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Sculpting the Bicyclo[3.1.0]hexane Template of Carbocyclic Nucleosides to Improve Recognition by Herpes Thymidine Kinase

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Abstract: The replacement of the furanose ring by a cyclopentane in nucleosides generates a group of analogues known generically as carbocyclic nucleosides. These compounds have increased chemical and enzymatic stability due to the absence of a true glycosyl bond that characterizes conventional nucleosides. The additional fusion of a cyclopropane ring to the cyclopentane produces a bicyclo[3.1.0]hexane system that depending on its location relative to the nucleobase is able to lock the embedded cyclopentane ring into conformations that mimic the typical north and south conformations of the furanose ring in conventional nucleosides. These bicyclo[3.1.0]hexane templates have already provided important clues to differentiate the contrasting conformational preferences between kinases and polymerases. Herein, we describe the design, synthesis, and phosphorylation pattern of a new bicyclo[3.1.0]hexane thymidine analogue that seems to possess an ideal spatial distribution of pharmacophores for an optimal interaction with herpes simplex 1 thymidine kinase. The bicyclo[3.1.0]hexane template represents a privileged rigid template for sculpting other carbocyclic nucleosides to meet the demands of specific receptors.

Introduction

The replacement of the furanose ring by a cyclopentane is the hallmark of carbocyclic nucleosides.[1] This apparently simple change provides excellent chemical and enzymatic stability due to the absence of a true glycosyl bond that characterizes conventional nucleosides. However, the absence of the furanose oxygen brings about a significant change in conformation due to the loss of important gauche and anomeric effects that in normal nucleosides maintain the ribose in the vicinity of either a 3′-endo (north) or 2′-endo (south) conformation.[2] For that reason, carbocyclic nucleosides adopt an atypical 1′-exo conformation that is governed mainly by the steric bulk of the nucleobase, which prefers to adopt an equatorial orientation.[3] We have successfully countered this 1′-exo bias of the cyclopentane ring of carbocyclic nucleosides by fusing to it a cyclopropane ring that, depending on the pattern of substitution, forces the embedded cyclopentane ring to adopt either a 2′-exo (north) or a 3′-exo (south) conformation (Figure 1), which are 18° away from the ideal north (3′-endo/2′-exo, $P = 0°$) or south (3′-exo/2′-endo, $P = 360°$) conformations described in the pseudorotational cycle of conventional nucleosides.[4] These bicyclo[3.1.0]hexane templates have already provided important clues to differentiate the contrasting conformational preferences between kinases and polymerases.[5−7]

An effective and specific interaction with appropriate viral kinases is of paramount importance for the development of selective antiviral agents. During the course of an earlier investigation, we found that in the case of the herpes simplex 1 thymidine kinase (HSV1-tk), the first phorphorylation step of the south bicyclo[3.1.0]hexane thymidine analogue (S-MCT,

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(1) (a) Marquez, V. E. *Advances in Drug Design;* JAI Press, Inc.: Greenwich, CT, 1994; Vol. 2, pp 89−146. (b) Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611−10670.
(2) Saenger, W. *Principles of Nucleic Acid Structure*; Springer-Verlag: New York, Berlin, Heilderberg, 1984; pp 9−28.
(3) Kalman, A.; Koritsanszky, T.; Beres, J.; Sagi, G. *Nucleosides Nucleotides* **1990**, *9*, 235−243.
(4) Altona, C.; Sundaralingam, M. *J. Am. Chem. Soc.* **1972**, *94*, 8205−8212.
(5) Marquez, V. E.; Ezzitouni, A.; Russ, P.; Siddiqui, M. A.; Ford, H.; Feldman, R. J.; Mitsuya, H.; George, C.; Barchi, J. J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 2780−2789.
(6) Marquez, V. E.; Ben-Kasus, T.; Barchi, J. J., Jr.; Green, K. M.; Nicklaus, M. C.; Agbaria, R. *J. Am. Chem. Soc.* **2004**, *126*, 543−549.
(7) Marquez, V. E.; Choi, Y.; Comin, M. J.; Russ, P.; George, C.; Huleihel, M.; Ben-Kasus, T.; Agbaria, R. *J. Am. Chem. Soc.* **2005**, *127*, 15145−15150.

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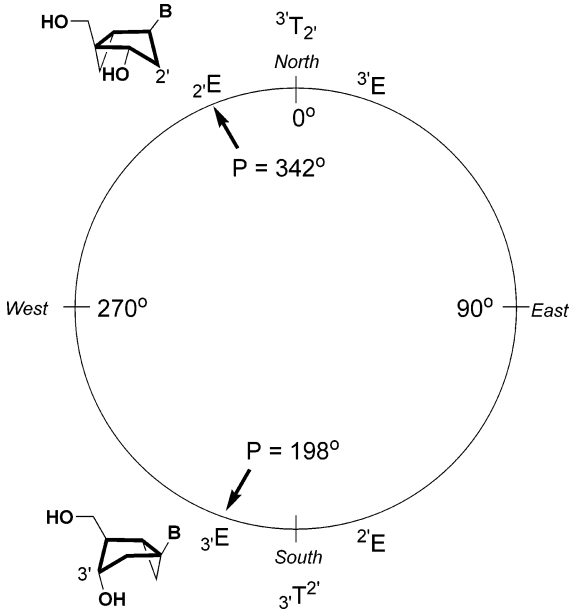


Figure 1. Pseudorotational cycle showing the range of north and south conformations and the locked positions of the embedded cyclopentane ring of bicyclo[3.1.0]hexane nucleosides (E = envelope; T = twist; superscripted and subscripted numbers indicate which atoms are displaced in an endo or exo orientation, respectively).

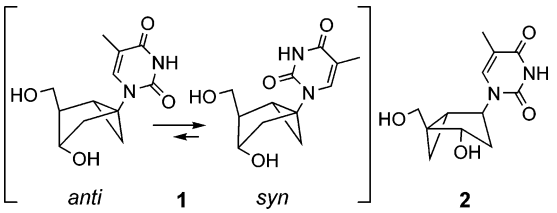


Figure 2. Structures of bicyclo[3.1.0]hexane nucleosides S-MCT (**1**) and N-MCT (**2**). The normal south-syn conformational bias in **1** is reinforced by the restricted rotation of the C−N bond. The preferred orientation in **2** (north) is anti.

1) was not very efficient and the amount of the 5′-monophosphate produced was comparable to that of the corresponding north counterpart (N-MCT, **2**), apparently with the enzyme making no clear distinction between the south and north antipodes.[6] We hypothesized that the expected south conformational penchant of HSV1-tk was being affected by other factors that countered this preference, such as a higher syn ⇆ anti energy barrier, that restricted free rotation of the C−N bond in **1** (Figure 2).[6,7]

Indeed, we have demonstrated that south bicyclo[3.1.0]hexane pyrimidine nucleosides have a high syn ⇆ anti energy barrier, which is directly related to the fusion of the cyclopropane ring immediately adjacent to the C−N bond.[6] The bicyclo[3.1.0]-hexane scaffold significantly enhances the normal south-syn conformational bias typical of south nucleosides[2] and forces the thymine ring to remain in the syn range as demonstrated both by crystallography and NOE studies of **1** in solution.[6−8] In an effort to alleviate this problem, we decided to reposition the fused cyclopropane ring in **1** to the other end of the molecule generating a new compound (**3**) that still maintained an intact southlike conformation but allowed the thymine ring to sample the anti range (Figure 3). Because compound **3** was prone to

