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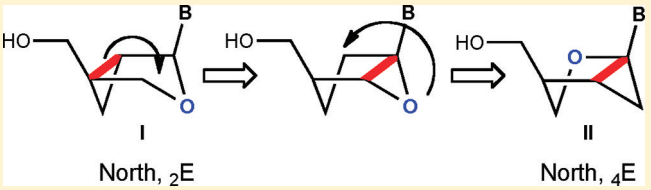
Synthesis of Conformationally North-Locked Pyrimidine Nucleosides Built on an Oxabicyclo[3.1.0]hexane Scaffold

Olaf R. Ludek and Victor E. Marquez*

Chemical Biology Laboratory, Center for Cancer Research, National Cancer Institute at Frederick, National Institutes of Health, Frederick, Maryland 21702, United States

Supporting Information

ABSTRACT: Beginning with a known 3-oxabicyclo[3.1.0]-hexane scaffold (I), the relocation of the fused cyclopropane ring bond and the shifting of the oxygen atom to an alternative location engendered a new 2-oxabicyclo[3.1.0]hexane template (II) that mimics more closely the tetrahydrofuran ring of conventional nucleosides. The synthesis of this new class of locked nucleosides involved a novel approach that required the isocyanate II (B = NCO) with a hydroxyl-protected scaffold as a pivotal intermediate that was obtained in 11 steps from a known dihydrofuran precursor. The completion of the nucleobases was successfully achieved by quenching the isocyanate with the lithium salts of the corresponding acrylic amides that led to the uracil and thymidine precursors in a single step. Ring closure of these intermediates led to the target, locked nucleosides. The anti-HIV activity of **29** (uridine analogue), **31** (thymidine analogue), and **34** (cytidine analogue) was explored in human osteosarcoma (HOS) cells or modified HOS cells (HOS-313) expressing the herpes simplex virus 1 thymidine kinase (HSV-1 TK). Only the cytidine analogue showed moderate activity in HOS-313 cells, which means that the compounds are not good substrates for the cellular kinases.



INTRODUCTION

The conformationally rigid bicyclo[3.1.0]hexane scaffold in **1** and **2** has been employed successfully to discern the North/South conformational preferences of several nucleoside(tide) binding enzymes for their natural substrates (Figure 1).[1]

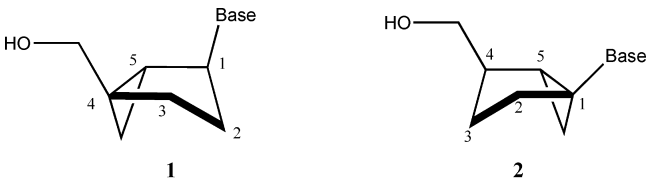


Figure 1. Conformationally locked nucleosides showing the value of *P* of the embedded cyclopentane ring in the pseudorotational cycle. Nucleoside numbering (clockwise) is used beginning with 1 at the point of attachment of the base. C_5 occupies the site of the oxygen; the carbon at the tip of the cyclopropane ring is excluded from the numbering.

However, in some enzymes, such as adenosine and cytidine deaminases, the degree of North/South discrimination occurs with a significant loss in binding affinity, even for the preferred rigid conformer.[2,3] This drop in affinity has been attributed to the missing oxygen, which could either interact with key amino acids at the active site through hydrogen bonding or participate in important electronic interaction with the base through the anomeric effect.[3,4]

In order to introduce an oxygen atom into the original bicyclo[3.1.0]hexane system, we previously synthesized a set of locked North/South isomers with an oxabicyclo[3.1.0]hexane template represented by structures **3** and **4** (Figure 2).[4]

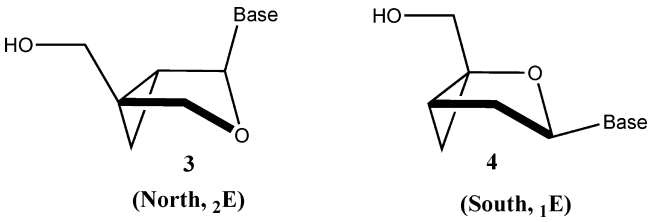


Figure 2. Structures of two oxabicyclo[3.1.0]hexane nucleosides and their positions in the pseudorotational cycle.

However, the position of the oxygen in compound **3** is not equivalent to that of a typical nucleoside, and hence, it is not a good partner for compound **4**, where the oxygen is in the corresponding position of a normal nucleoside. To overcome this deficiency, we propose reshuffling some bonds and atoms in compound **3**—as depicted in Figure 3—to restore the oxygen to a position equivalent to that corresponding to a conventional nucleoside.

With these changes implemented, both the South **4** ($_1$E) and the North **5** ($_4$E) isomers contain an embedded tetrahydrofuran ring that corresponds to equivalent nucleoside antipodes in the

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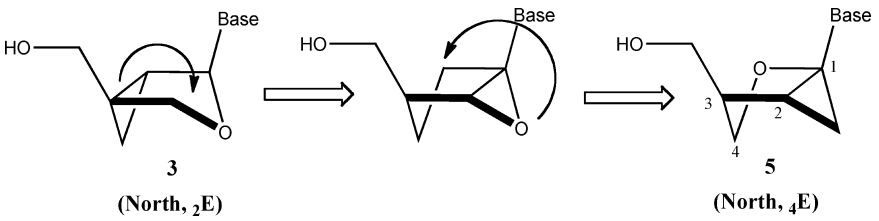


Figure 3. "Reshuffling" of the North oxabicyclo[3.1.0]hexane template **3** to generate a new North oxabicyclo[3.1.0]hexane scaffold (**5**) with a conventional glycosyl bond. The carbon at the tip of the cyclopropane ring is excluded from the numbering system.

South and North hemispheres, respectively, although both conformations appear significantly shifted toward the East (Figure 4). In the present investigation, we describe the

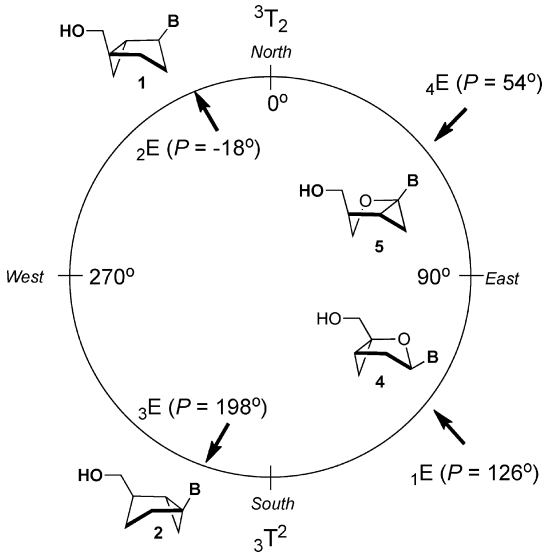


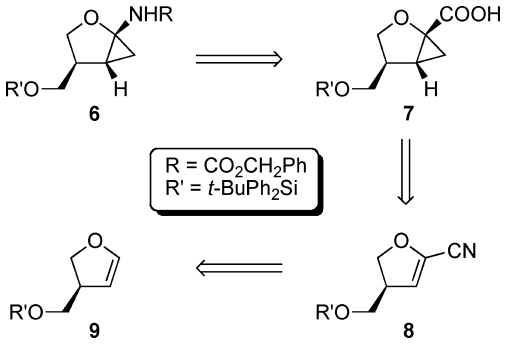
Figure 4. Pseudorotational cycle positions of both types of conformationally locked nucleosides: the bicyclo[3.1.0]hexanes **1** ($_2$E) and **2** ($_3$E) and the oxabicyclo[3.1.0]hexanes **4** ($_1$E) and **5** ($_4$E) relative to the perfect North (^{3}T$_2$) and South ($_3$T^2) conformations.

synthesis of three pyrimidine analogues with the template exhibited by **5**.

RESULTS AND DISCUSSION

The proposed approach was inspired on the strategy that was successful in the synthesis of the locked carbocyclic South series,[5] where the adjacency of the cyclopropane moiety to the anomeric/pseudoanomeric position prevented the use of a convergent glycosylation reaction. Therefore, we decided to pursue a linear strategy for the construction of the heterocyclic nucleobase, starting from the bicyclic amine **6** suitably protected with an easily removable group (Scheme 1). This amine, in turn, could be made from the corresponding carboxylic acid **7** via Curtius degradation, which is known to proceed under mild conditions without isomerization. In our previous work,[5] we have shown that carboxylic acids at the bridgehead of a bicyclo[3.1.0]hexane template could be obtained by reaction of an α,β-unsaturated nitrile with diazomethane and subsequent saponification of the nitrile. On the basis of such precedent, compound **8** was expected to react similarly. Carbon−carbon bond formation at the anomeric position of glycals is well documented[6] and could be used for the introduction of functionality at the 5-position of the chiral

Scheme 1. Retrosynthetic Analysis of the (North)-Oxabicyclo[3.1.0]hexane Scaffold



dihydrofuran **9**, a compound already reported by Jung et al.[7] The enantiomerically pure starting dihydrofuran **9** was thus prepared according to the published seven-step procedure using commercially available (*S*)-glycidol as a chiral precursor.[7,8]

Initially, we attempted to introduce a one-carbon side chain by regioselective lithiation of the enol ether moiety in **9** followed by reaction with an appropriate electrophile (Scheme 2). Although metalation of **9** with *t*-BuLi proceeded very fast at the desired 5-position in greater than 95% yield, as judged by ^{1}H NMR and TLC analysis of the reaction of **10** with CD_3OD showing no decomposition,[9] we were unable to alkylate **10** with one-carbon fragments such as *m*-formaldehyde or benzyl chloromethyl ether. In contrast to reports from Meyers et al.,[10] no reaction was observed with *m*-formaldehyde, while TLC showed a range of products resulting from decomposition of the starting material **9** when benzyl chloromethyl ether was used as the aklylating agent. The use of dimethyl carbonate as a one-carbon fragment in the alkylations of **10** resulted in formation of the methyl ester **11**; however, the yield was below 20%. Interestingly, when benzaldehyde was used as electrophile, **10** was alkylated in 68% yield (results not shown).

