t, J = 7 Hz, 3H); ^{13}C NMR δ 170.5, 170.1, 138.4, 138.2, 134.5, 133.7, 130.3, 130.2, 128.5, 128.4, 127.8, 127.6, 115.2, 114.2, 100.7, 99, 74.1, 73.8, 73.7, 73.6, 58.8, 58.4, 21.3, 21.2, 15.5, 15.4; IR (neat) 2975, 2932, 2866, 2358, 2336, 1748 cm^{-1}; FAB-LRMS calcd for $C_{14}H_{17}O_3$ (M − OAc): 233.13, found 233.13.

(4′*S*)-5′-*O*-Benzyl-4′-ethoxy-2′,3′-dideoxydidehydrothymidine (11). A two-necked flask was charged with thymine (16.6 mg, 0.132 mmol) and 2.5 mL CH_3CN. *N*,*O*-Bis(trimethylsilyl)acetamide (0.065 mL, 0.26 mmol) was added via syringe, and the mixture was stirred for 30 min. The solution went from a cloudy white suspension to a clear solution. Acetate **10** (35 mg, 0.12 mmol) was added dissolved in 1 mL of CH_3CN and the solution was cooled to 0 °C. $SnCl_4$ (15 μL, 0.13 mmol) was added via syringe down the sidearm of the flask to precool the solution. The solution was stirred at 0 °C for ∼20 min until no starting material was present by TLC (silica gel, 4:1 hexane/EtOAc). The reaction was quenched cold with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, dried with $MgSO_4$, and concentrated. The crude residue was purified by flash column chromatography (100% EtOAc → 100% MeOH gradient elution). The fractions were collected, concentrated, dissolved in CH_2Cl_2, and filtered to removed any silica particles. Coupled **11** (27 mg, 0.075 mmol, 63%) was obtained as a separable mixture of anomers: α-Anomer: ^{1}H NMR δ 9.74 (s, 1H), 7.4−7.25 (m, 5H), 6.93 (s, 1H), 6.38 (dd, J = 1.1 Hz, 5.6 Hz, 1H), 6.02 (dd, J = 0.8 Hz, 5.8 Hz, 1H), 4.61 (d, J = 12 Hz, 1H), 4.56 (d, J = 12 Hz, 1H), 3.83 (d, J = 10.5 Hz, 1H), 3.7−3.35 (m, 2H), 3.48 (d, J = 10.5 Hz, 1H), 1.9 (s, 3H), 1.18 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 164.2, 151.3, 137.7, 136.1, 133.9, 129, 128.6, 128, 127.8, 112.5, 111.4, 87.86, 73.69, 70.71, 58.86, 15.53, 12.57. β-Anomer: ^{1}H NMR δ 9.69 (s, 1H), 7.53 (s, 1H), 7.4−7.25 (m, 5H), 7.13 (s, 1H), 6.12 (s, 2H), 4.56 (s, 2H), 3.73 (s, 2H), 3.7−3.35 (m, 2H), 1.47 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 164.2, 151.1, 137.4, 136.4, 135.5, 131.3, 128.7, 128.2, 127.9, 114.2, 111.2, 88.67, 73.74, 72.9, 57.85, 15.33, 11.93. IR (neat) 1695 cm^{-1}. Anal. Calcd for $C_{19}H_{22}N_2O_5$: C, 63.67; H, 6.18; N, 7.82. Found: C, 63.62; H, 6.07; N, 7.58.