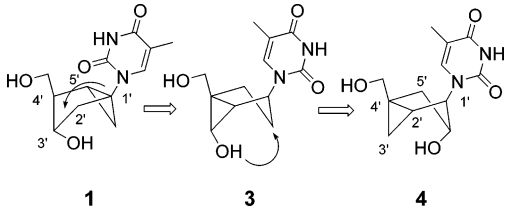
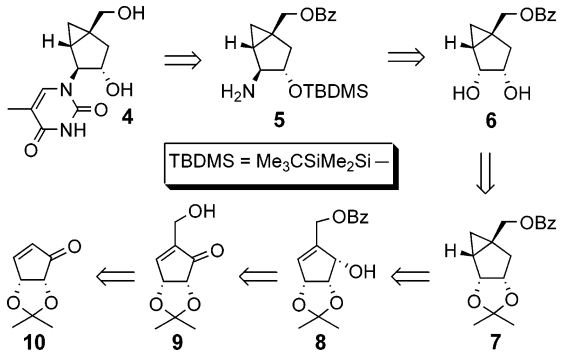


Figure 3. Two-step structural "reshuffling" of bicyclo[3.1.0]hexane nucleoside **1** into **4**. The first step allows rotation of the C−N bond to the anti orientation, and the second step repositions the critical OH group to the opposite tip of the ring.

Scheme 1. Retrosynthetic Analysis of Compound **4**



undergo ring opening at room temperature via a retro-aldol reaction,[9] the critical 3′-OH (nucleoside numbering) was then relocated to the opposite end of the pseudoboat ring (compare **3** vs **4**) where it could engage in H-bonding with the receptor in a manner akin to that of **1**.

A previous experiment with a simpler version of compound **3**, lacking the 3′-OH entirely, was encouraging to the extent that monophosphorylation by HSV-tk proceeded more efficiently than monophosphorylation of either **1** or **2**.[7] Unfortunately, phosphorylation to the diphosphate level, also catalyzed by HSV1-tk, did not proceed at all pointing to the critical role of the OH group.

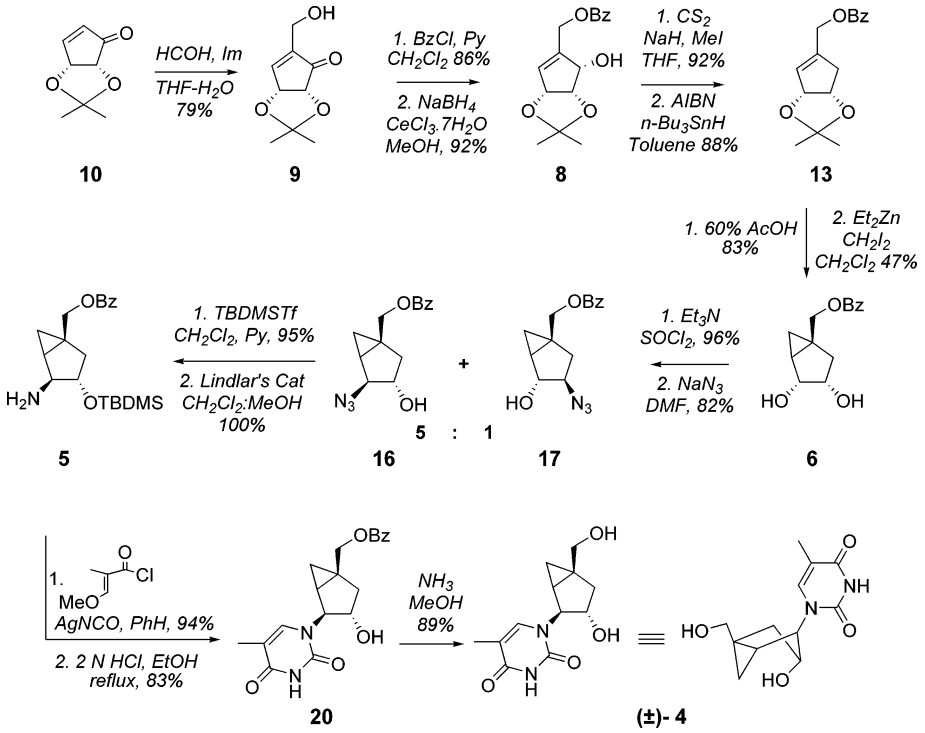
Results and Discussion

Synthesis. Preparation of target compound **4** required the development of a new synthetic approach. The retrosynthetic analysis is shown in Scheme 1. The thymine ring could be built in a linear fashion from the hydroxy-protected trans amino alcohol **5**. The synthesis of the key pseudosugar ring involved four fundamental steps: (1) a Baylis−Hillman reaction[11] to assemble the 5′-hydroxymethyl side chain; (2) a radical deoxygenation reaction[12] to eliminate the allylic hydroxyl group; (3) a vicinal-diol directed cyclopropanation reaction; (4) the regioselective opening of a cyclic sulfite to introduce the nitrogen substituent at the correct position and with the desired stereochemistry.[13]

The execution of the plan was carried out as outlined in Scheme 2. Plentiful D-ribose was converted into cyclopentenone **10** after six steps on a 10 g scale according to the literature.[10]

(8) Schelling, P.; Claus, M. T.; Johner, R.; Marquez, V. E.; Schulz, G. E.; Scapozza, L. *J. Biol. Chem.* **2004**, *279*, 32832−32838.
(9) Creary, X. *J. Org. Chem.* **1975**, *40*, 3326−3331.
(10) Moon, H. R.; Choi, W. J.; Kim, H. O.; Jeong, L. S. *Tetrahedron: Asymmetry* **2002**, *13*, 1189−1193.
(11) Basavaiah, D.; Rao, P. D.; Hynma, R. S. *Tetrahedron* **1996**, *52*, 8001−8062.
(12) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574−1585.
(13) Moon, H. R.; Kim, H. O.; Chun, M. W.; Jeong, L. S.; Marquez, V. E. *J. Org. Chem.* **1999**, *64*, 4733−4741.

Scheme 2. Synthesis of Target Compound (±)-**4**



With the use of a modality of the Baylis−Hillman reaction,[14] treatment of cyclopentenone **10** with imidazole generated in situ a stabilized nucleophilic anion that reacted with formaldehyde. After the elimination of the amine catalyst, the effective addition of a hydroxymethyl group resulted in the formation of cyclopentenone **9**. Protection of the primary alcohol as a benzoyl ester proceeded smoothly, and stereospecific hydride reduction of the carbonyl group afforded exclusively the allylic alcohol **8**. Unfortunately, radical deoxygenation through the intermediate xanthate proceeded with racemization due to the energetic equivalence of the two possible radical intermediates. We forged ahead nonetheless and continue the synthesis from racemate **13** because a racemic target compound would still allow testing of our fundamental hypothesis. Thus, cleavage of the ketal ring and treatment of the corresponding diol under modified Simmons−Smith cyclopropanation conditions proceeded with the desired diastereoselectivity to afford the critical bicylo[3.1.0]-hexane skeleton **6** (relative stereochemistry shown). Reaction of **6** with thionyl chloride gave almost quantitatively the corresponding cyclic sulfite that underwent nucleophilic attack with sodium azide to afford an easily separable 5:1 mixture of regioisomers in favor of the desired azido alcohol **16**. After protection of the free hydroxyl group as a silyl ether, reduction of the azide provided the requisite carbocyclic amine **5** in quantitative yield. In summary, the pseudosugar ring was prepared from cyclopentenone **10** after 11 synthetic steps in 15% overall yield. Subsequently, the thymine ring was readily constructed from amine **5** following conventional published methods.[15]

X-ray Structure. The crystal structure of (±)-**4** (Figure 4) confirmed that all the desired stereochemical elements were in place: (1) the anti disposition of the thymine ring and (2) the location of the OH group at the other extreme of the concave face of the bicyclo[3.1.0]hexane template.

