Synthesis and Evaluation of Multisubstrate Bicyclic Pyrimidine Nucleoside Inhibitors of Human Thymidine Phosphorylase

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A series of novel, multisubstrate, bicyclic pyrimidine nucleoside inhibitors of human thymidine phosphorylase (TP) is described. Thymidine phosphorylase has been implicated in angiogenesis and plays a significant role in tumor progression and metastasis. The presence and orientation of the phosphonate moiety (acting as a phosphate mimic) in these derivatives were critical for inhibitory activity. The most active compounds possessed a phosphonate group in an endo orientation. This was consistent with molecular modeling results that showed the endo isomer protein−ligand complex to be lower in energy than the exo complex.

Introduction

Tumor growth and metastasis are processes dependent on angiogenesis.[1−3] Inhibition of the formation of new blood vessels within a tumor has become one of the most active areas of research for the discovery of new cancer therapeutics.[4−6] Thymidine phosphorylase (TP[a]) has received considerable attention from several research groups, as reviewed by Cole et al. and others.[7−10] Specifically, TP has been shown to be identical to platelet-derived endothelial cell growth factor (PD-ECGF),[11−14] which has been implicated in angiogenesis and chemotaxis in human tumors.[15,16] Increased hypoxia correlates with elevated TP activity, and increased levels of this enzyme have been observed in colorectal, ovarian, pancreatic, and breast tumors.[10,17] It has been postulated that inhibition of TP would reduce tumor growth and metastasis by interfering with angiogenesis in tumor tissues.[18,19] Overexpression of TP has also been implicated in other hyperproliferative disease states including rheumatoid arthritis[20] and psoriasis.[21]

TP catalyzes the reversible phosphorolysis of thymidine to thymine and 2-deoxyribose 1-phosphate (Scheme 1).[22,23] The phosphorylated sugar product is further converted to 2-deoxy-D-ribose, which is thought to be responsible for the chemotactic activity of TP in vitro and the angiogenic activity of TP in vivo.[12,13] In addition, TP recognizes and inactivates a variety of 5-substituted pyrimidine 2′-deoxynucleoside derivatives with antitumor/antivirus activities, including 5-fluoro-2′-deoxyuridine and 5-trifluoromethyl-2′-deoxyuridine.[24]

X-ray crystallographic studies of the homologous pyrimidine nucleoside phosphorylase (PyNP)[25−27] and the functionally similar purine nucleoside phosphorylase (PNP)[28,29] suggest that large-scale conformational changes are required to bring the separate binding sites for the phosphate and the nucleoside into proximity, which is required for catalysis. Recently, Birck and Schramm determined through a study of kinetic isotope effects that human TP most likely proceeds through an S_N2-like transition state, unlike the dissociative transition states previously described for *N*-ribosyl transferases.[30] They suggest that the design of transition-state inhibitors would require mimics of the three components to be present: pyrimidine, 2′-deoxyribose, and the phosphate group.[30]

Relatively few TP inhibitors have been reported, and most are analogues of uracil or thymidine or analogues of nucleosides and acyclonucleosides.[31−42] To date, the most potent inhibitor of human TP is TPI (5-chloro-6-[1-(2-iminopyrrolidinyl)methyl]-uracil hydrochloride) (**1**) from Taiho Pharmaceutical Company with a K_i of 35 nM (Figure 1).[41,42] A combination of TPI and trifluorothymidine is currently in phase I clinical trials.[43,44] Recently, Freeman et al. have reported some aminoimidazolylmethyluracil analogues that are potent inhibitors of *E. coli* and human TP with IC_{50} values of about 20 nM.[45] However, the pharmacokinetic (PK) profiles were poor for these compounds and the nitro prodrugs that could be reduced to the amino inhibitors were also described.[45]

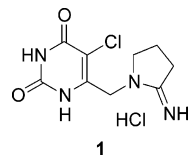

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Figure 1. Structure of Taiho Pharmaceutical inhibitor (TPI).

Multisubstrate inhibitors that bind to both the nucleoside and phosphate binding sites have not been extensively explored.[46,47] Multisubstrate inhibitors may have several advantages. There are fewer degrees of translational and rotational freedom being "frozen" upon binding of a multisubstrate inhibitor compared to the binding of two independent substrates. This corresponds to a lower entropic penalty for binding at the second site. In addition, these compounds have more points of interaction with the receptor compared to most single-substrate inhibitors, which improves the enthalpic contribution to binding. To our knowledge, all of the reported multisubstrate TP inhibitors have been tested for activity in *E. coli* TP assays but none have been tested against human TP.

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[a] Abbreviations: TP = Thymidine phosphorylase, PD-ECGF = Platelet-derived endothelial cell growth factor, TPI = Taiho Pharmaceutical Inhibitor

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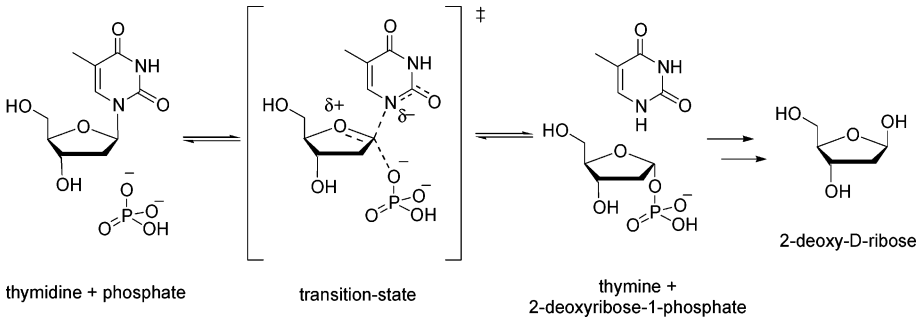
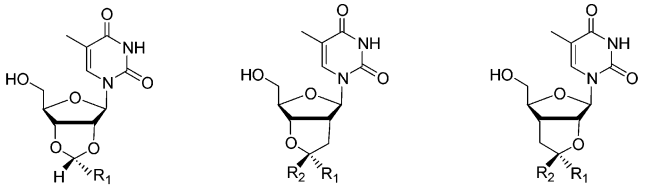
Scheme 1. Enzymatic Reaction Catalyzed by TP



Li and Ganem have reported a novel multisubstrate TP inhibitor **2**[48] (Table 1) that demonstrates nanomolar activity against human TP in an in vitro assay.[49] This nucleoside derivative contains an additional five-membered acetal ring fused to the ribose moiety. The acetal portion of the inhibitor bears an appended phosphonate group. In this report, we describe the synthesis of a novel series of multisubstrate analogues based on compound **2** and their activity against recombinant human TP (Table 1). Novel compounds **3**−**8** incorporate a nucleoside framework along with an acidic or polar group as the phosphate mimic. Since cell permeability is a common problem for phosphonates, we also evaluated alternatives to this moiety, including a carboxylic acid analogue **3** and an amide analogue **4**. In addition, concern over the potential lability of the acetal functionality in **2** encouraged us to assess the activity and stability of the 2′- and 3′-carbon analogues **5** and **7** and their corresponding diastereomers **6** and **8**. Finally, computational docking studies provided some insight into the binding orientation of these compounds, as well as the observed experimental trends in binding affinity.