(4′*S*)-4′-Ethoxy-2′,3′-dideoxythymidine (6). A solution of coupled **11** (11 mg, 0.030 mmol) in MeOH (2 mL) was stirred over 20% $Pd(OH)_2$/C (4 mg) under an H_2 atmosphere (1 atm) for 1 h. Argon was bubbled through the solution. Filtration of the reaction mixture through Celite and removal of solvent afforded **6** as a white solid and as a 1:1 mixture of diastereomers (7.0 mg, 0.047 mmol, 88%): ^{1}H NMR δ 9.1 (s, 1H), 9.05 (s, 1H), 7.43 (d, J = 1.1 Hz, 1H), 7.34 (d, J = 1.1 Hz, 1H), 6.45 (t, J = 6.6 Hz, 1H), 6.26 (d, J = 4.2 Hz, 0.5H), 6.24 (d, J = 3.8 Hz, 0.5H), 3.9−3.5 (m, 8H), 2.7−2 (m, 8H), 1.95 (s, 1.5H), 1.9 (s, 1.5H), 1.24 (t, J = 6.9 Hz, 1.5H), 1.17 (t, J = 7 Hz, 1.5H)); ^{13}C NMR (400 MHz) δ 163.8, 163.7, 150.8, 150.4, 136.0, 135.8, 111.4, 109.9, 109.8, 86.3, 86.1, 63.0, 62.6, 57.7, 57.6, 33.1, 31.6, 30.8, 30.0, 15.7, 15.6, 12.6; IR (neat) 3430, 1692 cm^{-1}; FAB−HRMS calcd for $C_{12}H_{18}N_2O_5$ (M + 1): 271.1294, found 271.1289.

(5*S*)-5-Ethoxy-5-(hydroxymethyl)-5*H*-furan-2-one (12). (−)-5-(Benzyloxymethyl)-5-ethoxy-5*H*-furan-2-one (**5**) (16 mg, 0.064 mmol) was dissolved in 1.5 mL of CH_2Cl_2 and cooled to −78 °C. BCl_3 (0.2 mL, 0.2 mmol) was added via syringe, and the solution was stirred for 20 min. The reaction was quenched cold with MeOH, and saturated aqueous $Na_2S_2O_3$ was added. The mixture was extracted with CH_2Cl_2, dried, and concentrated. The crude residue was purified by flash column chromatography (2:1 hexane/EtOAc) to yield alcohol **12** (8.4 mg, 0.053 mmol, 82%): $[\alpha]^{25}_D$ −59° (c = 1.13, $CHCl_3$); ^{1}H NMR δ_7.27 (d, J = 6.8 Hz, 1H), 6.27 (d, J = 5.6 Hz, 1H), 3.87 (dd, J = 6.4 Hz, J = 11.6 Hz, 1H), 3.73 (dd, J = 7.2 Hz, J = 11.6 Hz, 1H), 3.54, (m, 1H), 3.39 (m, 1H), 2.02 (t, J = 7.2 Hz, 1H), 1.19 (t, J = 6.8 Hz, 3H); ^{13}C NMR δ 169.6, 152.4, 125.8, 109.5, 65.4, 60.0, 15.1; IR (neat) 3432, 1765 cm^{-1}; FAB−HRMS calcd for $C_7H_{10}O_4$ (M + 1): 159.0657, found 159.0653.

(5*S*)-5-Ethoxy-5-(triethylsilanyloxymethyl)-5*H*-furan-2-one (13). Alcohol **12** (20.5 mg, 0.130 mmol) was dissolved in 2 mL of DMF. DMAP (15.8 mg, 0.130 mmol), imidazole (21.2 mg, 0.311 mmol), and TESCl (0.030 mL, 0.16 mmol) were added, and the mixture was stirred at room temperature for 12 h. The reaction was quenched with saturated aqueous NH_4Cl, extracted with CH_2Cl_2, washed with brine, dried with $MgSO_4$, and concentrated. The crude oil was purified by flash column chromatography (10:1 hexane/EtOAc) to yield TES protected alcohol **13** (34.9 mg, 0.128 mmol, 99%) as a yellow oil: $[\alpha]^{25}_D$ −55° (c = 0.74, CH_2Cl_2); ^{1}H NMR δ 7.16 (d, J = 6.0 Hz, 1H), 6.21 (d, J = 5.4 Hz, 1H), 3.89 (d, J = 10.8 Hz, 1H), 3.77 (d, J = 10.8 Hz, 1H), 3.52, (m, 1H), 3.38 (m, 1H), 1.17 (t, J = 6.9 Hz, 3H), 0.90 (t, J = 3.7 Hz, 9H), 0.55 (q, J = 7.7 Hz, 6H); ^{13}C NMR δ 169.8, 152.4, 125.5, 110.1, 65.1, 59.9, 15.2, 6.7, 4.4; IR (neat) 1772, 1082 cm^{-1}; FAB−HRMS calcd for $C_{13}H_{24}O_4Si$ (M + 1): 273.1522, found 273.1518.