Phosphorylation by HSV1-tk. Compound (±)-**4** was radiolabeled in the same manner as compound **1**.[6,7] The course of phosphorylation of (±)-**4** and **1** to the mono- (MP), di- (DP), and triphosphate (TP) stages in HSV-1-infected Vero cells was measured by HPLC (Table 1). The efficient phosphorylation of (±)-**4** relative to S-MCT (**1**) confirmed the success of our reshuffling strategy for all three important phosphorylation steps. Because the first two key phosphorylations are catalyzed by HSV1-tk, our results confirmed that this new compound has all the structural attributes for an effective and improved recognition by the viral enzyme. Because 5′-triphosphate levels are also more elevated for the new compound, it is safe to infer that its molecular architecture is favorably recognized by the cellular dinucleotide kinase as well.

Molecular Modeling and Conformational Analysis. Preliminary docking experiments showed that only one enantiomer of (±)-**4** closely matches the crystal structure of S-MCT (**1**) at the active site of HSV1-tk by forming a similar network of hydrogen bonds (Figure 5). In contrast to compound **1** (Figure 5A), which shows a hydrogen bond to Glu225, the new compound does not form a hydrogen bond to this amino acid (Figure 5B). However, it does show a stronger hydrogen bond to Glu83 and an additional hydrogen bond to Arg163 not seen with **1**. Both compounds form a hydrogen bond to Tyr101. The hydrogen bond network to the thymine nucleobase in both cases is nearly identical. Another reason that explains the superior substrate properties of (±)-**4** versus **1**, which motivated the execution of this work, is entropic. The orientation of the thymine ring in both **1** and (±)-**4** at the active site of HSV1-tk is anti. Compound **1** in solution has been shown to have the thymine ring in the syn orientation; however, the repositioning

(14) Luo, S.; Zhang, B.; He, J.; Janczuk, A.; Wang, P. G.; Cheng, J.-P. *Tetrahedron Lett.* **2002**, *43*, 7369−7371.
(15) Shealey, Y. F.; O'Dell, C. A.; Thorpe, M. C. *J. Heterocycl. Chem.* **1981**, *18*, 383−389.

Table 1. Phosphorylation Levels of **1** and (±)-**4** in HSV-1-Infected Vero Cells (pmoles/10^6 Cells)[a,b]

	S-MCT (**1**)		(±)-**4**	
metabolite	uninfected	infected	uninfected	infected
MP	0.15 ± 0.06	54 ± 14	0.28 ± 0.11	252 ± 32
DP	0.30 ± 0.07	74 ± 17	0.08 ± 0.04	187 ± 15
TP	1.61 ± 0.24	153 ± 10	0.08 ± 0.63	342 ± 26

[a] Cells were infected 2 h before treatment, and the metabolites were measured after 6 h. [b] MP = monophosphate; DP = diphosphate; TP = triphosphate. Cells were treated with 10 μM, 10 μCi/mL of drug. Data are mean ± SD (n = 3).

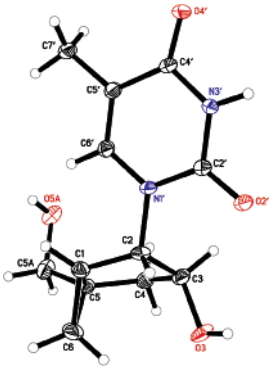


Figure 4. Crystal structure of compound (±)-**4** represented as one enantiomer (displacement ellipsoid plot drawn at the 50% probability level). The numbering system used corresponds to the IUPAC name.

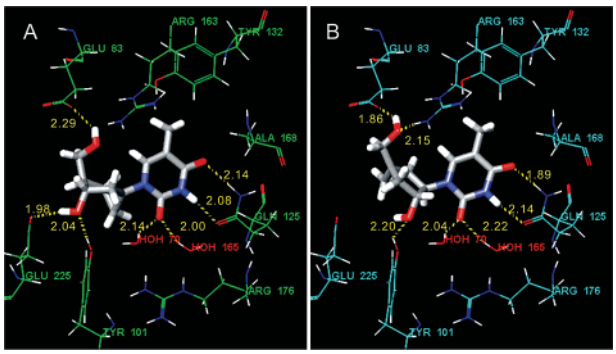


Figure 5. (A) HSV1-tk in complex with compound S-MCT (**1**) (result of redocking **1** into the crystal structure; rmsd from crystal coordinates: 0.278 Å). (B) Result of docking one enantiomer of (±)-**4** at the same active site.

of the cyclopropane ring leading to (±)-**4** flips this ring into the anti range. Therefore, relative to S-MCT (**1**), compound (±)-**4** has already prepaid the entropic penalty incurred in the flipping of the thymine ring in **1** from syn to anti when it binds to HSV-tk.

Surprisingly, the enantiomer of (±)-**4** shown to have the best fit at the active site of HSV-tk (Figure 5B) is the optical antipode of the compound derived according to the strategy outlined in Figure 3. Because this strategy was supposed to generate a southlike conformation, the better fit of the optical antipode, which should correspond to a northlike conformation, appears counter to our rationale. The problem is that because of the two-step reshuffling, the established rules of pseudorotation do not apply,[16] and the enantiomers of nucleosides (±)-**4** can no longer be described as canonical south and north

(16) The calculated pseudorotational angle including the cyclopropane ring and the virtual bond between 1′ and 5′ gave a value of P = 198.3°, which corresponds to a south ($_3$E) conformation. However, the maximum out-of-plane pucker (ν_2), which normally fluctuates between 35° and 45°, comes completely out of range as 100.07°.

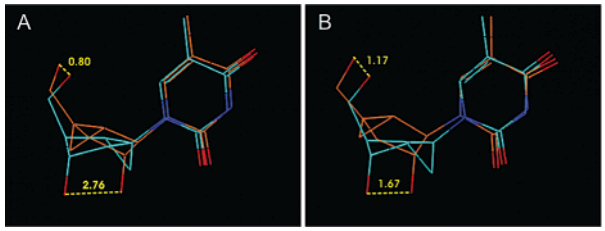


Figure 6. Superimposed docked poses of both enantiomers of (±)-**4** to that of docked S-MCT (**1**) at the active site of HSV-tk. Distances between critical OH groups are in angstroms.

conformers. Indeed, as a result of freeing **1** from its syn bias, according to Figure 3, it was necessary to include the cyclopropane ring and a virtual bond between 1′ and 5′ in (±)-**4** in order to consider the system to be south, thus violating some important pseudorotational rules.[16] Furthermore, the repositioned OH group is removed from its natural location relative to conventional 2′-deoxynucleosides.

To visualize the importance of the new added OH group in directing the docking of the compounds at the active site, we superimposed the individual docked poses of both enantiomers to that of S-MCT (**1**) at the active site of HSV-tk (Figure 6). It can be appreciated that the axial OH in one enantiomer appears displaced 2.76 Å from the axial OH in S-MCT (**1**) (Figure 6A), whereas the axial OH of the other enantiomer, corresponding to the one with the better fit, is displaced only 1.67 Å (Figure 6B). The displacement of the 5′-OH, although somewhat greater for the enantiomer with the best fit (1.17 Å), permits the formation of an additional hydrogen bond to Arg163 which maybe key to explaining why the compound is such a good substrate for HSV-tk (see Table 1).