Since we were unable to introduce the side chain at position 5 of the dihydrofurane system by this approach, we pursued a strategy derived from classical carbohydrate chemistry employing an OsO_4-catalyzed *cis*-dihydroxylation of the double bond in **9** with subsequent acetylation of the resulting hydroxy groups (92% yield, two steps, Scheme 3). The α- and β-anomers of **12** were obtained in a 1:1 ratio.[7] Introduction of the one-carbon fragment at C_1 was accomplished by a *C*-glycosylation reaction using $(CH_3)_3SiCN$ (TMSCN) as the nucleophile.[11] Because of the neighboring effect of the C_2 acetate in **12**, only the β-anomer **13** was obtained in 93% yield. We found that the reported solvent for this reaction, nitromethane, could be easily replaced with the more convenient solvent acetonitrile. DBU-promoted elimination of acetic acid from **13** led directly to the dihydrofuran intermediate **8** with a double bond suitable for cyclo-

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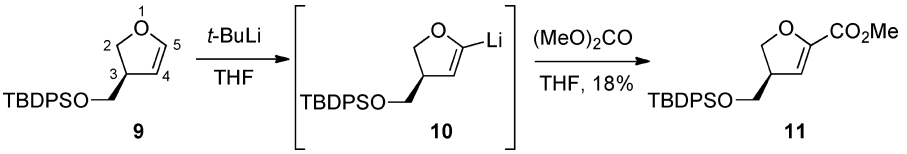
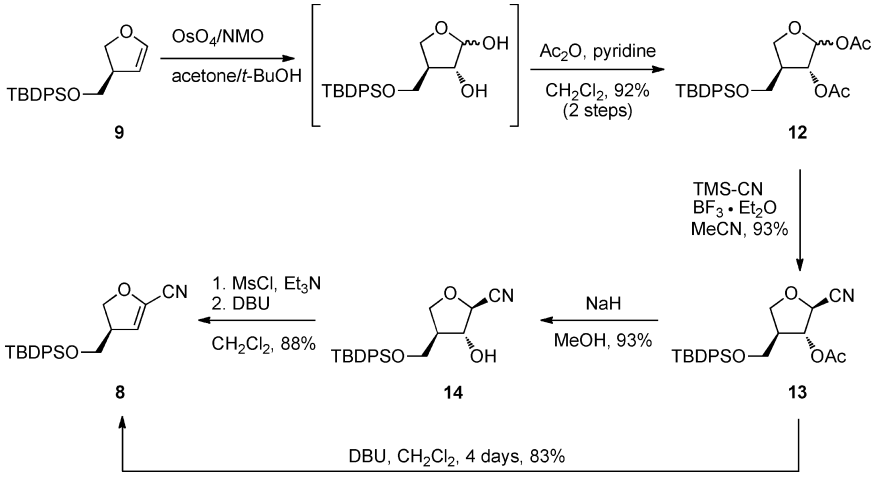
Scheme 2



Scheme 3

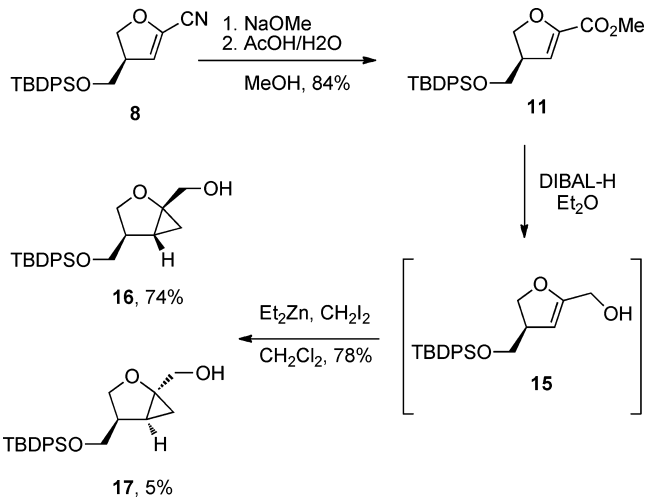


propanation. However, the reaction time for the elimination was very long (4 days); therefore, the secondary hydroxy group in **13** was readily deacetylated with sodium methoxide in methanol and subsequently mesylated. Elimination of the mesylate proceeded smoothly within minutes, and **8** was obtained in 82% over three steps.

From our expertise in constructing the bicyclo[3.1.0]hexane system locked in the southern hemisphere of the pseudorotational cycle,[5] we decided to introduce the cyclopropane ring to the double bond in **8** by forming a fused pyrazoline moiety via an 1,3-dipolar cycloaddition of diazomethane and subsequent light-mediated extrusion of nitrogen.[12] Surprisingly, the dihydrofuran **8** proved to be stable toward reaction with diazomethane, even under $Pd(OAc)_2$ catalysis.[13] It is likely that the fused vinyl ether system raises the energy of the LUMO of the dipolarophile and prevents formation of the cycloaddition product.[14] Switching to Simmons–Smith based methods (CH_2I_2/diethylzinc;[15] CH_2I_2/diethylzinc/O_2;[16] CH_2ICl/diethylzinc;[17] CH_2I_2/triethylaluminum;[18] CH_2I_2/Zn(Cu);[19] and CH_2I_2, Zn, CuCl, acetyl chloride[20]), which are used for cyclopropanating activated olefins, was also unsuccessful and in all cases unchanged starting material **8** was reisolated. In an attempt to influence the electronic properties of the C=C double bond, we converted the nitrile in **8** to the corresponding methyl ester (**11**) by reaction with sodium methoxide and subsequent hydrolysis of the imidate (see Scheme 4). Unfortunately, repeating the aforementioned methods for cyclopropanation on this α,β-unsaturated ester also failed, and no bicyclic product was isolated. Interestingly, cyclopropanation of **8** with dichlorocarbene,[21] generated from chloroform and sodium hydroxide, appeared to have been successful but subsequent attempts to remove the halogens with lithium aluminum hydride led to decomposition.

Finally, an effective cyclopropanation was achieved after diisobutylaluminium hydride (DIBAL-H) reduction of the ester side chain in **11** to the primary alcohol **15** and subsequent

Scheme 4



application of the Furukawa protocol of the Simmons–Smith reaction (Scheme 4).[15] Because the intermediate alcohol **15** was not stable at room temperature, the crude was immediately subjected to the cyclopropanation reaction. Aided by the bulky *tert*-butyldiphenylsilyl protecting group, the reaction proceeded with high stereoselectivity from the less shielded α-side of the molecule to form the desired isomer **16** and only a small amount of the undesired β-regioisomer **17** was formed (ratio 15:1, 78% combined yield after two steps). The bicyclic alcohols **16** and **17** are stable compounds and were easily separated by regular silica gel chromatography.