(5*S*)-2-Acetoxy-5-ethoxy-5-(triethylsilanyloxymethyl)-2,5-dihydrofuran (14). Acetate **14** (12.9 mg, 0.0408 mmol, 68%) was prepared by using the general procedure. The yellow oil was a 1:1 mixture of diastereomers: ^{1}H NMR δ 6.84 (s, 1H), 6.63 (s, 1H), 6.10 (m, 4H), 3.80 (m, 2H), 3.61, (m, 3H), 3.37 (m, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 1.16 (t, J = 6.9 Hz, 3H), 1.15 (t, J = 6.9 Hz, 3H), 0.92 (m, 18H), 0.58 (m, 12H); ^{13}C NMR δ 170.5, 170.1, 134.4, 133.6, 130.1, 129.9, 115.8, 114.8, 100.6, 99.0, 67.3, 66.5, 58.7, 58.2, 53.9, 21.2, 15.3, 15.2, 6.7, 4.4, 4.4.; IR (neat) 1751 cm^{-1}; FAB-LRMS calcd for $C_{13}H_{26}O_3Si$ (M-OAc): 257.17, found 257.15.

(5′*S*)-5′-Ethoxy-5′-*O*-triethylsilanyl-2′,3′-dideoxydidehydrothymidine (15). Protected nucleoside analogue **15** (80.8 mg, 0.211 mmol, 67%) was prepared by using the procedure for protected nucleoside analogue **11**. The anomers were separated by preparative TLC (2:1 hexane/EtOAc × 2). high R_f anomer: ^{1}H NMR δ 8.24 (bs, 1H), 7.27 (s, 1H), 6.87 (s, 1H) 6.33 (dd, J = 1.2 Hz, J = 5.7 Hz, 1H), 6.04 (dd, J = 0.9 Hz, J = 5.4 Hz 1H), 3.93 (d, J = 10.5 Hz, 1H), 3.65 (m, 3H), 1.91 (s, 3H), 1.12 (t, J = 6.9 Hz, 3H), 0.96 (t, J = 7.8 Hz, 9H), 0.62 (q, J = 7.8 Hz, 6H); low rf anomer: ^{1}H NMR δ 8.70 (bs, 1H), 7.50 (s, 1H), 7.06 (s, 1H) 6.14 (d, J = 6.0 Hz, 1H), 6.06 (d, J = 6.3 Hz, 1H), 3.84 (s, 2H), 3.50 (m, 1H), 3.39 (m, 1H), 1.91 (s, 3H), 1.19 (t, J = 6.9 Hz, 3H), 0.96 (t, J = 8.1 Hz, 9H), 0.63 (q, J = 7.8 Hz, 6H); ^{13}C NMR δ 163.5, 150.6, 135.8, 133.7, 130.8, 115.2, 110.7, 88.7, 65.8, 57.9, 15.3, 12.6, 6.8, 4.3; both anomers ^{13}C NMR δ 163.9, 150.9, 150.7, 135.9, 135.8, 135.0, 133.5, 130.9, 128.9, 115.1, 113.3, 111.1, 110.7, 88.7, 87.7, 65.8, 64.1, 58.7, 57.8, 15.5, 15.3, 12.5, 6.8, 6.7, 4.4, 4.3; IR (neat) 3187, 3058, 1699 cm^{-1}; FAB−HRMS calcd for $C_{18}H_{31}N_2O_5Si$ (M + H): 383.2002, found 383.2004.