One caveat about the docking predictions is that we are dealing with a static X-ray structure of an enzyme that executes two phosphorylation steps. For the first phosphorylation step, the enzyme appears to be more forgiving about the presence or absence of the OH group, since a simpler version of compound **3**, lacking the 3′-OH entirely, could be efficiently phosphorylated.[7] However, the presence and correct disposition of the OH becomes critical for phosphorylation to proceed beyond the monophosphate level.

Conclusions

We have shown that changes in the substitution pattern of rigid bicyclo[3.1.0]hexane nucleosides, which relative to normal nucleosides appear unconventional, can lead to the spatial optimization of pharmacophores and a vastly improved kinase activity by HSV1-tk. These changes include the relocation of the cyclopropane ring to relieve the molecule from the unusually high syn ⇆ anti energy barrier and the presence of a free hydroxyl group structurally equivalent to the 3′-hydroxyl group in nucleosides. These changes more than doubled the amount of triphosphate metabolite formed in HSV-1-infected cells (Table 1).

The enantioselective synthesis of both enantiomers of compound (±)-**4** is currently under way to identify the optimal substrate for HSV-tk. The results presented here support the concept that the bicyclo[3.1.0]hexane template of carbocyclic nucleosides is a privileged rigid scaffold that can be appropriately sculpted to fit the specific structural demands of an active site, such as HSV-tk, to improve enzyme recognition.

Experimental Methods

Preparation of Cell Extract for Metabolite Analysis. Vero cells cultures (4×10^6/25 mL flask) were infected with 1 PFU/cell of HSV-1. After a 2 h incubation period, the cells were incubated with radioactive [Me-^{3}H]-**1** or [Me-^{3}H]-(±)-**4**, 10 μM, 5 μCi/mL. These compounds were radiolabeled by Moravek Biochemicals, Brea, CA (specific activities 1100 and 1250 dpm/pmol for **1** and (±)-**4**, respectively). As a control, uninfected cells were treated with the radioactive compounds. At the end of a 6 h incubation period, the cells were washed three times with PBS, trypsinized, and recovered by centrifugation. The dry pellets were suspended in 250 μL of 60% methanol (HPLC grade) and heated at 95 °C for 3 min. After centrifugation at 12 000*g* for 10 min, the clear supernatant fractions were evaporated under nitrogen and redissolved in 250 μL of water. Aliquots of this solution were analyzed by anion-exchanged (SAX-10) HPLC.

HPLC Separation of Metabolites. The separation of **1**, (±)-**4**, and their phosphorylated metabolites was carried out using a Hewlett-Packard 1100 HPLC with a diode array UV absorption detector. A Partisil-10 SAX column (250 mm × 4.6 mm) was used with the following elution program: 0−5 min, 100% buffer A (0.01 M ammonium phosphate, native pH); 5−20 min, linear gradient to 25% buffer B (0.7 M ammonium phosphate with 10% methanol); 20−30 min, linear gradient to 100% buffer B; 30−40 min, 100% buffer B; 40−55 min, linear gradient to 100% buffer A and equilibration. The flow rate was 2 mL/min. One minute fractions were collected, and radioactivity was measured by scintillation spectrometry. Fractions containing radiolabeled compounds were quantitated on the basis of the known specific activity of the parent tritiated compounds.

Molecular Modeling. Docking of compound **1** and both enantiomers of (±)-**4** (only the one that binds effectively is shown in Figure 5B) was performed on the crystal structure 1OF1[8] complexed with S-MCT (**1**) using the program Glide 4.0,[17−19] part of the First Discovery suite, and run via the Maestro interface (Schrödinger, New York, NY). Because the crystal structure of 1OF1 is a dimer, duplicate parts were deleted. All water molecules were deleted too, except 70 and 165, both of which form critical hydrogen bond bridges between ligand **1** and the protein. The bound ligand (**1**) was adjusted manually and then the protein was prepared to produce a new receptor file in which all residues are neutralized except for those that are relatively close to the ligand or form salt bridges. A series of restrained energy minimizations were performed using the Impact[20] utility until the average root-mean-square deviation (rmsd) of the non-hydrogen atoms reached 0.3 Å. In order to study the binding modes of the inhibitors, grid files representing shape and properties of the receptor were generated. The three-dimensional structures of compounds **1** and **4** were constructed using the builder tool available through the Maestro interface. Their initial geometries were optimized using the OPLS_2005 force field, allowing up to 5000 steps of conjugate gradient energy minimization. The compounds were subjected to flexible docking using the precomputed grid files. For each compound, the 100 top-scored poses were saved and analyzed. The rmsd between the native conformation in crystal structure 1OF1 and the best (lowest energy) docked conformation as shown in Figure 5A was 0.278 Å, suggesting that Glide 4.0 predicts the binding modes quite well.

Synthetic Methods. General. All chemical reagents were commercially available. Melting points were taken on a Fisher−Jones apparatus and are uncorrected. Combi-flash column chromatography was performed on silica gel 60 (230−240 mesh) employing a Teledyne Isco instrument, and analytical TLC was performed on Analtech Uniplates silica gel GF. Unless otherwise indicated, NMR spectra were determined in $CDCl_3$ (99.8%) with residual $CHCl_3$ as the reference peak (7.26 and 77.0 ppm) and were recorded on a Varian 400 MHz spectrophotometer. The coupling constants are reported in Hertz, and the peak shifts are reported in the δ (ppm) scale; abbreviations s (singlet), d (doublet), dd (doublet-of-doublets), ddd (doublet-of-doublet-of-doublets), t (triplet), q (quartet), and m (multiplet). Positive-ion fast atom bombardment mass spectra (FABMS) were obtained on a VG 7070E mass spectrometer at an accelerating voltage of 6 kV and a resolution of 2000. Glycerol was used as the sample matrix, and ionization was effected by a beam of xenon atoms. Elemental analyses were performed by Atlantic Microlab. Inc., Norcross, GA. Infrared spectroscopy data was obtained neat with a Jasco FT-IR/615 spectrometer. Specific optical rotations were measured in a Perkin-Elmer model 241 polarimeter. All reaction glassware was oven-dried and cooled to room temperature in an argon atmosphere prior to use.

(3a*R*,6a*R*)-5-(Hydroxymethyl)-2,2-dimethyl-3a,6a-dihydrocyclopenta[1,2-*d*]1,3-dioxolan-4-one (9). To a solution of **10** (1.90 g, 12.30 mmol) in 1:1 THF/H_2O (40 mL) 37% formaldehyde (4.8 mL, 64.94 mmol) and imidazole (420 mg, 6.23 mmol) were added. The mixture was stirred at 0 °C for 4 h. The reaction mixture was extracted with ethyl acetate (3 × 100 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (silica gel) employing hexanes/ethyl acetate (7:3) as eluant to give 1.80 g (79% yield) of pure compound **9** as a colorless oil: $[\alpha<abv>]_D^{20} = -11$ (*c* 0.5, $CHCl_3$); IR (neat) 3459, 1718 cm^{-1}; ^{1}H NMR δ 7.43 (m, 1 H, H-6), 5.24 (m, 1 H, H-6a), 4.54 (d, J = 5.4 Hz, 1 H, H-3a), 4.40 (m*AB*, 2 H, $-CH_2OH$), 1.42 (s, 3 H, $-CH_3$), 1.41 (s, 3 H, $-CH_3$); ^{13}C NMR δ 202.4 (C-4), 152.9 (C-6), 145.8 (C-5), 115.6 ($-C(CH_3)_2$), 77.6 (C-3a), 77.0 (C-6a), 57.3 ($-CH_2$-OH), 27.4 (CH_3), 26.0 (CH_3); FABMS *m*/*z* (relative intensity) 185 (95), 127 (100). Anal. Calcd for $C_9H_{12}O_4 \cdot 0.1H_2O$: C, 58.16; H, 6.63. Found: C, 58.12; H, 6.71.