The stereochemical assignment of both isomers (**16**/**17**) was based on the distinct ^1H NMR spectra of both compounds (Figure 5). Because of the preferred boat-like conformation and the intrinsic rigidity of the oxobicyclo[3.1.0]hexane system, coupling constants can easily be predicted by Karplus' equation. The major isomer **16** shows only a *dd*-system for H_5, with

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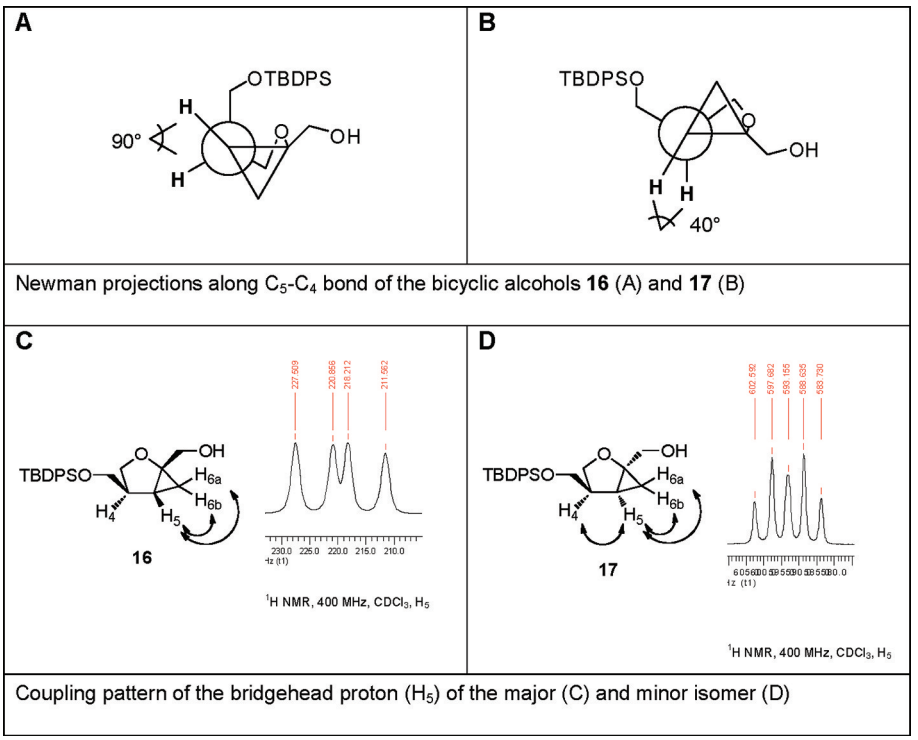

Figure 5. Stereochemical assignment of both isomers **16** and **17** based on ^{1}H NMR spectroscopy.

coupling constants of 9.3 and 4.8 Hz to the cyclopropyl protons H_{6a} and H_{6b}, respectively. No coupling is observed to H_4 as a result of a dihedral angle of 90° between H_4 and H_5. This result is in accordance with the predicted α-cyclopropanation. As for the minor isomer **17**, clearly the H_5 proton shows a *ddd*-coupling pattern, with coupling constants of 9.4 and 4.9 Hz to both cyclopropyl protons (H_{6a} and H_{6b}), as well as a 4.9 Hz coupling to H_4. A coupling constant of 4.9 Hz translates into a dihedral angle of about 40°, supporting the proposed β-side attack for the isolated minor isomer.

After having established the relative stereochemistry of both bicyclic alcohols **16** and **17**, the hydroxymethyl moiety in **16** had to be reoxidized to the corresponding carboxylic acid **7**. Therefore, the alcohol **16** was first oxidized to the aldehyde **18** by a Swern procedure, followed by sodium chlorite oxidation (Scheme 5). Later, this two-step procedure was changed in favor of a more convenient, one-step oxidation with sodium periodate and ruthenium(III) catalysis.[22]

The acid **7** was subjected to a Curtius degradation, using diphenylphosphoryl azide (DPPA) as azide source. Heating of the crude acyl azide in toluene afforded the intermediate isocyanate **20**, which was quenched by addition of benzyl alcohol to form the stable benzyl carbamate **6** (73%, three steps). Unfortunately, all attempts to generate the amine by hydrogenolytic benzyl cleavage failed and only products resulting from decomposition were observed by TLC analysis. Presumably, the strained nature of the hemiaminal in **21** leads to an opening of the cyclopropyl moiety and loss of structural integrity.[23] As an alternative, the intermediate isocyanate **20** was reacted with ammonia, leading to the urea **22** in 72% yield. Although acylations of ureas to form precursors of pyrimidine nucleobases are common procedures in nucleoside chemistry, we were unable to obtain the acyl urea upon reaction with **23** by this strategy, possibly due to the poor nucleophilicity of the urea moiety in **22**.

Finally, introduction of the nucleobase precursor was successfully achieved by quenching the intermediate isocyanate **20** with the lithium salts of the acrylic amides **24** and **25**, leading to the uracil and thymidine precursors **26** and **27**, which were obtained in 34 and 41% yield, respectively (Scheme 5).[24] Due to the instability of the glycon in strong acid media, the ring-closure was performed in aqueous ammonium hydroxide solution, followed by tetrabutylammonium fluoride (TBAF) desilylation in THF, to yield the uridine and thymidine analogues **29** and **31** in 81 and 86% yield, respectively, after two steps.

The cytidine derivative **34** was prepared from the uracil **28** by transformation into the triazolo compound **32** and subsequent ammonolysis (Scheme 6). Removal of the TBDPS group from **33** with TBAF afforded the targeted, conformationally locked cytidine derivative **34** in 73% yield over three steps.

The anti-HIV activity of compounds **29** (uridine analogue), **31** (thymidine analogue), and **34** (cytidine analogue) was initially explored using an already reported method.[25] Briefly, the procedure involves the use of an HIV-1 based vector containing wild-type HIV-1 RT that lacks a functional Env coding region and contains a luciferase reporter gene in the nef coding region. The vector was used to infect conventional human osteosarcoma (HOS) cells or a modified HOS cell line (HOS-313) that express the herpes simplex virus 1 thymidine kinase (HSV-1 TK). After 48 h, anti-HIV activity was determined by measuring the decrease in luciferase activity in infected cells. Only cells, which contain integrated viral DNA, will produce luciferase in the infectivity assay. All the compounds were inactive with the exception of the cytidine analogue, which had an EC_{50} of 23 μM in HOS-313 cells and an EC_{50} of 440 μM in HOS cells. These results mean that the compounds are not good substrates for the cellular kinases and

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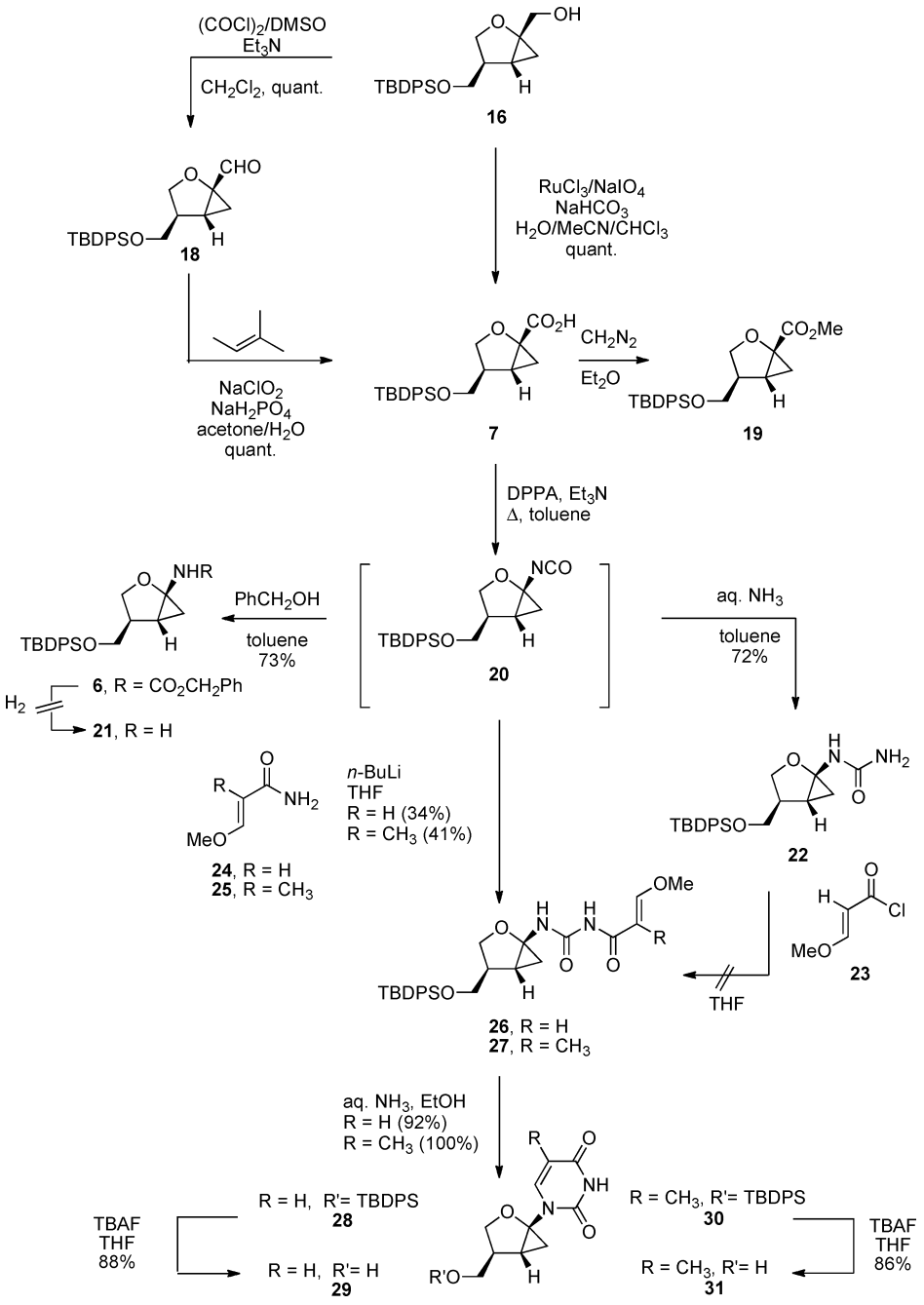
Scheme 5



even when phosphorylated by HSV-TK, as in HOS-313 cells, the anti-HIV activity was not very impressive.