(4′*S*)-4′-Ethoxy-2′,3′-dideoxydidehydrothymidine (7). Protected nucleoside analogue **15** (42.8 mg, 0.112 mmol) was dissolved in 4 mL of THF and then cooled to 0 °C. TBAF (1 M) in THF (0.12 mL, 0.12 mmol) was added via syringe. The reaction was stirred at 0 °C until no starting material was present (∼10 min) by TLC (silica gel, EtOAc). The reaction was concentrated and purified by preparative TLC (100% EtOAc) to yield both anomers of **7** as clear oils. The stereochemistry of the anomers was determined by 2D spectroscopy and NOE studies (see Supporting Information). (1*R*,4*S*) anomer: (8.7 mg, 0.032 mmol, 29%): $[\alpha]^{25}_D$ +88° (c = 0.35, $CHCl_3$); ^{1}H NMR δ 8.30 (bs, 1H), 7.35 (s, 1H), 7.12 (s, 1H), 6.23 (dd, J = 6.0 Hz, J = 1.8 Hz, 1H), 6.16 (d, J = 5.7 Hz, 1H), 3.87 (d, J = 11.7 Hz, 1H), 3.78 (d, J = 12.9 Hz, 1H), 3.52 (m, 1H), 3.41 (m, 1H), 2.29 (bs, 1H), 1.88 (s, 3H), 1.20 (t, J = 7.5 Hz, 3H); $_{13}$C NMR δ 163.4, 150.6, 135.8, 134.4, 130.8, 114.7, 111.2, 89.0, 65.9, 58.2, 15.2, 12.4; IR (neat) 3447, 3177, 3057, 1695 cm^{-1}; FAB−HRMS calcd for $C_{12}H_{17}N_2O_5$ (M + H): 269.1137, found 269.1138. (1*S*,4*S*) anomer: (9.2 mg, 0.034 mmol, 30%): $[\alpha]^{25}_D$ −66° (c = 0.31, $CHCl_3$); ^{1}H NMR (400 MHz) δ 8.92 (bs, 1H), 7.21 (d, J = 1.2 Hz, 1H), 6.94 (d, J = 1.6 Hz, 1H), 6.37 (dd, J = 6.0 Hz, J = 2.0 Hz, 1H), 6.11 (dd, J = 5.6 Hz, J = 1.6 Hz,

1H), 3.84 (dd, $J = 5.6$ Hz, $J = 11.6$ Hz, 1H), 3.75 (dd, $J = 5.2$ Hz, $J = 11.6$ Hz, 1H), 3.62 (q, $J = 7.2$ Hz, 2H), 2.35 (t, $J = 5.6$ Hz, 1H), 1.92 (d, $J = 1.2$ Hz, 3H), 1.20 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR δ 163.6, 150.8, 135.7, 135.2, 129.3, 113.4, 111.4, 87.7, 64.2, 59.0, 15.5, 12.5; IR (neat) 3421, 1696 cm^{-1}; FAB−HRMS calcd for $C_{12}H_{17}N_2O_5$ (M + H): 269.1137, found 269.1135; Anal. Calcd for $C_{19}H_{16}N_2O_5$: C, 53.73; H, 6.01; N, 10.44. Found: C, 53.96; H, 6.07; N, 10.21.

(3*S*,4*R*,5*S*)-5-(Benzyloxymethyl)-3,4-diol-5-ethoxy-dihydrofuran-2-one cyclohexanonide (20). Dry (3*S*,4*R*,5*S*)-lactone **19**[16](4.3 mg, 0.012 mmol) was dissolved in 0.5 mL of CH_2Cl_2 and cooled to −78 °C. Et_2AlCl (0.02 mL, 0.024 mmol) was added via syringe. The solution was stirred at −78 °C for 2 h. The reaction was quenched with cold saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, dried, and concentrated. Purification by preparative TLC (10:1 hexane:EtOAc × 2) gave **19** (3.3 mg, 0.0090 mmol) and epimerized **20** (1.0 mg, 0.0027 mmol). ^{1}H NMR spectrum matches the spectrum for its enantiomer synthesized by a known method:[16] ^{1}H NMR δ 7.40 (m, 3H), 7.25 (m, 2H), 4.90 (d, $J = 6.0$ Hz, 1H), 4.71 (d, $J = 5.7$ Hz, 1H), 4.60 (d, $J = 11.7$ Hz, 1H), 4.50 (d, $J = 11.7$ Hz, 1H), 4.00 (m, 1H), 3.85 (m, 1H), 3.72 (d, $J = 9.9$ Hz, 1H), 3.69 (d, $J = 9.6$ Hz, 1H), 1.70 (m, 10H), 1.23 (t, $J = 6.9$ Hz, 3H).