((3a*R*,6a*R*)-2,2-Dimethyl-4-oxo-3a,6a-dihydrocyclopenta[1,2-*d*]1,3-dioxolan-5-yl)methyl Benzoate (11). To a solution of **9** (1.5 g, 8.20 mmol) in CH_2Cl_2 (50 mL) benzoyl chloride (1.25 mL, 10.66 mmol) and pyridine (0.9 mL, 10.66 mmol) were added at 0 °C. The reaction mixture was stirred at the same temperature for 1 h and at room temperature for 1 h when NH_4Cl (ss, 30 mL) was added, and the aqueous phase was extracted with dichloromethane (2 × 30 mL). The combined organic phases were washed with NH_4Cl (ss, 30 mL), dried ($MgSO_4$), and concentrated. The residue was purified by Combi-flash column chromatography (silica gel) employing hexanes/ethyl acetate (17:3) as eluant to give 2.03 g (86% yield) of pure compound **11** as a colorless oil: $[\alpha<abv>]_D^{20} = 37.8$ (*c* 0.80, $CHCl_3$); IR (neat) 1726 cm^{-1}; ^{1}H NMR δ 8.05 (m, 2 H, Ph), 7.59 (m, 1 H, Ph), 7.49 (q, J = 2.0 Hz, 1 H, H-6), 7.47 (m, 2 H, Ph), 5.25 (m, 1 H, H-6a), 5.07 (dt, J = 15.0, 1.6 Hz, 1 H, $-CH_aHOBz$), 5.02 (dt, J = 15.0, 1.2 Hz, 1 H, $-CH_bOBz$), 4.57 (d, J = 5.5 Hz, 1 H, H-3a), 1.41 (s, 6 H, $-CH_3$); ^{13}C NMR δ 200.8 (C-4), 165.9 (*C*OOPh), 154.1 (C-6), 142.1 (C-5), 133.4 (Ph), 129.7 (Ph), 129.4 (Ph), 128.5 (Ph), 115.6 ($-C(CH_3)_2$), 77.4 (C-3a), 77.0 (C-6a), 58.2 ($-CH_2OBz$), 27.4 (CH_3), 26.1 (CH_3); FABMS *m*/*z* (relative intensity) 289 (74), 231 (47). Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.85; H, 5.66.

((4*S*,3a*S*,6a*R*)-4-Hydroxy-2,2-dimethyl-4,3a,6a-trihydrocyclopenta-[1,2-*d*]1,3-dioxolan-5-yl)methyl Benzoate (8). A solution of **11** (1.24 g, 4.30 mmol) in MeOH (30 mL) was treated with $CeCl_3 \cdot 7H_2O$ (800 mg, 2.15 mmol) and $NaBH_4$ (162 mg, 4.30 mmol) at 0 °C. The reaction mixture was stirred at that temperature for 30 min, pH was adjusted to 7 with acetic acid, and the solution was concentrated in vacuo. The residue was dissolved in $CHCl_3$ (3 × 50 mL), and the organic layer was washed with brine (2 × 20 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by Combi-flash column chromatography (silica gel) employing hexanes/ethyl acetate 4:1 as eluant solvent to afford 1.27 mg (92% yield) of **8** as a white solid: mp 74 °C,

(17) *Glide*, version 4.0; Schrodinger, LLC: New York, 2005.
(18) Friesner, R. A.; Banks, J. L.; Murphy, R. B.; Halgren, T. A.; Klicic, J. J.; Mainz, D. T.; Repasky, M. P.; Knoll, E. H.; Shelley, M.; Perry, J. K.; Shaw, D. E.; Francis, P.; Shenkin, P. S. *J. Med. Chem.* **2004**, *47*, 1739−1749.
(19) Halgren, T. A.; Murphy, R. B.; Friesner, R. A.; Beard, H. S.; Frye, L. L.; Pollard, W. T.; Banks, J. L. *J. Med. Chem.* **2004**, *47*, 1750−1759.
(20) *Impact*, version 4.0; Schrödinger, LLC: New York, 2005.

$[\alpha<abv>]_D^{20} = 22.9$ (*c* 0.60, $CHCl_3$); IR (neat) 3506, 1724 cm^{-1}; ^1H NMR δ 8.06 (m, 2 H, Ph), 7.57 (m, 1 H, Ph), 7.45 (m, 2 H, Ph), 5.88 (m, 1 H, H-6), 5.04 (m, 1 H, H-6a), 5.01 (m, 2 H, $-CH_2OBz$), 4.80 (t, $J = 5.7$ Hz, 1 H, H-3a), 4.58 (d, $J = 5.7$ Hz, 1 H, H-4), 2.80 (bs, 1 H, *OH*), 1.45 (s, 3 H, $-CH_3$), 1.41 (s, 3 H, $-CH_3$); ^{13}C NMR δ 166.1 (*C*OOPh), 144.3 (C-5), 133.1 (Ph), 129.9 (Ph), 129.6 (Ph), 128.4 (Ph), 127.6 (C-6), 112.4 ($-C(CH_3)_2$), 82.2 (C-6a), 77.4 (C-3a), 73.6 (C-4), 60.9 ($-CH_2OBz$), 27.6 (CH_3), 26.4 (CH_3); FABMS *m*/*z* (relative intensity) 291 (24), 275 (12). Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.33; H, 6.30.

[(3a*R*,6a*R*)-2,2-Dimethyl-4-(methylthiothioxomethoxy)-4,3a,6a-trihydrocyclopenta[3,4-*d*]1,3-dioxolan-5-yl]methyl Benzoate (12). A solution of **8** (1.12 mg, 3.48 mmol) in anhydrous THF (20 mL) was treated with CS_2 (1.50 mL, 24.22 mmol) at 0 °C. After stirring for 5 min, NaH (420 mg, 10.46 mmol) was added portionwise, and the reaction mixture was stirred for 30 min at room temperature. MeI (2.82 mL, 45.34 mmol) was added, and the mixture was stirred for extra 30 min. Then, it was cooled to 0 °C and water was added (10 mL). The mixture was extracted with ethyl acetate (3 × 30 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by Combi-flash column chromatography (silica gel) employing hexanes/ethyl acetate (19:1) as solvent to give 1.22 g (92% yield) of **12** as a white solid: mp 77 °C, $[\alpha<abv>]_D^{20} = -49.6$ (*c* 0.50, $CHCl_3$); IR (neat) 1720, 1069, 710 cm^{-1}; ^1H NMR δ 8.05 (m, 2 H, Ph), 7.58 (m, 1 H, Ph), 7.45 (m, 2 H, Ph), 6.24 (m, 1 H, H-4), 6.19 (m, 1 H, H-6), 5.08 (m, 2 H, H-6a, H-3a), 4.97 (m*AB*, $J = 14.2$ Hz, 2 H, $-CH_2$-OBz), 2.58 (s, 3 H, $-SCH_3$), 1.42 (s, 3 H, $-CH_3$), 1.38 (s, 3 H, $-CH_3$); ^{13}C NMR δ 215.4 ($-OC(S)SCH_3$), 165.9 (*C*OOPh), 140.1 (C-5), 133.2 (Ph), 131.8 (C-6), 129.7 (Ph), 129.6 (Ph), 128.4 (Ph), 113.0 ($-C(CH_3)_2$), 82.2 (C-6a)*, 82.2 (C-4)*, 76.8 (C-3a), 60.6 ($-CH_2OBz$), 27.4 (CH_3), 26.7 (CH_3), 19.2 ($-SCH_3$); FABMS *m*/*z* (relative intensity) 381 (9), 365 (4), 323 (34). Anal. Calcd for $C_{18}H_{20}O_5S_2 \cdot 0.3H_2O$: C, 56.08; H, 5.39; S, 16.64. Found: C, 55.85; H, 5.34; S, 16.52.