In summary, by exploiting the rigid nature of the oxobicyclo[3.1.0]hexane template we have been able to construct a new template, conceptually designed from known 3-oxabicyclo[3.1.0]hexane scaffold (compound **3**). The relocation of the fused cyclopropane ring bond and the shifting of the oxygen atom to an alternative location provided a new 2-oxabicyclo[3.1.0]hexane template target. This template posed a significant synthetic challenge since it has the nucleobase attached to an anomeric carbon that forms part of a fused cyclopropane ring. The synthesis of the 2-oxabicyclo[3.1.0]-hexane template involved a novel approach that was completed in eleven steps from a known dihydrofuran precursor. The completion of the pyrimidine nucleobase was successfully achieved by quenching the isocyanate intermediate **20** with the lithium salts of the corresponding acrylic amides.

EXPERIMENTAL SECTION

General Synthetic Methods. All experiments involving water-sensitive compounds were conducted under dry conditions (positive argon pressure) using standard syringe, cannula, and septa apparatus. All solvents were purchased anhydrous and stored over activated molecular sieves. Hexanes, ethyl acetate, methylene chloride, and methanol employed in chromatography were HPLC grade. Centrifugally accelerated, radial, thin-layer chromatography was performed on silica gel GF coated rotors with UV detection at 254 nm. Medium-pressure flash chromatography was performed on prepacked silica gel columns. TLC (analytical thin-layer chromatography) was performed on precoated plates of silica gel (250 μm) containing a fluorescence indicator. Sugar-containing compounds were visualized with the sugar

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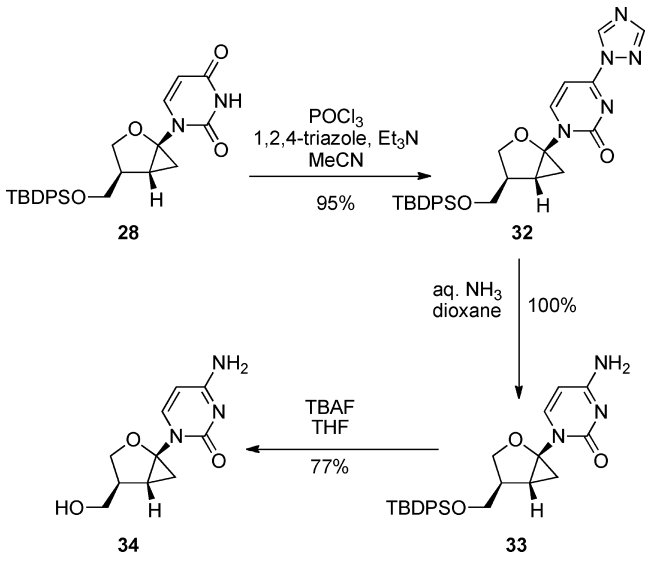
Scheme 6



spray reagent (5 mL of 4-methoxybenzaldehyde, 90 mL of ethanol, 5 mL of concentrated sulfuric acid, and 10 mL of glacial acetic acid) by heating with a heat gun. NMR spectra were recorded in a 400 MHz spectrometer. The coupling constants are reported in hertz, and the peak shifts are reported on the δ (ppm) scale: abbreviations s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad) and app (apparent). Mass spectra (FABMS) were obtained at an accelerating voltage of 6 kV and at a resolution of 2000. Glycerol was used as the sample matrix, and ionization was effected by a beam of xenon atoms. APCI and ESI mass spectra were obtained using a multimode ion source (LC/MSD SL) using the loop injection mode. Optical rotations were measured at 589 nm. Infrared spectroscopy data was obtained neat and an independent laboratory performed elemental analyses and HR MS.

(*R*)-Methyl 4-(*tert*-Butyldiphenylsilyloxymethyl)-4,5-dihydrofuran-2-carboxylate (11). The dihydrofuran **9** (100 mg, 0.295 mmol) was dissolved in dry THF (200 μL), and the solution was cooled to −78 °C under argon. At this temperature, *tert*-butyllithium (1.7 M in pentane, 225 μL, 0.384 mmol) was added dropwise, and the yellow solution was stirred for 15 min. The solution was warmed to 0 °C and stirred over an ice bath, whereupon the solution became colorless. After 45 min, the solution was cooled again to −78 °C, and dimethyl carbonate (133 mg, 1.48 mmol) was added. The reaction was stirred for 15 min at −78 °C, warmed to 0 °C, and stirred for an additional 1 h. Saturated ammonium chloride solution (50 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude was purified by flash chromatography on silica gel (EtOAc in hexanes 0−25%) to yield the methyl ester **11** (21.0 mg, 18%) as a colorless oil: $[\alpha]^{20}_D$ = −84.16 (*c* 1.0, $CHCl_3$); IR (neat) 3071, 2952, 2857, 1739, 1631, 1471, 1428, 1294, 1219, 1109, 997, 941, 823, 781, 739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.55 (m, 4 H), 7.40−7.30 (m, 6 H), 5.79 (d, 1 H, *J* = 3.0 Hz), 4.44 (dd, 1 H, *J* = 10.0, 9.5 Hz), 4.31 (dd, 1 H, *J* = 9.5, 6.6 Hz), 3.73 (s, 3 H); 3.60 (dd, 1 H, *J* = 10.0, 5.9 Hz), 3.53 (dd, 1 H, *J* = 10.0, 7.0 Hz), 2.32−2.22 (m, 1 H), 0.98 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 148.9, 135.5, 135.5, 133.3, 133.2, 129.7, 127.7, 112.2, 73.5, 65.4, 52.1, 46.2, 26.7, 19.2. Anal. Calcd for $C_{23}H_{28}O_4Si$: C, 69.66; H, 7.12. Found: C, 69.55; H, 7.17.

(2*S*,3*R*,4*R*)-4-*tert*-Butyldiphenylsilanyloxymethyl-2-cyanotetrahydrofuran-3-yl Acetate (13). The diacetate **12**[7] (1.10 g, 2.41 mmol) was dissolved in dry MeCN (20 mL) and TMSCN (1.08 g, 10.8 mmol) was added under argon at 0 °C. After adding a catalytic amount of $BF_3{\cdot}Et_2O$ (60 μL, 0.48 mmol) the mixture was allowed to reach room temperature and was stirred for 30 min. The reaction was quenched by the slow addition of satd aqueous $NaHCO_3$ solution (20 mL), and stirring was continued for 30 min at room temperature. The aqueous phase was diluted with water (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated. The crude was purified by flash chromatography on silica gel (EtOAc in hexanes 15−35%) to yield the title compound **13** (947 mg, 93%) as a colorless syrup: $[\alpha]^{20}_D$ = −8.30 (*c* 1.0, $CHCl_3$); IR (neat) 3071, 2931, 2857, 2358, 1477, 1589, 1472, 1427, 1364, 1225, 1104, 1041, 996, 936, 919, 822, 796, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.55 (m, 4 H), 7.40−7.30 (m, 6 H), 5.26 (dd, 1 H, *J* = 3.4, 2.3 Hz), 4.53 (d, 1 H, *J* = 2.3 Hz), 4.11 (dd, 1 H, *J* = 9.3, 7.5 Hz), 3.83 (dd, 1 H, *J* = 9.3, 7.4 Hz), 3.73 (dd, 1 H, *J* = 9.0, 4.9 Hz), 3.70 (dd, 1 H, *J* = 9.0, 5.2 Hz), 2.55−2.45 (m, 1 H), 2.01 (s, 3 H), 1.48 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 135.5, 132.8, 129.9, 127.8, 116.3, 79.2, 72.1, 70.6, 61.7, 48.0, 26.7, 20.6, 19.2; FAB-MS (*m*/*z*, relative intensity) 424.2 (MH^+, 42), 366 (100). Anal. Calcd for $C_{24}H_{29}NO_4Si$: C, 68.05; H, 6.90; N, 3.31. Found: C, 68.17; H, 6.96; N, 3.21.

(2*S*,3*R*,4*R*)-4-*tert*-Butyldiphenylsilyloxymethyl-3-hydroxytetrahydrofuran-2-carbonitrile (14). The acetate **13** (5.83 g, 13.8 mmol) was dissolved in dry methanol (150 mL), and the mixture was cooled to 0 °C. Sodium hydride (660 mg of 50% oil suspension, 13.8 mmol) was added in one portion, and the mixture was stirred at 0 °C until all starting material was consumed (15 min.). After neutralization with 1 N HCl, the solvent was evaporated and the residue was partitioned between water (250 mL) and CH_2Cl_2 (250 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 150 mL), and the combined extracts were dried ($MgSO_4$) and concentrated. The crude was purified by flash chromatography on silica gel (EtOAc in hexanes, 25−50%) to yield the title compound **14** (5.19 g, 99%) as a colorless oil: $[\alpha]^{20}_D$ = 0.38 (*c* 1.0, $CHCl_3$); IR (neat) 3470, 3071, 2931, 2857, 1589, 1471, 1427, 1390, 1361, 1188, 1109, 997, 938, 822, 796, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.60 (m, 4 H), 7.45−7.35 (m, 6 H), 4.56 (dd, 1 H, *J* = 7.7, 4.0 Hz), 4.44 (d, 1 H, *J* = 4.0 Hz), 4.10 (dd, 1 H, *J* = 9.1, 7.7 Hz), 3.77 (dd, 1 H, *J* = 9.1, 8.0 Hz), 3.74 (dd, 2 H, *J* = 6.8, 1.0 Hz), 2.47−2.38 (m, 1 H), 2.34 (d, 1 H, *J* = 4.0 Hz), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 132.8, 132.7, 130.0, 127.9, 117.5, 78.6, 72.9, 70.3, 62.3, 50.4, 26.8, 19.2; APCI-MS (*m*/*z*) 399.2 (M + NH_4^+). Anal. Calcd for $C_{22}H_{27}NO_3Si$: C, 69.25; H, 7.13; N, 3.67. Found: C, 69.07; H, 6.98; N, 3.70.