Table 1. Inhibition of TP by Multisubstrate Analogues



2, $R_1 = CH_2PO_3H_2$
3, $R_1 = CH_2COOH$
4, $R_1 = CH_2CONH_2$

5, $R_1 = CH_2PO_3H_2$, $R_2 = H$
6, $R_1 = H$, $R_2 = CH_2PO_3H_2$

7, $R_1 = CH_2PO_3H_2$, $R_2 = H$
8, $R_1 = H$, $R_2 = CH_2PO_3H_2$

compd	K_i (μM)[a]
2	0.236 ± 0.007
3	43.5[b]
4	no inhibition
5	8.03 ± 0.18
6	>500
7	1.05 ± 0.07
8	33.4 ± 4.0

[a] Values represent the mean of at least three experiments. Standard deviations are also shown. [b] Sample set $n = 2$. Average is reported.

Results and Discussion

Synthesis. Analogues **3**−**8** were prepared from a common intermediate, 5-methyluridine (**9**), which was synthesized in two steps as previously reported.[50,51] Carboxylic acid **3** and amide **4** were prepared in a manner analogous to that for phosphonate **2**, as shown in Scheme 2.[48] 5′-Benzoyl protected 5-methyluridine **10** was treated with methyl 3,3-dimethoxypropionate in concentrated HCl to give ester **11**. The ester intermediate **11** was then converted to carboxylic acid **3** with LiOH or to amide **4** with ammonia in methanol. The endo diastereomer was the major product in both instances.

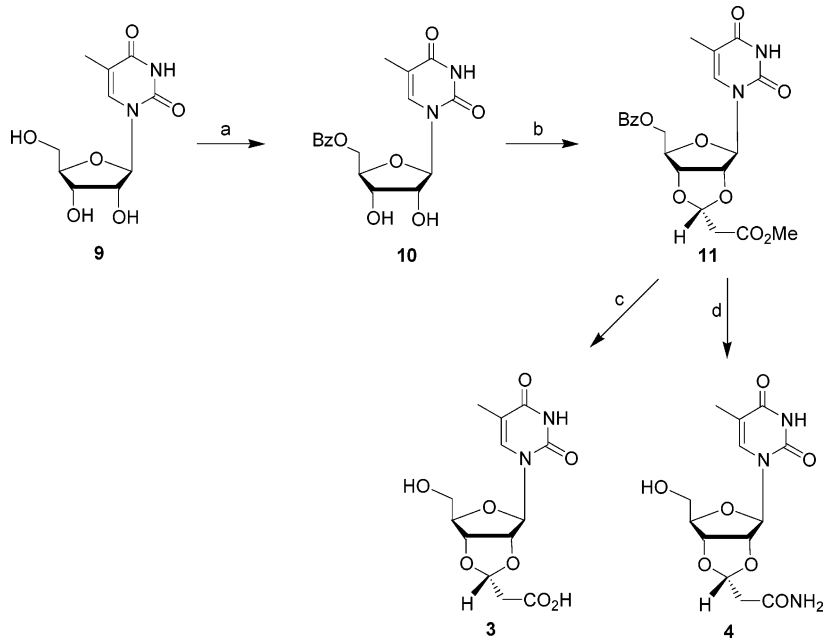
In order to generate the 2′-carbon (**5** and **6**; see Scheme 3) and 3′-carbon (**7** and **8**; see Scheme 4) analogues, a different synthetic strategy was used. Distinct protecting group strategies were employed in order to allow for the incorporation of a carbon moiety at either the 2′ or 3′ position. The synthesis of the 2′-carbon analogues (Scheme 3) began with the protection of the 3′- and 5′-hydroxyl groups as the disiloxane **12** using 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane.[52] This allowed the 2′-hydroxyl to be converted to the desired carbon moiety in a manner previously described by De Mesmaeker et al.[53]

Compound **12** (Scheme 3) was converted to the corresponding thioester with phenyl chlorothioformate, and the allyl group was incorporated at the 2′ position utilizing allyltributyltin and AIBN in benzene under photolysis conditions. A single diastereomer of **13** was isolated, as indicated by NMR analysis.[53] Allyl compound **13** was treated with osmium tetroxide to give a mixture of diols that underwent subsequent cleavage with sodium periodate to provide aldehyde **14**.[53] The Horner−Emmons−Wadsworth reaction followed by deprotection of the 3′,5′-disiloxane with TBAF gave the desired free diol **15** in excellent yield. Subsequent treatment with sodium methoxide in methanol induced the conjugate addition, affording the cyclized phosphonate esters **16** in a 3:1 diastereomeric mixture as evidenced by the integration of the vinyl protons in the ^{1}H NMR spectra. Addition of TMSBr to the mixture gave the phosphonic acids **5** and **6**, which were separated by preparative reverse-phase HPLC.

The synthesis of the 3′-carbon analogues (Scheme 4) began with the conversion of 5-methyluridine (**9**) to the completely protected glycoside **17** in two steps with di-*tert*-butylsilyl bis-(trifluoromethanesulfonate) (DiTBSOTf),[54] followed by TBSCl. Removal of the di-*tert*-butylsilyl group followed by protection of the 5′-alcohol gave **18**, which was converted to the thiocarbamate **19** with diimidazolethiocarbonyl. Allylation with allyltributyltin using photolytic conditions gave compound **20** in moderate yield.[53] Conversion to aldehyde **21** occurred smoothly upon treatment with osmium tetroxide followed by oxidative cleavage with sodium periodate.[53] Assembly of the cyclized phosphonate ester **22** was performed as described for the 2′-carbon analogue and proceeded in moderate yield over three steps. Finally, the ethyl groups of phosphonate ester **22** were removed with TMSBr and the 3:1 mixture of the desired diastereomeric products **8** and **7** was separated by preparative HPLC.

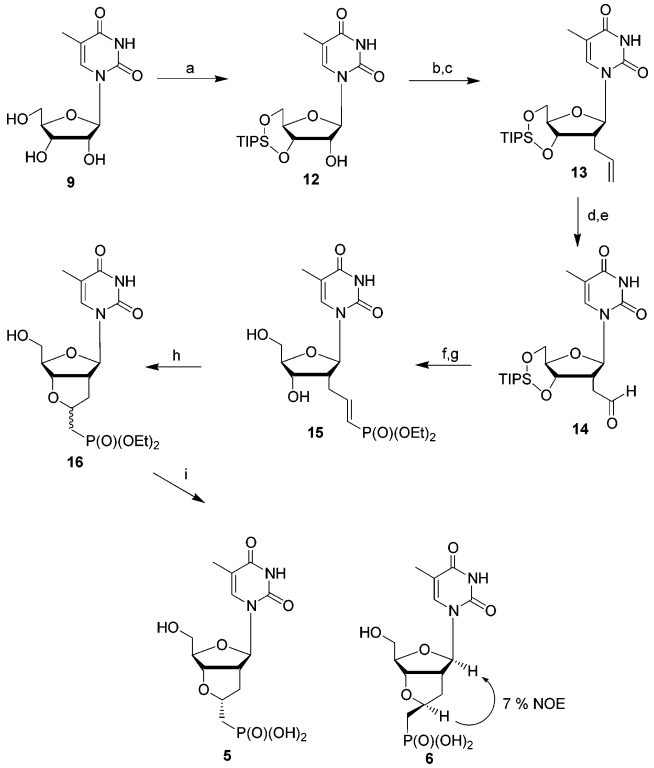
Stereochemistry Assignment. The stereochemistry of compound **2** was determined by a 2D ROESY NMR experiment, as reported by Ganem.[48] Cross-peaks were observed between the methine H adjacent to the phosphonate and the H_2 and H_3 on the ribose ring, indicating that **2** is the endo isomer. The 2′-carbon (**5** and **6**) and 3′-carbon (**7** and **8**) analogues were

Scheme 2. Synthesis of Carboxylic Acid **3** and Amide **4**[a]



[a] Reagents and conditions: (a) benzoic acid, Ph_3P, DIAD, 1,4-dioxane (92%);[48] (b) $H(CH_3O)_2CCH_2CO_2Me$, concentrated HCl, room temp, 16 h (43%); (c) LiOH, 1,4-dioxane, room temp, 1.5 h (47%); (d) 7 M NH_3/MeOH, room temp, 18 h (45%).