(3*S*,4*R*,5*R*)-5-(Benzyloxymethyl)-3,4-diol-5-ethoxydihydrofuran-2-one acetonide (21). A flask, equipped with reflux condenser and Soxhlett extractor containing 4 Å molecular sieves, was charged with diol **16**-β (32.3 mg, 0.114 mmol), 2,2-dimethoxypropane (0.25 mL, 2.9 mmol), and 15 mL of benzene. The solution was warmed to reflux, and a few crystals of TsOH were added. The reaction was kept at reflux for 30 min and then cooled to room temperature. The organic layer was washed with saturated aqueous $NaCO_3$ (×2) and DI H_2O (×2), dried, and concentrated to give pure acetonide **21** (35.5 mg, 0.110 mmol, 96%) as a colorless oil: $[\alpha]^{25}_D$ +12° ($c = 0.72$, $CHCl_3$); IR (thin film) ν_{max} 1799 cm^{-1}; ^{1}H NMR δ 7.37 (m, 5H), 4.90 (d, $J = 5.1$ Hz, 1H), 4.70 (d, $J = 12.1$ Hz, 1H), 4.61 (d, $J = 4.8$ Hz, 1H), 4.60 (d, $J = 12.5$ Hz, 1H), 3.85 (d, $J = 11.0$ Hz, 1H), 3.72 (d, $J = 11.0$ Hz, 1H), 3.69 (q, $J = 7.0$ Hz, 2H), 1.44 (s, 3H), 1.41 (s, 3H), 1.18 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR δ 173.6, 137.3, 127.9, 127.8, 114.5, 106.3, 79.3, 75.8, 73.6, 64.1, 59.0, 26.8, 26.1, 15.1; Anal. Calcd for $C_{16}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.16; H, 7.00.

(2*S*,3*S*,4*R*,5*R*)-2-Acetoxy-5-(benzyloxymethyl)-3,4-diol-5-ethoxytetrahydrofuran Acetonide (22). Acetate **22** (37.8 mg, 0.103 mmol, 94% yield) was prepared by using the general procedure: $[\alpha]^{25}_D$ +19° ($c = 0.655$, $CHCl_3$); ^{1}H NMR δ 7.34 (m, 5H), 5.94 (d, $J = 4.0$ Hz, 1H), 4.92 (dd, $J = 3.4$ Hz, $J = 5.4$ Hz, 1H), 4.68 (d, $J = 12.3$ Hz, 1H), 4.59 (d, $J = 5.4$ Hz, 1H), 4.58 (d, $J = 12.9$ Hz, 1H), 3.74 (d, $J = 10.8$ Hz, 1H), 3.68 (d, $J = 10.5$ Hz, 1H), 3.58 (m, 2H), 2.15 (s, 3H), 1.49 (s, 3H), 1.38 (s, 3H), 1.18 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR δ 168.9, 137.7, 128.2, 127.9, 127.6, 113.8, 105.6, 96.6, 82.5, 78.5, 73.4, 65.0, 57.1, 26.0, 25.7, 20.9, 15.4; IR (neat) 1748.5 cm^{-1}; FAB−HRMS calcd for $C_{19}H_{26}O_7$ (M + H): 367.1757, found 367.1758.