(*R*)-4-*tert*-Butyldiphenylsilyloxymethyl-4,5-dihydrofuran-2-carbonitrile (8). The nitrile **14** (1.38 g, 3.62 mmol) was dissolved in dry CH_2Cl_2 (40 mL) under argon. The solution was cooled to 0 °C, and triethylamine (1.51 mL, 10.9 mmol) was added. After stirring, mesyl chloride (420 μL, 5.43 mmol) was added dropwise, and the reaction was allowed to warm to room temperature. After 30 min, all starting material was consumed according to TLC (EtOAc/hexanes 1:3), and the mixture was treated dropwise with DBU (1.35 mL, 9.05 mmol). Stirring was continued until no mesylate could be detected by TLC analysis (30 min). Aqueous 1 N HCl (100 mL) was added, and after phase separation the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude was purified by flash chromatography on silica gel (EtOAc in hexanes, 0−25%) to yield the α,β-unsaturated nitrile **8** (1.16 g, 88%) as a colorless oil: $[\alpha]^{20}_D$ = −111.07 (*c* 1.0, $CHCl_3$); IR (neat) 3073, 2931, 2857, 2237, 1623, 1589, 1471, 1427, 1389, 1362, 1227, 1176, 1107, 997, 959, 917, 822 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63−7.58 (m, 4 H), 7.45−7.35 (m, 6 H), 5.70 (dd, 1 H, *J* = 2.6, 2.6 Hz), 4.47−4.40 (m, 1 H), 4.32 (ddd, 1 H, *J* = 9.1, 6.5, 2.6 Hz), 3.65−3.55 (m, 2 H), 3.35−3.25 (m, 1 H), 1.03 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 135.5, 133.1, 133.0, 131.2, 129.9, 127.8, 117.5, 111.6, 73.5, 64.7, 46.3, 26.7, 19.2. Anal. Calcd for $C_{22}H_{25}NO_2Si$: C, 72.69; H, 6.93; N, 3.85. Found: C, 72.66; H, 6.97; N, 3.79.

(*R*)-Methyl 4-(*tert*-Butyldiphenylsilyloxymethyl)-4,5-dihydrofuran-2-carboxylate (11). The nitrile **8** (4.68 g, 12.8 mmol) was dissolved in dry methanol (150 mL), and the mixture was cooled to 0 °C. Sodium hydride (560 mg, 55% oil suspension, 12.8 mmol) was added in portions, and the mixture was warmed to room temperature and stirred overnight. TLC analysis showed that all starting material had reacted and the mixture was acidified by the

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addition of 20% aqueous acetic acid. The solvent was evaporated, and the residue was partitioned between water (250 mL) and CH_2Cl_2 (250 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 150 mL), and the combined extracts were dried ($MgSO_4$) and concentrated. The crude was purified by flash chromatography on silica gel (EtOAc in hexanes, 5−30%) to yield the methyl ester **11** (3.20 g, 62%) as a colorless oil. The spectroscopic data were identical to those reported above.

((1*R*,4*R*,5*R*)-4-*tert*-Butyldiphenylsilyloxymethyl-2-oxabicyclo[3.1.0]hexan-1-yl)methanol (16) and ((1*S*,4*R*,5*S*)-4-*tert*-Butyldiphenylsilyloxymethyl-2-oxabicyclo[3.1.0]hexan-1-yl)methanol (17). The ester **11** (1.25 g, 3.15 mmol) was dissolved in anhydrous toluene (20 mL) and DIBAL-H (12.6 mL, 1.0 M in toluene, 12.6 mmol) was added at −78 °C under argon. The mixture was warmed to room temperature over 30 min and methanol (5 mL) was carefully added. An aqueous satd solution of Seignette salt (100 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude alcohol was used for the subsequent cyclopropanation without any further purification. Thus, the crude alcohol (1.02 g) was dissolved in dry CH_2Cl_2 (40 mL) at 0 °C under argon, and Et_2Zn (14.4 mL, 1.1 M in toluene, 15.8 mmol) was added dropwise. Immediately after the addition, CH_2I_2 (1.27 mL, 15.8 mmol) was added and the cooling bath was removed. The reaction was stirred at room temperature for 1 h, and satd ammonium chloride solution (100 mL) was added carefully. The aqueous phase was acidified with 1 N HCl to pH 3−2 and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated. The crude was purified by flash chromatography on silica gel (EtOAc in hexanes 30−50%) to yield the bicyclic alcohol **16** (895 mg, 74%) as a colorless syrup. As a minor byproduct, the diastereomer **17** (55.0 mg, 5%) was obtained as a colorless syrup.

*Compound **16**:* $[\alpha]^{20}_D$ = 8.44 (*c* 1.0, $CHCl_3$); IR (neat) 3448, 3070, 2929, 2857, 1589, 1471, 1427, 1389, 1361, 1231, 1185, 1107, 1029, 940, 910, 822, 791 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60−7.55 (m, 4 H), 7.40−7.30 (m, 6 H), 3.90 (d, 1 H, *J* = 9.6 Hz), 3.87 (d, 1 H, *J* = 12.5 Hz), 3.55−3.43 (m, 4 H), 2.39 (ddd, 1 H, *J* = 7.2, 7.2, 7.2 Hz), 1.70 (bs, 1 H), 1.23 (dd, 1 H, *J* = 9.3, 4.8 Hz), 0.99 (s, 9 H), 0.95 (dd, 1 H, *J* = 6.4, 4.8 Hz), 0.55 (dd, 1 H, *J* = 9.3, 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 133.6, 133.5, 129.7, 127.7, 68.7, 68.4, 65.4, 64.6, 44.3, 26.8, 21.0, 20.,11.4; ESI-MS (*m*/*z*) 383.2 (M + H^+), 405.1 (M + Na^+). Anal. Calcd for $C_{23}H_{30}O_3Si{\cdot}0.1H_2O$: C, 71.83; H, 7.92. Found: C, 71.61; H, 7.90.

*Compound **17**.* $[\alpha]^{20}_D$ = −30.27 (*c* 1.0, $CHCl_3$); IR (neat) 3430, 3073, 2930, 2875, 1783, 1589, 1471, 1427, 1389, 1242, 1109, 1044, 953, 823, 792, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68−7.60 (m, 4 H), 7.43−7.33 (m, 6 H), 4.08 (dd, 1 H, *J* = 9.7, 8.5 Hz), 3.99 (d, 1 H, *J* = 12.4 Hz), 3.72 (dd, 1 H, *J* = 10.0, 6.8 Hz), 3.62 (d, 1 H, *J* = 12.4 Hz), 3.60 (dd, 1 H, *J* = 10.0, 6.9 Hz), 3.20 (dd, 1 H, *J* = 9.7, 9.7 Hz), 2.86−2.76 (m, 1 H), 1.85−1.75 (bs, 1 H), 1.48 (ddd, 1 H, *J* = 9.4, 4.9, 4.9 Hz), 1.02 (s, 9 H), 0.99 (dd, 1 H, *J* = 6.8, 4.9 Hz), 0.47 (dd, 1 H, *J* = 9.4, 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 135.5, 133.6, 133.5, 129.7, 127.7, 127.7, 70.0, 69.2, 64.9, 64.5, 43.3, 26.8, 21.3, 19.2, 9.8; ESI-MS (*m*/*z*) 383.2 (M + H^+), 405.1 (M + Na^+). Anal. Calcd for $C_{23}H_{30}O_3Si$: C, 72.27; H, 7.90. Found: C, 71.80; H, 7.82.