Scheme 3. Synthesis of 2′-Carbon Analogues **5** and **6**[a]



[a] Reagents and conditions: (a) 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane, pyr (91%);[52] (b) phenyl chlorothioformate, NEt_3, DMAP, CH_2Cl_2 (71%); (c) allyltributyltin, AIBN, benzene, hν (94%); (d) OsO_4, NMO, acetone/H_2O (4:1); (e) $NaIO_4$, dioxane/H_2O (3:1) (72%, two steps); (f) NaH, $CH_2(PO(OEt)_2)_2$, THF (92%); (g) TBAF, THF (91%); (h) NaOMe, MeOH (80%); (i) TMSBr, DMF, (quantitative).

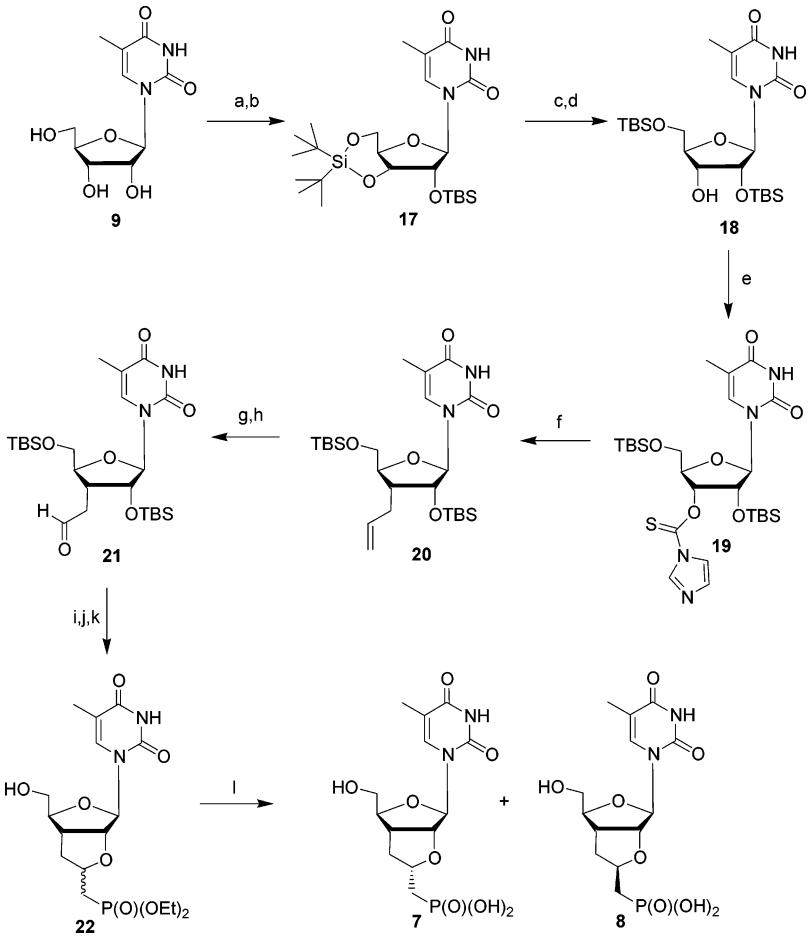
both generated as a pair of diastereomers in a 3:1 ratio, with opposite configurations at the carbon bearing the phosphonate moiety. Assignment of the stereochemistry for the 2′-carbon series was accomplished by NOE experiments. The anomeric proton in diastereomer **6** (Scheme 3) showed a 7% NOE upon irradiation of the methine proton adjacent to the phosphonate, indicating that **6**, the major diastereomer of the 2′-carbon series, is the exo isomer. The minor compound **5**, which displayed no enhancement of the anomeric proton signal upon irradiation of the methane adjacent to the phosphonate, was assigned the endo configuration. The 1D NOE difference, 2D NOESY, and 2D ROESY experiments were performed on **8** (the major 3′-carbon diastereomer), **7** (the minor 3′-carbon diastereomer), and **5** (the minor 2′-carbon diastereomer), but unfortunately, an indicative NOE was not observed in any of the experiments. Instead, the structural assignments for **7** and **8** were made by analogy to the 2′-carbon series. Therefore, the minor isomer **7** was assigned as the endo isomer and **8** was assigned as the exo. We expected the endo isomers **5** and **7** to be more active than the exo isomers **6** and **8** in the TP enzyme assay because of the orientation of the phosphonates being similar to that of active compound **2**. This in fact was the case, and the values are shown in Table 1.

Human Thymidine Phosphorylase Inhibitory Activity. A spectrophotometric assay described by Wataya and Santi[49] was used to determine the inhibitory effect of the synthesized analogues **2**−**8** against human TP. Enzyme activity was measured following the conversion of a chromagenic substrate, 5-nitro-2′-deoxyuridine, to 5-nitrouracil in the presence of excess phosphate. The reaction was initiated by addition of recombinant human TP (625 ng/mL), and the change in absorbance was monitored at 350 nm at 25 °C. All the compounds were tested against the known inhibitor **2**.

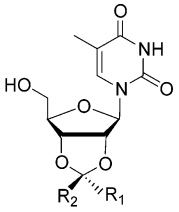
Replacement of the phosphonate group with a carboxylic acid (compound **3**) reduced the inhibitory activity of the analogue, and the substitution of an amide for the phosphonate (compound **4**) rendered the compound inactive. For both series of carbon analogues, the endo isomer was 30−60 times more active than the exo isomer but significantly less active than **2**.

Molecular Modeling. Conformational searches on the two diastereomers (endo and exo) of each of the three sets of phosphonate compounds **2** (endo and exo) (Figure 2), **5** and **6** (Table 1), and **7** and **8** (Table 1) were performed. The OPLS-AA force field,[55] with a distance-dependent dielectric of 4*r*, was used with the exception that ligand charges were fit to the electrostatic potential from ab initio calculations with the HF/

Scheme 4. Synthesis of 3′-Carbon Analogues **7** and **8**[a]



[a] Reagents and conditions: (a) *t*-Bu_2SiOTf_2, DMF (99%);[54] (b) TBSCl, imidazole, DMF (84%); (c) HF·pyr, THF (92%); (d) TBSOTf, 2,6-lutidine, CH_2Cl_2 (88%); (e) diimidazolethiocarbonyl, CH_2Cl_2 (99%); (f) allyltributyltin, CH_2Cl_2/benzene (2:3), hν (53%); (g) OsO_4, NMO, acetone/H_2O (4:1); (h) $NaIO_4$, dioxane/H_2O (3:1) (64%, two steps); (i) NaH, $CH_2(PO_3Et_2)_2$, THF (91%); (j) TBAF, THF; (k) NaOMe, MeOH (58%, two steps); (l) TMSBr, DMF (quantitative).