(3*S*,4*R*,5*R*)-5-(Benzyloxymethyl)-5-ethoxy-2,3,4-triacetoxytetrahydrofuran (23). Acetate **23** was prepared by using the general procedure except 3.3 equiv of Dibal was added at the beginning of the reaction and then 6 equiv of pyridine, 2.2 equiv of DMAP, and 8 equiv of Ac_2O were used. The ^{1}H NMR spectrum of the crude material indicated a 0.6:1 mixture of anomeric acetates which were separated by flash chromatography on SiO_2, eluting with 2:5 EtOAc/hexane to give **23**: anomer 1 of **23** (14 mg, 0.034 mmol, 22%): ^{1}H NMR δ 7.30 (m, 5H), 6.18 (d, $J = 4.1$ Hz, 1H), 5.71 (dd, $J = 4.9$, $J = 4.1$ Hz, 1H), 5.43 (d, $J = 4.9$ Hz, 1H), 4.58 (d, $J = 12.2$ Hz, 1H), 4.43 (d, $J = 12.2$ Hz, 1H), 3.63 (d, $J = 10.7$ Hz, 1H), 3.60 (m, 2H), 3.54 (d, $J = 10.7$ Hz, 1H), 2.09 (s, 3H), 2.01 (s, 3H), 1.93 (s, 3H), 1.20 (t, $J = 7.1$ Hz, 3H); anomer 2 of **23** (20 mg, 0.049 mmol, 31%): ^{1}H NMR δ 7.27−7.38 (m, 6H), 6.34 (d, $J = 5.0$ Hz, 1H), 5.55 (t, $J = 5.0$ Hz, 1H), 5.42 (d, $J = 5.0$ Hz, 1H), 4.58 (d, $J = 12.2$ Hz, 1H), 4.45 (d, $J = 12.2$ Hz, 1H), 3.68 (d, $J = 10.6$ Hz, 1H), 3.59 (d, $J = 10.6$ Hz, 1H), 3.54−3.65 (m, 2H), 2.05 (s, 3H), 2.02 (s, 3H), 1.97 (s, 3H), 1.18 (t, $J = 7.1$ Hz, 3H); IR (thin film) ν_{max} 2933, 1753 cm^{-1}. Anal. Calcd for $C_{20}H_{26}O_9$; C, 58.53; H, 6.39. Found; C, 58.35; H, 6.15. Also obtained was 2,3-diacetoxy lactone (6.0 mg, 0.016 mmol, 15%) as a colorless oil: ^{1}H NMR δ 7.37−7.27 (m, 5H), 5.94 (d, $J = 4.9$ Hz, 1H), 5.53 (d, $J = 4.9$ Hz, 1H), 4.60 (d, $J = 12.1$ Hz, 1H), 4.46 (d, $J = 12.1$ Hz, 1H), 3.83 (d, $J = 10.8$ Hz, 1H), 3.71 (m, 2H), 3.65 (d, $J = 10.8$ HZ, 1H), 2.11 (s, 3H), 1.93 (s, 3H), 1.22 (t, $J = 7.1$ Hz, 3H).

(4*R*,5*R*)-5-(Benzyloxymethyl)-5-ethoxy-4-hydroxydihydrofuran-2-one (24). Acetonide **21** (50 mg, 0.16 mmol) was dissolved in THF (2 mL), and dry ethylene glycol (0.1 mL) was added. This solution was degassed by freeze−pump−thaw (3 cycles). A degassed solution of SmI_2 (9 mL, 0.17 M in THF)[19] was added via cannula, and the resulting mixture was stirred at room temperature for 0.5 h before quenching by addition of saturated aqueous $NaHCO_3$. The mixture was extracted with Et_2O (2 × 40 mL). The organic phase was washed with 10% $Na_2S_2O_3$ solution, washed with brine, dried, and evaporated to give a pale brown oil. Flash column chromatography of the crude product (1:4 EtOAc/hexane) gave lactone **24** (38.1 mg, 0.143 mmol, 92%) as a colorless oil: $[\alpha]^{25}_D$ −20° ($c = 0.44$, $CHCl_3$); ^{1}H NMR δ 7.39 (m, 5H), 4.64 (d, $J = 12.1$ Hz, 1H), 4.58 (d, $J = 11.8$ Hz, 1H), 4.37 (ddd, $J = 1.5$ Hz, $J = 3.7$ Hz, $J = 6.2$ Hz, 1H), 3.95 (d, $J = 10.6$ Hz, 1H), 3.76 (d, $J = 10.6$ Hz, 1H), 3.60 (m, 2H), 2.96 (ddd, $J = 1.1$, $J = 6.2$ Hz, $J = 18.0$ Hz, 1H), 2.67 (dd, $J = 1.1$ Hz, $J = 3.7$ Hz, 1H), 2.46 (dd, $J = 1.5$ Hz, $J = 18.3$ Hz, 1H), 1.18 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR δ 174.6, 136.8, 128.7, 128.4, 128.0, 109.4, 73.7, 72.6, 65.2, 58.7, 36.6, 15.3; IR (neat) ν_{max} 3455, 1795 cm^{-1}; FAB−HRMS calcd for $C_{14}H_{18}O_5$ (M + H): 267.1232, found 267.1239.