(1*R*,4*R*,5*R*)-4-*tert*-Butyldiphenylsilyloxymethyl-2-oxabicyclo-[3.1.0]hexane-1-carboxylic Acid (7). *Method A.* Oxalyl chloride (206 μL, 2.36 mmol) was dissolved in dry CH_2Cl_2 (10 mL) under argon, and the solution was cooled to −78 °C. Dimethyl sulfoxide (DMSO, 335 μL, 4.72 mmol) was added dropwise, and the reaction was stirred for 5 min at that temperature. The primary alcohol **16** (450 mg, 1.18 mmol) was added to the mixture (disolved in 5.0 mL of dry CH_2Cl_2), and the reaction was stirred for 1 h at −78 °C. Triethylamine (987 μL, 7.08 mmol) was added, and the mixture was warmed to room temperature and stirred for 1 h. Satd aqueous ammonium chloride solution (50 mL) was added, and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic washings were dried ($MgSO_4$) and concentrated. The crude aldehyde **18** was sufficiently pure to be used in the next oxidation step without any further purification: ^1H NMR (400 MHz, $CDCl_3$) δ 9.42 (s, 1 H), 7.58−7.53 (m, 4 H), 7.40−7.29 (m, 6 H), 4.04 (dd, 1 H, *J* = 9.7, 2.4 Hz), 3.71 (dd, 1 H, *J* = 9.7, 6.8 Hz), 3.49 (d, 2 H, *J* = 7.3 Hz), 2.45 (dddd, 1 H, *J* = 7.2, 7.2, 7.2, 2.4 Hz), 2.01 (dd, 1 H, *J* = 9.6, 6.1 Hz), 1.51 (dd, 1 H, *J* = 9.6, 6.4 Hz), 1.39 (dd, 1 H, *J* = 6.2, 6.2 Hz), 0.98 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 135.5, 133.2, 133.2, 129.8, 127.7, 74.3, 71.0, 64.8, 43.6, 31.0, 26.8, 19.2, 18.4.

The crude aldehyde **18** (450 mg, 1.18 mmol), dissolved in acetone (5.0 mL), was slowly added to a stirred mixture of sodium chlorite (374 mg, 4.13 mmol), sodium dihydrogenphosphate (142 mg, 1.18 mmol), and 2-methylbut-2-ene (543 μL, 5.13 mmol) in water/acetone (2:1, 15 mL) at 0 °C. The cooling bath was removed, and the mixture was stirred at room temperature for 1 h. The mixture was acidified with 1 N HCl to pH 2−3, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to yield the crude acid **7** (465 mg, quant) as a slightly yellow syrup, which was used in the following Curtius reaction without any further purification: ^1H NMR (400 MHz, $CDCl_3$) δ 7.60−7.54 (m, 4 H), 7.38−7.28 (m, 6 H), 4.07 (dd, 1 H, *J* = 9.6, 2.2 Hz), 3.67 (dd, 1 H, *J* = 9.6, 7.0 Hz), 3.54 (dd, 1 H, *J* = 10.4, 7.3 Hz), 3.50 (dd, 1 H, *J* = 10.4, 8.0 Hz), 2.47−2.40 (m, 1 H), 2.00 (dd, 1 H, *J* = 9.5, 6.1 Hz), 1.54 (dd, 1 H, *J* = 9.5, 6.1 Hz), 1.31 (dd, 1 H, *J* = 6.1, 6.1 Hz), 0.97 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 134.5, 134.5, 132.3, 132.2, 128.9, 126.7, 70.2, 64.7, 63.8, 42.9, 29.1, 25.8, 18.2, 17.7; ESI-MS (*m*/*z*) 419.2 (M + Na^+).

An analytical sample was prepared by quantitative conversion to the methyl ester with an etheral solution of diazomethane. The solvent was evaporated, and the crude was purified by flash chromatography (EtOAc in hexanes 0−30%) to yield the methyl ester **19** as a colorless oil: $[\alpha]^{20}_D$ = 61.32 (*c* 1.0, $CHCl_3$); IR (neat) 3073, 2930, 2857, 1729, 1440, 1428, 1377, 1349, 1193, 1150, 1109, 1040, 822, 771, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65−7.60 (m, 4 H), 7.45−7.30 (m, 6 H), 4.10 (dd, 1 H, *J* = 9.6, 2.4 Hz), 3.73 (s, 3 H), 3.70 (dd, 1 H, *J* = 9.6, 7.0 Hz), 3.58 (dd, 1 H, *J* = 8.5, 5.5 Hz), 3.54 (dd, 1 H, *J* = 8.5, 6.0 Hz), 2.46 (dddd, 1 H, *J* = 7.0, 7.0, 7.0, 2.4 Hz), 1.99 (dd, 1 H, *J* = 9.5, 6.0 Hz), 1.48 (dd, 1 H, *J* = 9.5, 6.0 Hz), 1.29 (dd, 1 H, *J* = 6.0, 6.0 Hz), 1.01 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 135.5, 133.4, 133.3, 129.7, 127.7, 70.9, 66.1, 65.0, 52.3, 43.9, 29.1, 26.7, 19.2, 18.3; ESI-MS (*m*/*z*) 428.2 (M + NH_4^+), 433.1 (M + Na^+). Anal. Calcd for $C_{24}H_{30}O_4Si$: C, 70.21; H, 7.36. Found: C, 70.42; H, 7.66.

Method B. The bicyclic alcohol **16** (800 mg, 2.09 mmol) was dissolved in a mixture of water (30 mL), acetonitrile (20 mL), and chloroform (20 mL) to which sodium periodate (2.46 g, 11.5 mmol) and sodium bicarbonate (1.05 g, 12.5 mmol) were added. To this mixture was added a catalytic amount of ruthenium(III) chloride (43.4 mg, 0.21 mmol), and the reaction was stirred overnight at room temperature. After full conversion to the carbocylic acid, the mixture was diluted with water (100 mL) and acifified to pH 2−3 by the addition of 1 N HCl. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), and the combined extracts were filtered over a short pad of Celite and concentrated. The crude acid **7** (830 mg, quant) was used as such without any further purification. The analytical data were identical to those reported in method A.

Benzyl (1*R*,4*R*,5*R*)-4-*tert*-Butyldiphenylsilyloxymethyl-2-oxabicyclo[3.1.0]hexan-1-ylcarbamate (6). The carbocyclic acid **7** (450 mg, 1.13 mmol) was dissolved in dry toluene (10 mL) and cooled to 0 °C under argon. Triethylamine (236 μL, 1.70 mmol) and diphenylphosphoryl azide (DPPA, 319 μL, 1.48 mmol) were added, and the mixture was warmed to room temperature and stirred for 2 h. The mixture was heated to 80 °C for 2 h and then cooled to 0 °C again. Benzyl alcohol (293 μL, 2.83 mmol) was added, and the mixture was stirred at room temperature for 30 min and then warmed to 80 °C for 2 h. After being cooled to room temperature, the solvent was evaporated and the crude was directly purified by flash chromatography on silica gel (EtOAc in hexanes 50−70%) to yield the Cbz-protected amine **6** (414 mg, 73%) as a colorless foam: $[\alpha]^{20}_D$ = 13.32 (*c* 1.0, $CHCl_3$); IR (neat) 3321, 3069, 2930, 2857, 1733, 1589, 1489, 1427, 1389, 1227, 1190, 1106, 1084, 960, 822, 803, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65−7.60 (m 4 H), 7.42−7.20 (m, 11 H), 5.58 (bs, 1 H), 5.06 (s, 2 H), 3.99 (dd, 1 H, *J* = 9.5, 2.1 Hz), 3.84−3.74 (m, 2 H), 3.55 (dd, 1 H, *J* = 9.5, 7.0 Hz), 2.39 (dddd, 1 H, *J* = 7.4,

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7.4, 7.0, 2.1 Hz), 1.55−1.47 (m, 1 H), 1.27−1.20 (m, 1 H), 1.03 (s, 9 H), 1.03−1.00 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 136.1, 135.6, 133.7, 133.6, 129.7, 128.7, 128.6, 128.5, 128.1, 127.7, 73.5, 69.1, 66.9, 65.2, 44.4, 26.8, 23.5, 19.2, 16.3; ESI-MS (m/z) 502.2 (M + H$^+$), 524.2 (M + Na$^+$), 540.1 (M + K$^+$); HR-FABMS m/z calcd for $C_{30}H_{36}NO_4Si$ (M + H) 502.2414, found 502.2391.