2 (endo), $R_1 = CH_2PO_3H_2$, $R_2 = H$
2 (exo), $R_1 = H$, $R_2 = CH_2PO_3H_2$

Figure 2. Diastereomers of compound **2**.

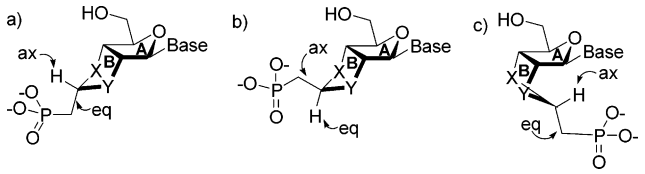


Figure 3. Conformers of the (a) endo and (b, c) exo diastereomers. The trans ring conformation is shown in parts a and b, whereas part c shows the cis ring conformation. The labels "ax" and "eq" refer to pseudoaxial and pseudoequatorial positions on the B-ring, respectively. The word "base" has been substituted for the pyrimidine ring in this depiction.

6-31G* basis set. Five-thousand steps of the mixed MCMM/LMOD searching method were performed with Macromodel.[56]

In each case, the global minimum for the endo diastereomer was lower in energy than that of the exo isomer by 0.3−0.9 kcal/mol. Comparison of the three-dimensional conformations of the endo and exo diastereomers highlights the factors that contribute to the lower internal energy of the endo compound. The two primary differences between these diastereomers are the conformation of the B-ring in relation to the ribose A-ring, as well as the orientation of the phosphonomethyl group (pseudoaxial or pseudoequatorial) (Figure 3). On the basis of model studies of the unsubstituted bicycle, the all-trans conformation of the B-ring is preferred over the folded conformation (cf. Figure 3a vs Figure 3c). In addition, the pseudoequatorial position is favored over the pseudoaxial. The endo diastereomer permits a conformation where the B-ring is in the more stable trans conformation *and* the phosphonomethyl group is pseudoequatorial (Figure 3a), whereas the exo diastereomer must sacrifice either the ring conformation in order to allow the phosphonomethyl group to occupy the pseudoequatorial position (Figure 3c) or vice versa (Figure 3b).

While the endo diastereomer is lower in energy than the exo diastereomer for all three sets of compounds, the intrinsic rotational preference of the phosphonomethyl group differs among the groups. In the compound pairs of **2** (endo and exo) and **7** and **8**, the phosphonate lies closer to the 5′-carbon of the ribose ring than to the 1′-carbon in the lowest-energy structure; the opposite is true for the diastereomeric pair of in the 2′-carbon series of **5** and **6**. Presumably, the orientational preference of the phosphonate is influenced by electrostatic repulsion

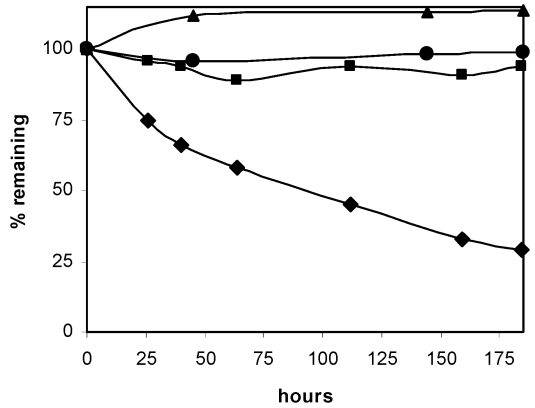


Figure 4. Plot of the % remaining (HPLC integration analysis) versus time for the analogues **2**, **5**, **7**, and **8** when incubated at 37 °C at pH 1.0: compound **2** (◆), compound **5** (▲), compound **7** (■), compound **8** (●).

between the lone 2′ or 3′ oxygen in compounds **7** and **8** and **5** and **6**, respectively.

Docking studies were performed on compounds **2** and **5**−**8** in an effort to understand the differences in experimental binding affinities. The compounds were docked to our homology model of human thymidine phosphorylase using the methods we previously reported.[39] In each case, the protein−ligand complex with the endo isomer was lower in energy than the exo complex, which explains the tighter binding of **5** compared to **6** and of **7** compared to **8**. In addition, the phosphate group was bound in a pocket located closer to the 5′-carbon than the to the 1′-carbon of the ribose ring. The fact that the rotational preference of the phosphate differs from the uncomplexed molecule in both compounds **5** and **6**, as mentioned above, may provide some insight into the reduced activity of these compounds compared to analogues **7** and **8**. Furthermore, there is a hydrogen-bond interaction between the 2′-oxygen in **7** and **8** with His116 that is lost in compounds **5** and **6** when the 2′-oxygen is replaced by carbon. There were no obvious dissimilarities in the docked structures of **2** and **5** that might explain their comparable observed binding energy differences.

Stability in Acidic Buffer. To determine whether the carbon analogues **5**, **7**, and **8** were more stable in acidic conditions compared to lead compound **2**, a kinetic study was performed. The half-life of compound **2** was determined to be 98 h at 37 °C in pH 1.0 buffer, whereas the carbon analogues **5**, **7**, and **8** were unchanged under these same conditions (Figure 4). The decomposition of compound **2** is presumed to occur through hydrolysis of the acetal ring, although the products were not isolated or characterized.

Conclusions

A series of multisubstrate inhibitors of TP incorporating a nucleoside framework and an acidic or polar group were prepared. Replacement of the phosphonate with a carboxylic acid reduced the activity of the compound against TP, and the replacement of the phosphonate with an amide rendered the compound inactive. When the five-membered acetal ring was replaced with either the 2′-carbon ether or the 3′-carbon ether, the chemical stability to low pH was increased but the activity in the human TP enzymatic assay was reduced. The diastereomers of each series of the carbon analogues exhibited significantly different activities, indicating that the orientation of the phosphonate group is critical. The most active compounds **5** and **7** possess an endo phosphonate, which is consistent with the phosphonate orientation in **2**. Molecular modeling results suggest that the protein−ligand complex with the endo isomer is lower in energy than the exo complex.

Experimental Section

General. All commercially available reagents were used without further purification unless otherwise specified. All reactions were performed under nitrogen atmosphere unless otherwise specified. NMR spectra were obtained on a Bruker Ultrashield 300 MHz spectrometer at 300 MHz for ^{1}H NMR and at 75 MHz for ^{13}C NMR with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on an AGI-150 mass spectrometer using an electrospray technique. Elemental analyses were performed by Numega Labs, San Diego, CA, on a Perkin-Elmer 2400-2 CHNS analyzer. All final compounds were analyzed on an HPLC, equipped with a Waters 1525 pump, a Waters 2487 dual λ Absorbance detector, a Waters 717 Plus autosampler using a Phenomenex Synergi RP-18 250 mm × 4.6 mm reverse-phase column with a 5−15% methanol/water gradient containing 0.1% TFA (method 1) and using a Thermo Electron Aquasil C-18 250 mm × 4.6 mm reverse phase column with a 5% isocratic acetonitrile, 95% water containing 0.1% TFA system (method 2). Final compounds were shown to be at least 95% pure based on the 254 nm UV wavelength under these conditions. The flow rates for the analytical and semipreparative experiments were 1 and 4 mL/min, respectively. The semipreparative separations were performed with a system equipped with a GBC pump LC 1150, GBC LC 5100 photodiode array detector, LC 1445 system organizer, and a Vydac C-18 column (10 mm × 250 mm).