(±)-(2,2-Dimethyl-4,3a,6a-trihydrocyclopenta[3,4-*d*]1,3-dioxolan-5-yl)methyl Benzoate (13). A solution of **12** (1.00 g, 1.45 mmol) and AIBN (304 mg, 0.97 mmol) in anhydrous toluene (20 mL) was heated to 50 °C under a blanket of argon. Tri-*n*-butyltin hydride (3.05 mL, 5.96 mmol) was slowly added, and when the addition was completed, the reaction mixture was stirred at 120 °C for 1.5 h. The solvent was removed in vacuo, and the residue was purified by Combi-flash column chromatography (silica gel) employing hexanes/ethyl acetate (19:1) as solvent to give 621 mg (88% yield) of **13** as a colorless oil: IR (neat) 1712 cm^{-1}; ^1H NMR δ 8.06 (m, 2 H, Ph), 7.58 (m, 1 H, Ph), 7.45 (m, 2 H, Ph), 5.81 (m, 1 H, H-6), 5.15 (m, 1 H, H-6a), 4.89 (m*AB*, 2 H, $-CH_2OBz$), 4.83 (td, $J = 5.9$, 1.2 Hz, 1 H, H-3a), 2.68 (m, 1 H, H-4_a),2.57 (m, 1 H, H-4_b), 1.44 (s, 3 H, $-CH_3$), 1.36 (s, 3 H, $-CH_3$); ^{13}C NMR δ 166.1 (*C*OOPh), 141.1 (C-5), 133.1 (Ph), 129.9 (Ph), 129.6 (Ph), 128.4 (Ph), 126.8 (C-6), 109.9 ($-C(CH_3)_2$), 85.0 (C-6a), 78.0 (C-3a), 62.9 ($-CH_2OBz$), 39.1 (C-4), 27.4 (CH_3), 25.6 (CH_3); FABMS *m*/*z* (relative intensity) 259 (8), 217 (59). Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 69.69; H, 6.83.

(±)-(3,4-Dihydroxycyclopent-1-enyl)methyl Benzoate (14). A solution of **13** (536 mg, 1.96 mmol) in 60% aqueous acetic acid (5 mL) was heated to 50 °C for 1 h. The solvent was removed in vacuo, and the residue was purified by Combi-flash column chromatography (silica gel) employing hexanes/ethyl acetate (2:3) as solvent to give 344 mg (75% yield) of **14** as a colorless oil: IR (neat) 3358, 1718 cm^{-1}; ^1H NMR δ 8.03 (m, 2 H, Ph), 7.55 (m, 1 H, Ph), 7.42 (m, 2 H, Ph), 5.78 (m, 1 H, H-2), 4.86 (m*AB*, 2 H, $-CH_2OBz$), 4.63 (m, 1 H, H-3), 4.39 (m, 1 H, H-4), 2.66 (m, 1 H, H-5_a), 2.42 (m, 1 H, H-5_b); ^{13}C NMR δ 166.2 (*C*OOPh), 141.9 (C-1), 133.2 (Ph), 129.8 (Ph), 129.7 (Ph), 128.5 (Ph), 127.3 (C-2), 75.8 (C-3), 71.1 (C-4), 63.0 ($-CH_2OBz$), 40.0 (C-5); FABMS *m*/*z* (relative intensity) 235 (14), 217 (82). Anal. Calcd for $C_{13}H_{14}O_4.0 \cdot 2H_2O$: C, 65.69; H, 6.11. Found: C, 65.62; H, 6.15.

(±)-(3,4-Dihydroxybicyclo[3.1.0]hexyl)methyl Benzoate (6). Diethylzinc (1.0 M in hexanes, 13 mL, 15.00 mmol) and a solution of diiodomethane (1.10 mL, 14.50 mmol) in dichloromethane (10 mL) were added to a solution of **14** (1.29 g, 5.52 mmol) in dichloromethane (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 48 h. NH_4Cl (ss, 15 mL) was added, and the mixture was extracted with dichloromethane (3 × 30 mL). The organic phase was dried and concentrated in vacuo. The residue was purified by Combi-flash column chromatography (silica gel) employing hexanes/ethyl acetate (3:2) as eluant to give 699 mg (51% yield) of **6** as a colorless oil and 385 mg (30% yield) of a regioisomeric mixture of monoylated alcohols. Compound **6**: IR (neat) 3423, 1714 cm^{-1}; ^1H NMR δ 8.04 (m, 2 H, Ph), 7.57 (m, 1 H, Ph), 7.45 (m, 2 H, Ph), 4.54 (t, $J = 5.4$ Hz, 1 H, H-4), 4.29 (*AB*q, $J = 11.6$ Hz, 2 H, $-CH_2OBz$), 4.16 (t, $J = 6.2$ Hz, 1 H, H-3), 2.26 (ddd, $J = 14.1$, 6.6, 1.8 Hz, 1 H, H-2_a), 2.12 (d, $J = 14.1$ Hz, 1 H, H-2_b), 2.05 (bs, 2 H, *OH*), 1.65 (m, 1 H, H-5), 1.36 (t, $J = 4.4$ Hz, 1 H, H-6_a), 0.68 (m, 1 H, H-6_b); ^{13}C NMR δ 166.6 ($-COOPh$), 133.0 (Ph), 130.2 (Ph), 129.6 (Ph), 128.4 (Ph), 75.3 (C-4), 71.3 (C-3), 69.1 ($-CH_2OBz$), 37.0 (C-2), 27.8 (C-5), 26.9 (C-1), 13.3 (C-6); FABMS *m*/*z* (relative intensity) 249 (34), 231 (44). Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.43; H, 6.54.