1-((1*R*,4*R*,5*R*)-4-*tert*-Butyldiphenylsilyloxymethyl-2-oxabicyclo[3.1.0]hexan-1-yl)urea (22). The carbocyclic acid **7** (260 mg, 0.656 mmol) was dissolved in dry CH_2Cl_2 (6.0 mL) and cooled to 0 °C under argon. Triethylamine (137 μL, 0.984 mmol) and diphenylphosphoryl azide (DPPA, 184 μL, 0.852 mmol) were added, and the mixture was warmed to room temperature and stirred for 24 h. After evaporation of the solvent, the crude acyl azide was purified by flash chromatography (EtOAc in hexanes 5−30%) over a short pad of silica gel. The clean acyl azide was subsequently dissolved in dry toluene (6.0 mL), heated to 90 °C for 4 h, and then cooled to 0 °C. Concentrated aqueous ammonia solution (500 μL) was added, and the mixture was stirred at room temperature for 2 h. The solvent was evaporated, and the crude was directly purified by flash chromatography on silica gel (EtOAc in hexanes 40−70%) to yield the urea **22** (194 mg, 72%) as a colorless foam: $[\alpha]^{20}_D$ = 45.90 (*c* 1.0, $CHCl_3$); IR (neat) 3482, 3318, 3209, 2929, 2857, 1681, 1589, 1427, 1360, 1307, 1194, 1109, 1025, 966, 933, 822, 790, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.60 (m, 4 H), 7.45−7.30 (m, 7 H), 6.50 (bs, 1 H), 5.90 (bs, 1 H), 4.08 (dd, 1 H, *J* = 9.5, 2.3 Hz), 3.68 (dd, 1 H, *J* = 9.5, 6.7 Hz), 3.59 (dd, 1 H, *J* = 10.0, 6.5 Hz), 3.46 (dd, 1 H, *J* = 10.0, 8.0 Hz), 2.46 (dddd, 1 H, *J* = 6.7, 6.7, 6.7, 2.3 Hz), 1.85 (dd, 1 H, *J* = 9.5, 5.9 Hz), 1.56 (dd, 1 H, *J* = 9.5, 5.9 Hz), 1.18 (dd, 1 H, *J* = 5.9, 5.9 Hz), 1.03 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 135.5, 135.5, 133.5, 133.3, 129.2, 127.7, 127.7, 70.9, 67.7, 65.0, 44.0, 28.2, 26.8, 19.2, 16.3; HRFAB-MS m/z calcd for $C_{23}H_{31}N_2O_3Si$ (M + H$^+$) 411.2104, found 411.2120.

(*E*)-3-Methoxyacrylamide (24). (*E*)-3-Methoxyacryloyl chloride (1.00 g, 8.3 mmol) was dissolved in dry CH_2Cl_2 (90 mL) under argon and cooled to −20 °C. Aqueous concentrated ammonia solution (1.90 mL, 33.2 mmol) was added dropwise, and the mixture was vigorously stirred at −20 °C for 1 h and then warmed to room temperature. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel (MeOH in CH_2Cl_2 0−10%) to yield the acrylamide **24** (720 mg, 86%) as a colorless solid: mp 126−129 °C; IR (neat) 3318, 3143, 1639, 1580, 1437, 1408, 1326, 1262, 1218, 1175, 1121, 964, 933, 820 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.29 (d, 1 H, *J* = 12.5 Hz), 7.10−7.00 (bs, 1 H), 6.60−6.50 (bs, 1 H), 5.25 (d, 1 H, *J* = 12.5 Hz), 3.55 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.8, 159.6, 99.4, 57.4; ESI-MS (m/z) 102.1 (M + H$^+$), 124.0 (M + Na$^+$). Anal. Calcd for $C_4H_7NO_2{\cdot}0.25H_2O$: C, 45.49; H, 7.16; N, 13.26. Found: C, 45.46; H, 6.94; N, 13.14.

(*E*)-3-Methoxy-2-methylacrylamide (25). (*E*)-3-Methoxy-2-methylacryloyl chloride (1.00 g, 7.43 mmol) was dissolved in dry CH_2Cl_2 (90 mL) under argon and cooled to −20 °C. Aqueous concentrated ammonia solution (1.90 mL, 33.2 mmol) was added dropwise, and the mixture was vigorously stirred at −20 °C for 1 h and then warmed to room temperature. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel (MeOH in CH_2Cl_2 0−10%) to yield the acrylamide **25** (625 mg, 83%) as a colorless solid: mp 105−107 °C; IR (neat) 3332, 3161, 1656, 1590, 1429, 1383, 1359, 1238, 1177, 1144, 971, 885, 813 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.04 (q, 1 H, *J* = 1.2 Hz), 6.90−6.50 (bs, 2 H), 3.65 (s, 3 H), 1.55 (d, 3 H, *J* = 1.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.9, 154.9, 108.3, 60.8, 9.9; ESI-MS (m/z) 116.1 (M + H$^+$), 138.0 (M + Na$^+$). Anal. Calcd for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.33; H, 7.97; N, 12.05.

(*E*)-*N*-((1*R*,4*R*,5*R*)-4-*tert*-Butyldiphenylsilyloxymethyl-2-oxabicyclo[3.1.0]hexan-1-ylcarbamoyl)-3-methoxyacrylamide (26). The carboxylic acid **7** (200 mg, 0.505 mmol) was dissolved in dry CH_2Cl_2 (4.0 mL) and cooled to 0 °C under argon. Triethylamine (120 μL, 0.857 mmol) and diphenylphosphoryl azide (DPPA, 164 μL, 0.758 mmol) were added, and the mixture was warmed to room temperature and stirred for 24 h. After evaporation of the solvent, the crude acyl azide was purified by flash chromatography (EtOAc in hexanes 5−30%) over a short pad of silica gel. The clean acyl azide was subsequently dissolved in dry toluene (6.0 mL), heated to 90 °C for 4 h, and then cooled to −78 °C. To this crude isocyanate, was added dropwise a solution of freshly prepared lithium salt of (*E*)-3-methoxyacrylamide [prepared by the dropwise addition of *n*-butyl lithium (1.6 M in hexanes, 1.01 mmol, 630 μL) to a solution of (*E*)-3-methoxyacrylamide (102 mg, 1.01 mmol) in dry THF (5.0 mL) at −78 °C under argon and stirring for 0.5 h at this temperature], and the mixture was stirred for 0.5 h at this temperature. The reaction was quenched by the careful addition of satd aqueous ammonium chloride solution (50 mL) and 1 N HCl (2 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated. The crude product was purified by chromatography on silica gel (EtOAc in hexanes 50−70%) to yield the acyl urea **26** (85.0 mg, 34%) as a colorless foam:; $[\alpha]^{20}_D$ = 30.15 (*c* 1.0, $CHCl_3$); IR (neat) 3260, 2931, 1702, 1660, 1616, 1532, 1470, 1428, 1359, 1241, 1109, 984, 805 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (bs, 1 H), 9.20 (bs, 1H), 7.66−7.60 (m, 4 H), 7.58 (d, 1 H, *J* = 12.2 Hz), 7.40−7.32 (m, 6 H), 5.19 (d, 1 H, *J* = 12.2 Hz), 4.03 (dd, 1 H, *J* = 9.5, 2.5 Hz), 3.78 (dd, 1 H, *J* = 9.0, 7.5 Hz), 3.74 (dd, 1 H, *J* = 9.0, 6.5 Hz), 3.60 (dd, 1 H, *J* = 9.5, 7.1 Hz), 3.56 (s, 3 H), 2.40 (dddd, 1 H, *J* = 7.5, 7.3, 7.3, 2.5 Hz), 1.57 (dd, 1 H, *J* = 9.6, 5.0 Hz), 1.25 (dd, 1 H, *J* = 6.5, 5.0 Hz), 1.08 (dd, 1 H, *J* = 9.6, 6.5 Hz), 1.02 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 163.7, 155.2, 135.5, 133.6, 133.6, 129.6, 127.7, 97.3, 72.5, 69.5, 65.2, 57.7, 44.9, 26.8, 23.4, 19.2, 16.6; APCI-MS m/z 495.2 (M + H$^+$). Anal. Calcd for $C_{27}H_{34}N_2O_5Si$: C, 65.56; H, 6.93; N, 5.66. Found: C, 65.55; H, 6.67; N, 5.34.

1-((1*R*,4*R*,5*R*)-4-*tert*-Butyldiphenylsilyloxymethyl-2-oxabicyclo[3.1.0]hexan-1-yl)pyrimidine-2,4(1*H*,3*H*)-dione (28). The urea **26** (80.0 mg, 0.162 mmol) was dissolved in ethanol (3.0 mL) and treated with concentrated aqueous ammonium hydroxide solution (3.0 mL) at room temperature. The solution was heated in a sealed pressure tube at 100 °C for 5 h. After the solution was cooled to room temperature, the solvent was evaporated and the residue was purified by chromatography on a chromatotron (MeOH in CH_2Cl_2 0−5%) to yield the uracil derivative **28** (68.8 mg, 92%) as a colorless foam: $[\alpha]^{20}_D$ = 24.26 (*c* 1.0, $CHCl_3$); IR (neat) 3061, 2931, 2856, 1692, 1427, 1385, 1290, 1206, 1107, 955, 821, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (bs, 1 H), 7.66−7.60 (m, 4 H), 7.45−7.34 (m, 6 H), 7.18 (d, 1 H, *J* = 8.0 Hz), 5.56 (dd, 1 H, *J* = 8.0, 2.2 Hz), 4.11 (dd, 1 H, *J* = 9.4, 3.4 Hz), 3.87 (dd, 1 H, *J* = 10.1, 7.4 Hz), 3.83 (dd, 1 H, *J* = 10.1, 7.4 Hz), 3.72 (dd, 1 H, *J* = 9.4, 7.5 Hz), 2.52 (dddd,, 1 H *J* = 7.3, 7.3, 7.3, 3.4 Hz), 1.86 (dd, 1 H, *J* = 10.1, 5.3 Hz), 1.45 (dd, 1 H, *J* = 7.0, 5.3 Hz), 1.25 (dd, 1 H, *J* = 10.1, 7.0 Hz), 1.05 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 150.1, 144.7, 135.6, 135.5, 133.4, 133.4, 129.8, 127.6, 102.6, 79.2, 71.2, 64.9, 44.8, 26.9, 24.4, 19.3, 17.9; APCI-MS m/z 463.2 (M + H$^+$), 385.1 (M − C_6H_6)$^+$. Anal. Calcd for $C_{26}H_{30}N_2O_4Si$: C, 67.50; H, 6.54; N, 6.06. Found: C, 67.56; H, 6.67; N, 5.84.