Synthesis of Pyrimidine-2,4-dione 14. *N*-Methylmorpholine *N*-oxide (230 mg, 1.96 mmol) was added to a solution of pyrimidine-2,4-dione **13**[53] (908 mg, 1.78 mmol) in 9.6 mL of acetone and 2.4 mL of water, followed by the addition of a 0.0185 g/mL aqueous solution of osmium tetroxide (1.2 mL, 0.089 mmol). The reaction mixture turned from colorless to orange immediately and was stirred at room temperature for 105 min. A saturated, aqueous solution of sodium thiosulfate (3 mL) was added, followed by 3 mL of water, and the mixture was extracted twice with ethyl acetate. The organic layers were washed twice with saturated sodium bicarbonate solution and once with brine, dried (Na_2SO_4), and concentrated to afford 963 mg (99%) of a mixture of diols as an off-white foam: IR (film, cm^{-1}) 3437, 1695; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 1H), 5.91 (s, 0.5H), 5.78 (s, 0.5H), 4.52−4.40 (m, 1H), 4.28−4.18 (m, 2H), 4.01−3.85 (m, 3H), 3.76−3.45 (m, 3H), 2.72−2.62 (m, 0.5H), 2.44−2.35 (m, 0.5H), 1.93 (s, 3H), 1.14−0.96 (m, 28H); ES MS *m*/*z* $(M + Na)^+$ 581.6. Sodium periodate (730 mg, 3.41 mmol) was added to a solution of the crude diols (954 mg, 1.71 mmol) in 19 mL of 1,4-dioxane and 6.5 mL of water. The solution was stirred at room temperature for 35 min. The reaction mixture was diluted with ethyl acetate, washed twice with saturated sodium bicarbonate solution and once with brine, dried (Na_2SO_4), and concentrated. The resulting residue was purified by flash chromatography, eluting with 1:1 ethyl acetate/hexanes to afford 656 mg (73%) of aldehyde **14** as a white foam: mp 60−65 °C; IR (film, cm^{-1}) 3189, 1696; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.45 (s, 1H), 7.31 (d, J = 1.2 Hz, 1H), 5.78 (d, J = 4.4 Hz, 1H), 4.59 (t, J = 7.2 Hz, 1H), 4.05 (d, J = 4.1 Hz, 2H), 3.93−3.88 (m, 1H), 3.03−2.93 (m, 1H), 2.91−2.82 (m, 1H), 2.63 (dd, J = 17.3, 5.0 Hz, 1H), 1.93 (d, J = 1.2 Hz, 3H), 1.12−0.97 (m, 28H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.7, 163.9, 150.5, 134.6, 111.0, 87.8, 83.9, 69.7, 61.3, 43.0, 40.3, 17.4, 17.3, 17.20, 17.18, 16.89, 16.86, 16.82, 16.77, 13.3, 13.0, 12.8, 12.6 (2C); ES MS *m*/*z* $(M - H)^-$ 525.8. Anal. ($C_{24}H_{42}N_2O_7Si_2$) C, H, N.

Synthesis of Phosphonic Acid Diethyl Ester 15. Tetraethyl methylenediphosphonate (0.22 mL, 0.88 mmol) was added dropwise to a mixture of sodium hydride (60% dispersion in oil, 35 mg, 0.88 mmol) in 4 mL of dry THF at 0 °C under nitrogen, and the reaction mixture was stirred for 10 min and then stirred at room temperature for 20 min. The reaction mixture was cooled to 0 °C, a solution of aldehyde **14 (**267 mg, 0.507 mmol) in 2 mL of dry THF was added, and the resulting solution was stirred at room temperature for 19

h. The reaction mixture was concentrated, and the residue was purified by flash chromatography, eluting first with 1:1 ethyl acetate/hexanes and then with 100% ethyl acetate to afford 312 mg (92%) of the phosphonate ester as a white foam: IR (film, cm^{-1}) 3169, 1710, 1694, 1682; ^1H NMR (300 MHz, $CDCl_3$) δ 8.89 (s, 1H), 7.34 (s, 1H), 6.92−6.73 (m, 1H), 5.85−5.73 (m, 2H), 4.55 (t, J = 7.3 Hz, 1H), 4.13−3.98 (m, 6H), 3.94−3.88 (m, 1H), 2.83−2.70 (m, 1H), 2.48−2.33 (m, 2H), 1.92 (s, 3H), 1.31 (t, J = 7.1 Hz, 6H), 1.12−0.97 (m, 28H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 150.0, 149.9 (d, J = 4.3 Hz), 134.9, 119.6 (d, J = 186.5 Hz), 110.7, 88.2, 83.7, 69.5, 61.7 (dd, J = 5.6, 2.9 Hz), 61.0, 47.4, 31.2 (d, J = 23.2 Hz), 17.5, 17.4, 17.3, 17.2, 17.1, 17.0, 16.9, 16.44, 16.36, 13.4, 13.1, 12.8, 12.7, 12.6; ES MS m/z $(M + H)^+$ 661.7; MALDI-FTMS m/z $(M + H)^+$ calcd 661.3100, obsd 661.3105. A 1.0 M solution of tetrabutylammonium fluoride (1.40 mL, 1.40 mmol) was added dropwise to a solution of the phosphonate ester (452 mg, 0.684 mmol) in 12 mL of dry THF, and the resulting solution was stirred at room temperature under nitrogen for 25 min. The reaction mixture was concentrated, and the resulting residue was purified by flash chromatography, eluting first with 95:5 dichloromethane/methanol and then with 9:1 dichloromethane/methanol to give 262 mg (91%) of alcohol **15** as a sticky, white foam: IR (film, cm^{-1}) 3371, 3063, 1688; ^1H NMR (300 MHz, methanol-d_4) δ 7.77 (s, 1H), 6.78−6.58 (m, 1H), 6.06 (d, J = 9.0 Hz, 1H), 5.79 (dd, J = 21.6, 17.2 Hz, 1H), 4.28 (d, J = 4.9 Hz, 1H), 4.08−3.96 (m, 5H), 3.76−3.73 (m, 2H), 2.70−2.58 (m, 1H), 2.53−2.30 (m, 2H), 1.88 (s, 3H), 1.29 (t, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 152.8, 152.6 (d, J = 4.4 Hz), 138.0, 119.1 (d, J = 186.8 Hz), 112.2, 89.3, 89.0, 74.0, 63.5, 63.4 (d, J = 5.8 Hz), 30.7, 30.4, 16.7 (d, J = 6.1 Hz), 12.5; ES MS m/z $(M + Na)^+$ 441.3; MALDI-FTMS m/z $(M + H)^+$ calcd 419.1578, obsd 419.1582.