((4*S*,6*S*,1*R*,2*R*)-8-Oxo-7,9-dioxa-8-thiatricyclo[4.3.0.0⟨2,4⟩]non-4-yl)methyl Benzoate (15). Et_3N (1.20 mL, 8.70 mmol) and $SOCl_2$ (0.24 mL, 3.26 mmol) were added to a solution of **6** (540 mg, 2.18 mmol) in dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred at the same temperature for 10 min and was then partitioned between water (20 mL) and ethyl ether (40 mL). The organic phase was washed with brine (2 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by Combi-flash column chromatography (silica gel) employing hexanes/ethyl acetate (4:1) as eluant to give 615 mg (96% yield) of a diasteriomeric mixture **15** as a colorless oil: ^1H NMR δ 8.04 (m, 2 H, Ph), 7.59 (m, 1 H, Ph), 7.46 (m, 2 H, Ph), 5.69 (t, $J = 5.9$ Hz, 1 H, H-1), 5.55 (dd, $J = 7.4$, 5.3 Hz, 1 H, H-1′), 5.45 (t, $J = 6.8$ Hz, 1 H, H-6), 5.21 (td, $J = 7.4$, 2.0 Hz, 1 H, H-6′), 4.34 (d, $J = 11.9$ Hz, 1 H, $-CH_aHOBz$), 4.33 (d, $J = 11.9$ Hz, 1 H, $-CH_a$-HOBz′), 4.24 (d, $J = 11.9$ Hz, 1 H, $-CHH_bOBz$), 4.22 (d, $J = 11.9$ Hz, 1 H, $-CHH_bOBz'$), 2.58 (ddd, $J = 15.4$, 7.2, 2.0 Hz, 1 H, H-5_a), 2.51 (ddd, $J = 15.2$, 7.8, 1.8 Hz, 1 H, H-5_a′), 2.40 (d, $J = 15.4$ Hz, 2 H, H-5_b, H-5_b′), 1.86 (m, 2 H, H-2, H-2′), 1.81 (dd, $J = 6.1$, 4.3 Hz, 1 H, H-3_a), 1.19 (m, 1 H, H-3_b), 0.99 (m, 1 H, H-3_a′), 0.92 (dd, $J = 5.9$, 4.3 Hz 1 H, H-3_b′); ^{13}C NMR δ 166.3 ($-COOPh$), 133.2 (Ph), 129.9 (Ph), 129.8 (Ph), 129.6 (Ph), 128.45 (Ph), 128.43 (Ph), 90.9 (C-1′), 89.5 (C-6′), 87.9 (C-1), 84.7 (C-6), 68.5 ($-CH_2OBz$), 67.9 ($-CH_2$-OBz′), 35.3 (C-5′), 33.9 (C-5), 33.3 (C-4), 33.1 (C-4′), 27.3 (C-2), 26.7 (C-2′), 18.6 (C-3), 15.5 (C-3′); FABMS *m*/*z* (relative intensity) 295 (24), 231 (21), 173 (18). Anal. Calcd for $C_{14}H_{14}O_5S$: C, 57.13; H, 4.79. Found: C, 57.47; H, 4.89.

[(±)-4-(Diazoazamvinyl)-3-hydroxybicyclo[3.1.0]hexyl]methyl Benzoate (16) and [(±)-3-(Diazoazamvinyl)-4-hydroxybicyclo[3.1.0]-hexyl]methyl Benzoate (17). A solution of **15** (1.74 g, 5.91 mmol) in anhydrous DMF (20 mL) was treated with sodium azide (780 mg, 11.82 mmol) at 100 °C for 15 h. Water (20 mL) was added, and the mixture was extracted with ethyl acetate (3 × 20 mL); the organic phase was washed with brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by Combi-flash column chromatography (silica gel) employing hexanes/ethyl acetate (3:1) as solvent to give 1.25 g (78%) of **16** and 207 mg (13%) of undesired regioisomer **17** (91% overall yield). Compound **16**: IR (neat) 3463, 2091, 1715 cm^{-1}; ^1H NMR δ 8.03 (m, 2 H, Ph), 7.53 (m, 1 H, Ph), 7.41 (m, 2 H, Ph), 4.35 (*AB*q, $J = 11.7$ Hz, 2 H, $-CH_2OBz$), 4.24 (d, $J = 6.8$ Hz, 1 H, H-3), 4.64 (s, 1 H, H-4), 2.35 (ddd, $J = 14.2$, 7.0, 2.2 Hz, 1 H, H-2_a), 1.91 (d, $J = 14.2$ Hz, 1 H, H-2_b), 1.72 (bs, 1 H, $-OH$), 1.60 (ddd, $J = 9.2$, 4.1, 1.6 Hz, 1 H, H-5), 1.23 (dd, $J = 5.5$, 4.5 Hz, 1 H, H-6_a), 0.87 (ddd, $J = 9.2$, 5.3, 2.0 Hz, 1 H, H-6_b); ^{13}C NMR δ 166.6 ($-COOPh$), 133.0 (Ph), 130.2 (Ph), 129.6 (Ph), 128.4 (Ph), 78.1 (C-3), 69.6 (C-4), 68.5 ($-CH_2OBz$), 37.9 (C-2), 29.2 (C-1), 26.1 (C-5), 15.0 (C-6); FABMS *m*/*z* (relative intensity) 274 (19), 256 (15). Anal. Calcd for $C_{14}H_{15}N_3O_3 \cdot 0.1H_2O$: C, 61.13; H, 5.57; N, 15.28. Found: C, 61.35;

H, 5.76; N, 14.93. Compound **17**: IR (neat) 3463, 2091, 1715 cm^{-1}; ^1H NMR δ 8.04 (m, 2 H, Ph), 7.58 (m, 1 H, Ph), 7.46 (m, 2 H, Ph), 4.39 (dd, J = 7.0, 5.1 Hz, 1 H, H-4), 4.30 (*AB*q, J = 11.7 Hz, 2 H, $-CH_2OBz$), 3.37 (dt, J = 9.8, 7.4 Hz, 1 H, H-3), 2.35 (dd, J = 12.7, 7.6 Hz, 1 H, H-2_a), 1.97 (ddd, J = 12.7, 9.8, 1.2 Hz, 1 H, H-2_b), 1.90 (bs, 1 H, $-OH$), 1.66 (m, 1 H, H-5), 0.97 (dd, J = 6.1, 4.1 Hz, 1 H, H-6_a), 0.73 (m, 1 H, H-6_b); ^{13}C NMR δ 166.5 ($-COOPh$), 133.1 (Ph), 130.0 (Ph), 129.6 (Ph), 128.4 (Ph), 78.2 (C-4), 68.5 ($-CH_2OBz$), 64.9 (C-3), 32.9 (C-2), 25.7 (C-5), 24.9 (C-1), 11.1 (C-6); FABMS *m*/*z* (relative intensity) 274 (14), 256 (12). Anal. Calcd for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.39. Found: C, 61.57; H, 5.59; N, 14.25.

(±)-[4-(Diazoazamvinyl)-3-(1,1,2,2-tetramethyl-1-silapropoxy)-bicyclo[3.1.0]hexyl] Methyl Benzoate (18). To a solution of **16** (484 mg, 1.77 mmol) in anhydrous dichloromethane (10 mL), pyridine (0.2 mL, 2.66 mmol) and TBDMSTf (0.61 mL, 2.66mmol) were added. The reaction mixture was stirred at 0 °C for 1 h. Brine (10 mL) and dichloromethane (20 mL) were added, and the aqueous phase was extracted with dichloromethane (2 × 20 mL). The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by Combi-flash column chromatography (silica gel) employing hexanes as solvent to give 685 mg (100% yield) of **18** as a colorless oil: IR (neat) 2092, 1718 cm^{-1}; ^1H NMR δ 8.07 (m, 2 H, Ph), 7.56 (m, 1 H, Ph), 7.45 (m, 2 H, Ph), 4.47 (d, J = 11.7 Hz, 1 H, $-CH_aHOBz$), 4.30 (d, J = 11.7 Hz, 1 H, $-CH_bHOBz$), 4.16 (dd, J = 6.5, 1.5 Hz, 1 H, H-3), 3.57 (s, 1 H, H-4), 2.31 (ddd, J = 13.8, 6.6, 2.0 Hz, 1 H, H-2_a), 1.85 (d, J = 13.8 Hz, 1 H, H-2_b), 1.57 (ddd, J = 9.1, 4.1, 1.5 Hz, 1 H, H-5), 1.30 (m, 1 H, H-6_a), 0.87 (s, 9 H, $-C(CH_3)_3$), 0.85 (m, 1 H, H-6_b), 0.05 (s, 3 H, $-CH_3$), 0.05 (s, 3 H, $-CH_3$); ^{13}C NMR δ 166.6 ($-COOBz$), 132.9 (Ph), 130.3 (Ph), 129.6 (Ph), 128.3 (Ph), 78.3 (C-3), 70.1 (C-4), 68.6 ($-CH_2OBz$), 38.2 (C-2), 29.1 (C-1), 25.9 (C-5), 25.7 ($C(CH_3)_3$), 17.8 ($-C(CH_3)_3$), 14.7 (C-6), −4.9 ($-CH_3$), −5.0 ($-CH_3$); FABMS *m*/*z* (relative intensity) 388 (4), 345 (4). Anal. Calcd for $C_{20}H_{29}N_3O_3Si$: C, 61.98; H, 7.54; N, 10.84. Found: C, 62.09; H, 7.60; N, 10.67.