(4*R*,5*R*)-5-(Benzyloxymethyl)-2,4-diacetoxy-5-ethoxytetrahydrofuran (25). Acetate **25** was prepared by using the general procedure except Dibal (2.3 equiv) was only added at the beginning of the reaction, the reaction stirred at −78 °C for 3 h, and then 4 equiv of pyridine, 2 equiv of DMAP, and 8 equiv of Ac_2O were added. Flash column chromatography of the crude product (1:8 EtOAc/hexane) gave the impure diacetate **25** (14 mg, 0.040 mmol, 39%) as a colorless oil (5:1 mixture of anomers): ^{1}H NMR major anomer δ 7.33 (m, 5H), 6.27 (d, $J = 5.9$ Hz, 1H), 5.18 (d, $J = 5.1$ Hz, 1H), 4.61 (d, $J = 12.1$ Hz, 1H), 4.50 (d, $J = 12.4$ Hz, 1H), 3.72 (d, $J = 10.3$ Hz, 1H), 3.64 (d, $J = 10.6$ Hz, 1H), 3.60 (m, 2H), 2.75 (dt, $J = 5.5$ Hz, $J = 15.0$ Hz, 1H), 2.05 (s, 3H), 1.96 (s, 3H), 1.17 (t, $J = 7.0$ Hz, 3H); minor anomer 6.38 (dd, $J = 6.3$ Hz, $J = 4.5$ Hz, 1H), 5.33 (dd, $J = 5.7$ Hz, $J = 1.7$ Hz, 1H), 2.56 (ddd, $J = 14.7$ Hz, $J = 5.7$ Hz, $J = 4.5$ Hz, 1H), 2.31 (ddd, $J = 14.7$ Hz, $J = 6.3$ Hz, $J = 1.7$ Hz, 1H), 2.07 (s, 3H), 1.91 (s, 3H); both anomers ^{13}C NMR δ 169.8, 169.4, 137.7, 127.9, 127.7, 127.6, 109.6, 109.1, 97.5, 97.3, 74.7, 74.5, 73.5, 65.4, 65.1, 57.1, 57.0, 37.9, 37.3, 21.2, 21.0, 21.0, 20.8, 15.4, 15.2; IR (thin film) ν_{max} 1749 cm^{-1}; FAB-LRMS calcd for $C_{16}H_{21}O_5$ (M − OAc): 293.15, found 293.14.

(4*R*,5*R*)-5-Ethoxy-4-hydroxy-5-(hydroxymethyl)dihydrofuran-2-one (26). Lactone **25** (30.3 mg, 0.114 mmol) was dissolved in 2.5 mL of EtOH and stirred over 10% Pd/C (15 mg) under a H_2 atmosphere (1 atm) until no starting material was present (∼1 h) by TLC (silica gel, 1:1 hexane:EtOAc). Argon was bubbled through the solution. The solution was filtered through Celite and then concentrated to give dialcohol **26** (20 mg, 0.11 mmol) in quantitative yield as a colorless oil: $[\alpha]^{25}_D$ −3° ($c = 0.5$, $CHCl_3$); ^{1}H NMR δ 4.44 (ddd, $J = 1.6$ Hz, $J = 3.6$ Hz, $J = 5.6$ Hz, 1H), 4.11 (dd, $J = 4.0$ Hz, $J = 12.0$ Hz, 1H), 3.97 (dd, $J = 7.6$ Hz, $J = 12.0$ Hz, 1H), 3.70 (m, 2H), 3.01 (dd, $J = 6.4$ Hz, $J = 18.0$ Hz, 1H), 2.83 (d, $J = 3.6$ Hz, 1H), 2.52 (dd, $J = 1.6$ Hz, $J = 18.4$ Hz, 1H), 1.97 (t, $J = 4.9$ Hz, 1H), 1.22 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR δ 174.9, 109.7, 72.5, 59.0, 58.8, 37.1, 15.4 cm^{-1}; IR (neat) 3421, 1772; FAB−HRMS calcd for $C_7H_{12}O_5$ (M + H): 177.0763, found 177.0756.