Synthesis of Phosphonic Acid Diethyl Ester 16. Sodium methoxide (14 mg, 0.26 mmol) was added to a solution of alcohol **15** (88 mg, 0.21 mmol) in 3 mL of dry methanol, and the reaction mixture was stirred at room temperature under nitrogen for 42 h. Then 1 N HCl (0.6 mL) was added to achieve a pH of 2, and the reaction mixture was concentrated. The residue was taken up in acetone and filtered to remove the sodium salts, and the filtrate was concentrated to give a colorless oil. The resulting residue was purified by flash chromatography, eluting with 95:5 dichloromethane/methanol to afford 70 mg (80%) of mixture **16** as a sticky white foam: IR (film, cm^{-1}) 3421, 3062, 1690; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 1.2 Hz, 0.3H), 7.41 (d, J = 1.2 Hz, 0.7H), 5.84 (d, J = 6.5 Hz, 0.3H), 5.80 (d, J = 6.5 Hz, 0.7H), 4.77 (dd, J = 7.5, 3.3 Hz, 0.7H), 4.55 (dd, J = 6.9, 2.0 Hz, 0.3H), 4.49−4.23 (m, 2H), 4.19−4.06 (m, 4H), 3.97−3.87 (m, 1H), 3.84−3.76 (m, 1H), 3.13−2.98 (m, 1H), 2.45−1.95 (m, 3H), 1.92 (s, 3H), 1.90−1.79 (m, 1H), 1.33 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, major diastereomer) δ 163.6, 150.49, 136.5, 111.3, 91.5, 85.5, 83.4, 73.7, 62.8, 61.93 (dd, J = 9.6, 6.2 Hz), 50.1, 34.6 (d, J = 284 Hz), 30.9, 16.4 (dd, J = 5.9, 1.1 Hz), 12.53; ^{13}C NMR (75 MHz, $CDCl_3$, minor diastereomer) δ 163.7, 150.53, 137.2, 111.1, 94.1, 85.4, 85.2, 73.7, 63.1, 61.89 (d, J = 9.7, 6.6 Hz), 49.9, 34.7 (d, J = 259 Hz), 31.1, 16.4 (dd, J = 5.9, 1.1 Hz), 12.50; ES MS m/z $(M + Na)^+$ 441.4; MALDI-FTMS m/z $(M + H)^+$ calcd 419.1578, obsd 419.1591.

Synthesis of Phosphonic Acids 5 and 6. Trimethylsilyl bromide (1.55 mL, 11.7 mmol) was added dropwise to a stirred solution of **16** (249 mg, 0.594 mmol) in 7.5 mL of dry DMF under nitrogen at −78 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 23 h. The solvent was removed in vacuo, and the resulting residue was purified by ion-exchange chromatography (Sephadex-CM, C25 resin), followed by lyophilization, providing 246 mg of **5** and **6** as a white solid and a mixture of diastereomers in a 3:1 ratio (as determined by HPLC). The diastereomers were separated by preparative HPLC. Fractions containing the purified diastereomers were pooled, concentrated in vacuo, triturated with ether, and dried under high vacuum.

5: mp >300 °C; ^1H NMR (300 MHz, D_2O, minor diastereomer) δ 7.58 (s, 1H), 5.91 (d, J = 5.5 Hz, 1H), 4.53−4.45 (m, 1H), 4.28−4.17 (m, 2H), 3.79−3.63 (m, 2H), 3.18−3.08 (m, 1H), 2.50−2.38 (m, 1H), 2.24−1.90 (m, 2H), 1.83−1.70 (m, 1H), 1.82 (s, 3H); ^{13}C NMR (75 MHz, D_2O, minor diastereomer) δ 166.9, 152.2, 138.3, 111.8, 92.2, 85.7, 84.3, 79.5, 62.1, 50.1, 36.4, 34.6 (d, J = 127 Hz), 11.9; ES MS m/z $(M - H)^-$ 361.4; MALDI FTMS m/z $(M + Na)^+$ calcd 385.0771, obsd 385.0773.

6: mp >300 °C; ^1H NMR (300 MHz, D_2O, major diastereomer) δ 7.56 (s, 1H), 5.87 (d, J = 6.4 Hz, 1H), 4.45−4.34 (m, 1H), 4.07−4.01 (m, 1H), 3.82−3.67 (m, 2H), 3.16−3.07 (m, 1H), 2.30−1.94 (m, 3H), 1.88−1.76 (m, 1H), 1.81 (s, 3H); ^{13}C NMR (75 MHz, D_2O, major diastereomer) δ 166.8, 152.2, 138.1, 112.1, 90.4, 85.1, 83.4, 74.8, 62.0, 49.4, 36.3, 32.7 (d, J = 133 Hz), 11.9; ES MS m/z $(M - H)^-$ 361.4; MALDI FTMS m/z $(M + Na)^+$ calcd 385.0771, obsd 385.0780.

Synthesis of 19. To a solution of alcohol **18** (0.772 g, 1.59 mmol) in CH_2Cl_2 (16 mL) was added DMAP (0.059 g, 0.48 mmol), followed by 1,1′-thiocarbonyldiimidazole (0.369 g, 2.07 mmol) at room temperature under nitrogen, and the reaction mixture was stirred for 19 h. The solvent was removed in vacuo, and purification by flash chromatography (elution with 40% ethyl acetate/hexanes) gave **19** (0.943 g, 99%) as a white foam: mp 86−88 °C; IR (CCl_4, cm^{-1}) 3179, 3127, 3060, 2956, 2933, 1696; ^1H NMR (300 MHz, $CDCl_3$) δ 9.51 (s, 1H), 8.45 (s, 1H), 7.69 (bs, 1H), 7.47 (d, J = 1.2 Hz, 1H), 7.10 (bs, 1H), 6.21 (d, J = 7.2 Hz, 1H), 5.79 (dd, J = 5.3, 1.6 Hz, 1H), 4.45 (dd, J = 7.1, 5.4 Hz, 1H), 4.40 (d, J = 1.6 Hz, 1H), 3.99 (q, J = 9.7 Hz, 2H), 1.96 (d, J = 1.0 Hz, 3H), 0.99 (s, 9H), 0.77 (s, 9H), 0.20 (s, 3H), 0.19 (s, 3H), −0.03 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.3, 163.6, 150.6, 137.4, 134.4, 131.1, 117.6, 111.7, 86.9, 82.7, 81.1, 73.9, 63.2, 25.9, 25.2, 18.3, 17.6, 12.4, −5.2, −5.23, −5.39, −5.4; ES MS m/z $(M + H)^+$ 597.9. Anal. ($C_{26}H_{44}N_4O_6SSi_2$) C, H, N.