(±)-[3-Hydroxy-4-(5-methyl-2,4-dioxo(1,3-dihydropyrimidinyl))-bicyclo[3.1.0]hexyl] Methyl Benzoate (20). Lindlar's catalyst (80 mg) was added to a solution of **18** (667 mg, 1.72 mmol) in dichloromethane/methanol (1:1, 25 mL). The reaction mixture was stirred under H_2 (g) atmosphere (1 atm) at room temperature overnight. The suspension was filtered through a Celite pad, and the solvent was removed in vacuo to give 622 mg (100% yield) of **5** as a colorless oil that was used as such in the next step. To a suspension of AgNCO (480 mg, 3.16 mmol, dried overnight under vacuum at 100 °C) in anhydrous benzene (10 mL) a solution of (2*E*)-3-methoxy-2-methylprop-2-enoyl chloride (500 mg, 3.50 mmol) in anhydrous benzene (5 mL) was added dropwise under argon. The mixture was heated at reflux for 1 h and then was allowed to reach room temperature. The supernatant was added through canula to a solution of **5** (610 mg, 1.72 mmol) in anhydrous benzene (5 mL) at 10 °C. The reaction mixture was allowed to reach room temperature and was stirred for 3 h. The solvent was removed in vacuo, and the residue was purified by Combi-flash chromatography (hexanes/ethyl acetate, 1:1) to afford 793 mg (94% yield) of **19** as a colorless oil that was used as such in the next step. Thus, compound **19** (771 mg, 1.53 mmol) was dissolved in ethanol (15 mL), and 2 N HCl (1.5 mL) was added. The reaction mixture was refluxed for 15 h. The solvent was removed in vacuo, and the residue was coevaporated with ethanol (3 × 10 mL) and purified by Combi-flash chromatography (CH_2Cl_2/MeOH, 19:1) to give 452 mg (83% yield) of pure **20** as a white solid: mp 165−167 °C, IR (neat) 2927, 2855, 1702, 1693 cm^{-1}; ^1H NMR δ 10.09 (bs, N*H*), 8.03 (m, 2 H, Ph), 7.60 (m, 1 H, Ph), 7.36 (m, 2 H, Ph), 7.36 (d, J = 0.9 Hz, 1 H, H-6), 4.75 (d, J = 12.1 Hz, 1 H, $-CH_a$-HOBz), 4.74 (s, 1 H, H-4), 4.29 (d, J = 12.1 Hz, 1 H, $-CH_bHOBz$), 4.16 (d, J = 6.9 Hz, 1 H, H-3), 2.41 (dd, J = 14.4, 6.9 Hz, 1 H, H-2_a), 1.99 (d, J = 14.4 Hz, 1 H, H-2_b), 1.58 (d, J = 0.9 Hz, 1 H, $-CH_3$), 1.49 (m, 2 H, H-5, H-6_a), 0.95 (m, 1 H, H-6_b); ^{13}C NMR δ 166.6 ($-COOBz$), 164.0 (C-4), 151.5 (C-2), 136.3 (C-6), 133.5 (Ph), 129.6 (Ph), 128.6 (Ph), 111.2 (C-5), 78.8 (C-3′), 67.8 ($-CH_2OBz$), 66.0 (C-4′), 35.8 (C-2′), 31.0 (C-1′), 25.0 (C-5′), 14.2 (C-6′), 12.3 ($-CH_3$); FABMS *m*/*z* (relative intensity) 357 (55), 235 (100). Anal. Calcd for $C_{19}H_{20}N_2O_5 \cdot 0.6H_2O$: C, 62.19; H, 5.82; N, 7.63. Found: C, 61.94; H, 5.90; N, 7.32.

(±)-[3-Hydroxy-5-(hydroxymethyl)bicyclo[3.1.0]hex-2-yl]-5-methyl-1,3-dihydropyrimidine-2,4-dione ((±)-4). Compound **20** (367 mg, 1.03 mmol) was treated with methanolic ammonia (5 mL) at 70 °C for 40 h. The volatiles were removed, and the residue was purified by Combi-flash chromatography (CH_2Cl_2/MeOH, 93:7) to give 224 mg (89% yield) of pure (±)-**4** as a white solid: mp 114−116 °C, IR (neat) 3371, 3008, 1682, 1634 cm^{-1}; ^1H NMR (CD_3OD) δ 7.93 (d, J = 1.2 Hz, 1 H, H-6), 4.69 (s, 1 H, H-2′), 4.04 (d, J = 7.3 Hz, 1 H, H-3′), 4.02 (d, J = 11.7 Hz, 1 H, $-CH_aHOH$), 3.34 (d, J = 11.7 Hz, 1 H, $-CH_b$-OH), 2.44 (ddd, J = 14.3, 7.3, 2.0 Hz, 1 H, H-$4'_a$), 1.86 (d, J = 1,2 Hz, 3 H, $-CH_3$), 1.71 (d, J = 14.3 Hz, 1 H, H-$4'_b$), 1.32 (ddd, J = 9.2, 4.0, 1.4 Hz, 1 H, H-1′), 1.16 (dd, J = 4.9, 4.0 Hz, 1 H, H-$6'_a$), 0.77 (ddd, J = 9.2, 4.9, 2.0 Hz, 1 H, H-6_b); ^{13}C NMR δ 166.5 (C-4), 152.9 (C-2), 139.9 (C-6), 111.2 (C-5), 80.1 (C-3′), 66.4 (C-2′), 66.3 ($-CH_2$-OH), 37.1 (C-5′), 34.6 (C-4′), 26.2 (C-1′), 15.0 (C-6′), 12.4 ($-CH_3$); FABMS *m*/*z* (relative intensity) 253 (100). Anal. Calcd for $C_{12}H_{16}N_2O_4 \cdot 1.3H_2O$: C, 52.31; H, 6.81; N, 10.17. Found: C, 52.04; H, 6.53; N, 9.88. X-ray structure: diffraction quality crystals of compound (±)-**4** were grown by slow evaporation from water. Single-crystal X-ray diffraction data on (±)-**4** were collected at 103 °K using Mo Kα radiation and a Bruker APEX II CCD area detector (see the Supporting Information for details). Atomic coordinates for compound (±)-**4** have been deposited with the Cambridge Crystallographic Data Centre (deposition number 629315). Copies of the data can be obtained, free of charge, upon application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, U.K. [fax, +44(0)-1223-336033 or e-mail, deposit@ccdc.cam.ac.uk].

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Supporting Information Available: ^1H and ^{13}C NMR spectra of new compounds, complete crystallographic data of compound **4**, and crystallographic data in CIF format. This material is free of charge via the Internet at http://pubs.acs.org.

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