(4*R*,5*R*)-4,6-Diol-5-ethoxydihydrofuran-2-one Acetonide (27). Lactone **27** was prepared by using the procedure for acetonide **21**. Lactone **27** (11.4 mg, 0.0527 mmol, 59%) was

obtained as a clear oil: $[\alpha]^{25}_D$ +5° (c = 0.57, CH_2Cl_2); ^{1}H NMR δ 4.27 (d, J = 5.4 Hz, 1H), 4.07 (d, J = 12.9 Hz, 1H), 3.99 (d, J = 12.3 Hz, 1H), 3.65 (m, 2H), 2.94 (dd, J = 5.4 Hz, J = 18.0 Hz, 1H), 2.46 (d, J = 18.0 Hz, 1H), 1.48 (s, 3H), 1.38 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 175.0, 103.7, 99.2, 70.8, 61.6, 58.6, 35.2, 26.4, 21.0, 15.5; IR (neat) 1799 cm^{-1}; FAB−HRMS calcd for $C_{10}H_{16}O_5$ (M + H): 217.1076, found 217.1073.

(4*R*,5*R*)-2-Acetoxy-4,6-diol-5-ethoxydihydrofuran-2-one Acetonide (28). Acetate **28** (20.7 mg, 0.0795 mmol, 54% yield) was prepared by using the general procedure and obtained as a 1:1 mixture of diastereomers and as a clear oil: ^{1}H NMR δ 6.53 (dd, J = 4.8 Hz, J = 6.2 Hz, 1H), 6.35 (d, J = 5.7 Hz, 1H), 4.24 (d, J = 5.1 Hz, 1H), 4.15 (d, J = 5.4 Hz, 1H), 3.97 (d, J = 12.5 Hz, 1H), 3.97 (s, 2H), 3.91 (d, J = 12.5 Hz, 1H), 3.63 (m, 2H), 3.48 (m, 2H), 2.58 (dt, J = 5.5 Hz, J = 20.1 Hz, 1H), 2.38 (m, 3H), 2.13 (s, 3H), 2.10 (s, 3H), 1.47 (s, 3H), 1.46 (s, 3H), 1.41 (s, 3H), 1.37 (s, 3H), 1.18 (t, J = 6.0 Hz, 3H), 1.16 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 170.1, 104.9, 103.5, 99.0, 98.7, 98.4, 98.3, 74.7, 73.1, 63.2, 62.5, 57.3, 56.9, 38.0, 37.3, 27.5, 27.0, 21.4, 21.2, 20.7, 20.1, 15.7, 15.5; IR (neat) 1749 cm^{-1}; FAB−HRMS calcd for $C_{10}H_{17}O_4$ (M − OAc): 201.1127, found 201.1127.

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Supporting Information Available: ^{1}H NMR spectra for compounds **20** and **23**; ^{1}H and ^{13}C NMR spectra for compounds **4c**, **6**, (1*S*,4*S*)-**7**, (1*R*,4*S*)-**7**, **10**, **12**, **13**, **14**, **15, 21, 22**, **24**, **26**, **27**, and **28**; NOE spectra for compounds (1*S*,4*S*)-**7** and (1*R*,4*S*)-**7**; ^{1}H−^{1}H 2D (COSY) spectra for compounds (1*S*,4*S*)-**7** and (1*R*,4*S*)-**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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