Synthesis of Pyrimidine-2,4-dione 20. A solution of **19** (0.911 g, 1.53 mmol) and AIBN (0.126 g, 0.765 mmol) in 26 mL of CH_2Cl_2/benzene (2:3) was degassed with nitrogen for 5 min. Allyltributyltin (2.37 mL, 0.765 mmol) was added, and the solution was irradiated for 3 h with a high-pressure 450 W Hanovia mercury lamp. The solvent was removed in vacuo, and purification by flash chromatography (elution with a gradient of 10−30% ethyl acetate in hexanes) afforded **20** (0.309 g, 40%), a white foam, as the major product: IR (CCl_4, cm^{-1}) 2953, 2935, 2862, 1682; ^1H NMR (300 MHz, $CDCl_3$) δ 8.43 (bs, 1H), 7.71 (d, J = 1.2 Hz, 1H), 5.69−5.83 (m, 1H), 5.66 (d, J = 1.6 Hz, 1H), 5.03−5.11 (m, 2H), 4.29 (d, J = 4.3 Hz, 1H), 4.11 (d, J = 11.9 Hz, 1H), 4.04 (d, J = 8.9 Hz, 1H), 3.72 (dd, J = 12, 2.5 Hz, 1H), 2.34−2.43 (m, 1H), 1.99−2.18 (m, 2H), 1.92 (d, J = 1.2 Hz, 3H), 0.95 (s, 9H), 0.90 (s, 9H), 0.21 (s, 3H), 0.14 (s, 3H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 150.3, 135.7, 116.6, 109.6, 90.9, 84.6, 62.4, 40.8, 28.8, 26.0, 25.8, 18.6, 18.1, 12.7, −4.2, −5.2, −5.3, −5.5; ESI MS m/z $(M + Na)^+$ 533.8. Anal. ($C_{25}H_{46}N_2O_5Si_2$) C, H, N.

Synthesis of Aldehyde 21. To a solution of **20** in 24 mL of acetone/H_2O (4:1) was added NMO (0.30 g, 2.58 mmol) and OsO_4 (0.030 mg, 0.118 mmol) at room temperature, and the reaction mixture was stirred for 3 h. Freshly prepared saturated aqueous $Na_2S_2O_3$ (4.6 mL) was added to the reaction mixture followed by water (4.6 mL). The solution was extracted three times with ethyl acetate, and the combined organic layers were washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. Purification by flash chromatography (elution with a gradient of 50−100% ethyl acetate in hexanes) gave a 1:1 mixture of diastereomeric diols (0.818 g, 67%) as a white foam: IR (CCl_4, cm^{-1}) 3429, 3185, 3063, 2958, 2929, 2865, 1708; ^1H NMR (300 MHz, $CDCl_3$) δ 8.88 (bs, 1H), 8.66 (bs, 1H), 7.71 (d, J = 1.2 Hz, 1H), 7.61 (d, J = 1.2 Hz), 5.68 (d, J = 1.6 Hz, 1H), 5.64 (s, 1H), 4.42 (d, J = 4.0 Hz, 1H), 4.38 (d, J = 4.8 Hz, 1H), 4.03−4.14 (m, 4H), 3.60−3.75 (m, 6H), 3.36−3.49 (m, 2H), 3.01 (bs, 1H), 2.70 (bs, 1H), 2.30−2.40 (m, 1H), 2.18−2.28 (m, 3H), 1.91 (d, J = 1.1 Hz, 3H), 1.88 (d, J = 1.1 Hz, 3H), 1.30−1.39 (m, 4H), 0.95 (s, 9H), 0.94 (s, 9H), 0.91 (s, 9H), 0.90 (s, 9H), 0.24 (s, 3H), 0.19 (s, 3H), 0.14 (s, 3H), 0.138 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H), 0.11 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, isomer A) δ 163.8, 150.3, 135.7, 109.7, 90.9, 84.7, 78.0, 70.8, 66.9, 62.3, 38.5, 27.8, 26.0, 25.8, 18.6, 18.1, 12.6, −5.1, −5.2, −5.3, −5.4; ^{13}C NMR (75 MHz, $CDCl_3$, isomer B) δ 164.0, 150.4, 136.0,

109.3, 91.5, 85.2, 78.0, 69.8, 67.0, 62.7, 37.6, 27.4, 26.0, 25.8, 18.7, 18.1, 12.6, −4.0, −4.3, −5.0, −5.5; ES MS *m*/*z* $(M + H)^+$ 511.7. To a solution of the mixture of diols (0.818 g, 1.5 mmol) in 21 mL of dioxane/water (3:1) was added sodium periodate (0.643 g, 3.0 mmol) at room temperature, giving a milky suspension. The mixture was stirred for 2 h and then diluted with water and ethyl acetate. The layers were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. The solvent was removed in vacuo, and purification by flash chromatography (elution with 15−25% ethyl acetate in hexanes) afforded aldehyde **21** (0.679 g, 88%) as a white foam: mp 72−74 °C; IR (CCl_4, cm^{-1}) 3397, 3134, 2955, 2932, 2860, 1686; ^1H NMR (300 MHz, $CDCl_3$) δ 9.82 (s, 1H), 8.18 (bs, 1H), 7.58 (d, $J = 1.2$ Hz, 1H), 5.75 (d, $J = 2.2$ Hz, 1H), 4.43 (dd, $J = 5.2$, 2.2 Hz, 1H), 4.04 (dd, $J = 11.9$, 2.4 Hz), 3.99 (dt, $J = 8.4$ Hz, 1H), 3.75 (dd, $J = 11.7$, 2.4 Hz, 1H), 2.90 (dd, $J = 18$, 8.3 Hz, 1H), 2.60−2.68 (m, 1H), 2.50 (dd, $J = 18$, 5.2 Hz, 1H), 1.93 (d, $J = 1.1$ Hz, 3H), 0.94 (s, 9H), 0.88 (s, 9H), 0.15 (s, 3H), 0.12 (s, 6H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 199.9, 163.7, 150.2, 135.4, 110.1, 90.6, 84.2, 76.9, 62.5, 39.9, 36.0, 25.9, 25.7, 18.5, 17.9, 12.7, −4.5, −5.2, −5.3, −5.5; ESI MS *m*/*z* $(M - H)^-$ 511.6. Anal. ($C_{24}H_{44}N_2O_6Si_2$) C, H, N.

Synthesis of Phosphonic Acid Diethyl Ester 22. To a suspension of sodium hydride (0.054 g, 2.26 mmol) in anhydrous THF (18 mL) at 0 °C under nitrogen was added tetraethylmethylene diphosphonate (0.65 g, 2.26 mmol) dropwise. The mixture was stirred for 10 min at 0 °C and 20 min at room temperature. Aldehyde **21** (0.678 g, 1.33 mmol) in anhydrous THF (7 mL) was added to the solution at 0 °C, and the reaction mixture was allowed to slowly warm to room temperature and stirred overnight. The solvent was removed in vacuo, and purification by flash chromatography (elution with 60−90% ethyl acetate in hexanes) afforded the phosphonate ester (0.781 g, 91%) as a white foam: mp 50−53 °C; IR (CCl_4, cm^{-1}) 3171, 3051, 2950, 2854, 1694; ^1H NMR (300 MHz, $CDCl_3$) δ 8.11 (bs, 1H), 7.63 (d, $J = 1.2$ Hz, 1H), 6.58−6.76 (m, 1H), 5.66−5.80 (m, 2H), 4.31 (dd, $J = 4.2$, 1.5 Hz, 1H), 4.02−4.12 (m, 4H), 3.70 (dd, $J = 12$, 2.5 Hz, 1H), 2.50−2.64 (m, 1H), 2.14−2.27 (m, 2H), 1.92 (d, $J = 1.2$ Hz, 3H), 1.32 (t, $J = 8.6$ Hz, 6H), 0.94 (s, 9H), 0.90 (s, 9H), 0.19 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H), 0.10 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 150.3, 149.7 (d, $J = 4.8$ Hz), 135.4, 119.4 (d, $J = 188$ Hz), 109.9, 90.8, 84.2, 76.9, 62.2, 61.7 (dd, $J = 5.7$, 1.8 Hz), 40.2, 29.2 (d, $J = 22.7$ Hz), 26.0, 25.8, 18.5, 18.0, 16.3 (d, $J = 6.4$ Hz), 12.7, −4.2, −5.2, −5.3, −5.5; ESI MS *m*/*z* $(M + Na)^+$ 669.8; MALDI-FTMS *m*/*z* $(M + H)^+$ calcd 647.3307, obsd 647.3309. Anal. ($C_{29}H_{55}N_2O_8PSi_2$) C, N. H: calcd, 8.57; found, 8.99. To a solution of the phosphonate ester (0.905 g, 1.40 mmol) in anhydrous THF (23 mL) at room temperature was added dropwise a 1.0 M TBAF solution in THF (2.8 mL, 2.8 mmol), and the solution was stirred overnight. The solvent was removed in vacuo, and purification by flash chromatography (elution with a gradient of 2−10% methanol in methylene chloride) gave an inseparable mixture of the diol and the diastereomeric cyclized alcohols **22**. To a solution of the mixture of diols and **22** (0.385 g, 0.921mmol) in anhydrous MeOH (15 mL) was added 0.5 M sodium methoxide in MeOH (2.22 mL, 1.11 mmol) at room temperature, and the reaction mixture was stirred overnight. The reaction was quenched with 1 N HCl, and the pH was adjusted to 5. The solvent was removed in vacuo, the crude mixture was dissolved in acetone, and the salts were removed by filtration. The filtrate was concentrated in vacuo, and purification by flash chromatography (elution with a gradient of 2−10% methanol in methylene chloride) afforded **22** (0.339 g, 58%) as an inseparable 3:1 mixture of diastereomers (determined by NMR) and as a sticky white foam: IR (CCl_4, cm^{-1}) 3400, 3056, 2987, 2935, 2822, 1685; ^1H NMR (300 MHz, $CDCl_3$) δ 8.91 (bs, 1H), 7.21 (d, $J = 1.2$ Hz, 0.3H), 7.15 (d, $J = 1.2$ Hz, 0.7H), 5.75 (d, $J = 2.4$ Hz, 0.3H), 5.56 (d, $J = 2.4$ Hz, 0.7H), 4.82 (dd, $J = 7.3$, 2.2 Hz, 0.7H), 4.64 (dd, $J = 7.3$, 2.2 Hz, 0.3H), 4.23−4.49 (m, 1H), 4.07−4.17 (m, 4H), 3.91−3.97 (m, 2H), 3.68−3.74 (m, 1H), 3.28 (q, $J = 7.5$ Hz, 1H), 2.87−2.90 (m, 1H), 2.21−2.43 (m, 1H), 1.98−2.10 (m, 3H), 1.90 (d, $J = 1.1$ Hz, 3H), 1.33 (t, $J = 7.1$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, major diastereomer) δ 163.6, 150.2, 138.2, 111.0, 95.5, 88.0, 86.1, 74.3, 62.6, 61.9 (dd, $J = 13.3$, $J = 6.2$ Hz), 43.9, 36.9 (d, $J = 6.0$ Hz), 31.8 (d, $J = 139$ Hz), 16.4 (d, $J = 6$ Hz), 12.3; ^{13}C NMR (75 MHz, $CDCl_3$, minor diastereomer) δ 163.9, 150.6, 138.0, 110.9, 93.5, 88.9, 86.1, 74.3, 62.3, 61.9 (dd, $J = 13.3$, 6.2 Hz), 44.3, 36.3 (d, $J = 6.0$ Hz), 32.4 (d, $J = 139.7$ Hz), 16.4 (d, $J = 6$ Hz), 12.5; MALDI FTMS *m*/*z* $(M + H)^+$ calcd 419.1578, obsd 419.1588.

Synthesis of Phosphonic Acids 7 and 8. To a solution of the phosphonate esters **22** (0.300 g, 0.717 mmol) in anhydrous DMF at −78 °C was added TMSBr dropwise, and the reaction mixture was allowed to warm to room temperature and was stirred overnight. The solvent was removed in vacuo, and purification by ion-exchange chromatography (Sephadex-CM, C-25 resin) followed by lyophilization provided **7** and **8** (114 mg, 44% yield) as a white solid as a 3:1 mixture of diastereomers (determined by HPLC). The diastereomers were purified by preparative HPLC. Fractions containing the purified diastereomers were pooled, concentrated in vacuo, triturated with ethyl ether, and dried under high vacuum.

7: ^1H NMR (300 MHz, D_2O, minor diastereomer) δ 7.53 (s, 1H), 5.95 (s, 1H), 4.57−4.59 (m, 1H), 4.30 (bs, 1H), 4.04−4.08 (m, 1H), 3.81 (dd, $J = 13.1$, 5.5 Hz, 1H), 3.66 (dd, $J = 13.1$, 5.5 Hz, 1H), 2.92−3.00 (m, 1H), 2.36−2.46 (m, 1H), 2.12−2.25 (m, 1H), 1.93−2.04 (m, 1H), 1.83 (s, 3H), 1.59−1.69 (m, 1H); ^{13}C NMR (75 MHz, D_2O, minor diastereomer) δ 166.9, 151.9, 138.5, 111.6, 90.8, 88.7, 88.4, 79.4, 62.0, 44.9, 35.9, 33.2 (d, $J = 111$ Hz), 11.8; MALDI FTMS *m*/*z* $(M + Na)^+$ calcd 385.0771, obsd 385.0763.

8: mp 295−298 °C (dec); ^1H NMR (300 MHz, D_2O, major diastereomer) δ 7.48 (s, 1H), 5.83 (d, $J = 2.15$ Hz, 1H), 4.40−4.48 (m, 1H), 3.97−4.02 (m, 1H), 3.83 (dd, $J = 12.5$, 3.0 Hz, 1H), 3.69 (dd, $J = 12.5$, 5.6 Hz, 1H), 3.01 (q, $J = 7.4$ Hz, 1H), 1.91−2.22 (m, 3H), 1.83 (s, 4H); ^{13}C NMR (75 MHz, D_2O, major diastereomer) δ 166.9, 151.9, 138.8 (d, $J = 16$ Hz), 111.8, 92.2, 87.8, 85.8, 75.8, 62.3, 44.8, 36.4, 33.2 (d, $J = 220$ Hz), 11.8; ESI MS *m*/*z* $(M - H)^-$ 361.4; MALDI FTMS *m*/*z* $(M + Na)^+$ calcd 385.0771, obsd 385.0777.

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Supporting Information Available: Elemental analysis of selected compounds, experimental procedures and characterization of compounds **3**, **4**, **11**, **17**, and **18**, and HPLC analysis of traces of compounds **4**−**8** under two diverse conditions. This material is available free of charge via the Internet at http://pubs.acs.org.

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