1-((1*R*,4*S*,5*R*)-4-Hydroxymethyl-2-oxabicyclo[3.1.0]hexan-1-yl)pyrimidine-2,4(1*H*,3*H*)-dione (29). The silylated nucleoside **28** (40.0 mg, 86.5 μmol) was dissolved in THF (2.0 mL) at 0 °C, and a 1 M solution of tetrabutylammonium fluoride (TBAF, 173 μL, 0.173 mmol) was added dropwise. The cooling bath was removed, and the mixture was stirred for 6 h at room temperature. The solvent was evaporated, and the crude nucleoside was purified by chromatography on a chromatotron (MeOH in CH_2Cl_2 0−10%) to yield the title compound **29** (17.1 mg, 88%) as a colorless foam. The nucleoside was redissolved in a mixture of acetonitrile/water (1:1, 3.0 mL) and was lyophilized to yield the uracil derivative **29** as a colorless cotton: $[\alpha]^{20}_D$ = 42.68 (*c* 1.0, MeOH); IR (neat) 3398, 3035, 2853, 1671, 1455, 1390, 1294, 1203, 1051, 989, 974, 879, 850 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.66 (d, 1 H, *J* = 8.0 Hz), 5.64 (d, 1 H, *J* = 8.0 Hz), 4.05 (dd, 1 H, *J* = 9.3, 2.8 Hz), 3.75−3.68 (m, 3 H), 2.46 (ddd, 1 H, *J* = 13.8, 6.4, 2.8 Hz), 1.91 (dd, 1 H, *J* = 10.0, 5.3 Hz), 1.43 (dd, 1 H, *J* = 6.9, 5.3 Hz), 1.27 (dd, 1 H, *J* = 10.0, 6.9 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 164.8, 150.9, 145.8, 101.6, 79.4, 70.4, 63.1, 44.8, 24.3, 15.9; APCI-MS m/z 225.0 (M + H$^+$); 242.1 (M + NH_4^+). HRFAB-MS m/z calcd for $C_{10}H_{13}N_2O_4$ (M + H$^+$) 225.0875, found 225.0868.

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(*E*)-*N*-((1*R*,4*R*,5*R*)-4-(*tert*-Butyldiphenylsilyloxymethyl)-2-oxabicyclo[3.1.0]hexan-1-ylcarbamoyl)-3-methoxy-2-methylacrylamide (27). The carboxylic acid 7 (200 mg, 0.505 mmol) was dissolved in dry CH_2Cl_2 (4.0 mL) and cooled to 0 °C under argon. Triethylamine (120 μL, 0.857 mmol) and diphenylphosphoryl azide (DPPA, 164 μL, 0.758 mmol) were added, and the mixture was warmed to room temperature and stirred for 24 h. After evaporation of the solvent, the crude acyl azide was purified by flash chromatography (EtOAc in hexanes 5−30%) over a short pad of silica gel. The clean acyl azide was subsequently dissolved in dry toluene (6.0 mL), heated to 90 °C for 4 h, and then cooled to −78 °C. To the crude isocyanate was added dropwise a solution of the freshly prepared lithium salt of (*E*)-3-methoxy-2-methylacrylamide [prepared by dropwise addition of *n*-butyl lithium (1.6 M in hexanes, 1.01 mmol, 630 μL) to a solution of (*E*)-3-methoxy-2-methylacrylamide (116 mg, 1.01 mmol) in dry THF (5.0 mL) at −78 °C under argon and stirring for 0.5 h at this temperature], and the mixture was stirred for 0.5 h at this temperature. The reaction was quenched by the careful addition of satd aqueous ammonium chloride solution (50 mL) and 1 N HCl (2 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated. The crude product was purified by chromatography on silica gel (EtOAc in hexanes 40−60%) to yield the acyl urea **27** (105 mg, 41%) as a colorless foam: $[\alpha]^{20}_D$ = 28.87 (*c* 1.0, $CHCl_3$); IR (neat) 3260, 2931, 2857, 1702, 1660, 1616, 1532, 1470, 1428, 1294, 1241, 1195, 1108, 905 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.45 (bs, 1 H), 7.85 (bs, 1 H), 7.65−7.60 (m, 4 H), 7.45−7.35 (m, 6 H), 7.28 (q, 1 H, *J* = 1.0 Hz), 4.07 (dd, 1 H, *J* = 9.4, 2.2 Hz), 3.82 (s, 3 H), 3.76 (d, 2 H, *J* = 7.6 Hz), 3.58 (dd, 1 H, *J* = 9.4, 7.0 Hz), 2.38 (dddd, 1 H, *J* = 7.6, 7.6, 7.5, 2.2 Hz), 1.72 (d, 3 H, *J* = 1.0 Hz), 1.53 (dd, 1 H, *J* = 9.5, 5.0 Hz), 1.28 (dd, 1 H, *J* = 6.5, 5.0 Hz), 1.06 (dd, 1 H, *J* = 9.5, 6.5 Hz), 1.03 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 158.8, 153.9, 135.5, 133.7, 133.71, 129.6, 127.7, 106.7, 72.4, 69.3, 65.2, 61.6, 44.8, 26.8, 23.2, 19.2, 16.4, 8.8; ESI-MS *m*/*z* 509.2 (M + H^+), 531.2 (M + Na^+). Anal. Calcd for $C_{28}H_{36}N_2O_5Si$: C, 66.11; H, 7.13; N, 5.51. Found: C, 66.27; H, 7.12; N, 5.42

1-((1*R*,4*S*,5*R*)-4-Hydroxymethyl-2-oxabicyclo[3.1.0]hexan-1-yl)-5-methylpyridine-2,4(1*H*,3*H*)-dione (31). The urea **27** (100 mg, 0.197 mmol) was dissolved in ethanol (3.0 mL) and treated with concentrated aqueous ammonium hydroxide solution (3.0 mL) at room temperature. The solution was heated in a sealed pressure tube at 100 °C for 24 h. After the mixture was cooled to room temperature, the solvent was evaporated and the residue was dried under high vacuum. Subsequently, the crude silylated nucleoside **30** was dissolved in THF (2.0 mL) at 0 °C, and a 1 M solution of tetrabutylammonium fluoride (TBAF, 393 μL, 0.393 mmol) was added dropwise. The cooling bath was removed, and the mixture was stirred for 6 h at room temperature. The solvent was evaporated, and the crude nucleoside was purified by chromatography on a chromatotron (MeOH in CH_2Cl_2 0−10%) to yield the title compound **31** (41.3 mg, 88%) as a colorless foam. The nucleoside was redissolved in a mixture of acetonitrile/water (1:1, 3.0 mL) and was lyophilized to yield the thymine derivative **31** as a colorless cotton: $[\alpha]^{20}_D$ = 45.28 (*c* 1.0, MeOH); IR (neat) 3439, 3059, 2905, 1668, 1446, 1389, 1290, 1196, 1019, 950, 862, 758 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.49 (q, 1 H, *J* = 1.1 Hz), 4.05 (dd, 1 H, *J* = 9.3, 2.8 Hz), 3.78−3.67 (m, 3 H), 2.45 (ddd, 1 H, *J* = 13.7, 6.2, 2.8 Hz), 1.91 (dd, 1 H, *J* = 10.0, 5.3 Hz), 1.83 (d, 3 H, *J* = 1.1 Hz), 1.42 (dd, 1 H, *J* = 6.8, 5.3 Hz), 1.25 (dd, 1 H, *J* = 10.0, 6.8 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 165.0, 151.2, 141.4, 110.4, 79.2, 70.2, 63.2, 44.4, 24.3, 15.9, 10.7; APCI-MS *m*/*z* 239.1 (M + H^+). Anal. Calcd for $C_{11}H_{14}N_2O_4 \cdot 0.80\ H_2O$: C, 52.29; H, 6.22; N, 11.09. Found: C, 52.68; H, 5.94; N, 10.72.

1-((1*R*,4*R*,5*R*)-4-(*tert*-Butyldiphenylsilyloxymethyl)-2-oxabicyclo[3.1.0]hexan-1-yl)-4-(1*H*-1,2,4-triazol-1-yl)-pyrimidin-2(1*H*)-one (32). Triazole (358 mg, 5.19 mmol) was dissolved in dry acetonitrile (10 mL) at 0 °C. Phosphoryl chloride (47.5 μL, 0.591 mmol) was added dropwise, followed by a slow addition of triethylamine (796 μL, 5.71 mmol), and the mixture was stirred for 1 h at 0 °C. A solution of the uracil derivative **28** (80.0 mg, 0.173 mmol) in dry acetonitrile (2.0 mL) was slowly added, and the mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by the addition of satd aqueous sodium bicarbonate solution (50 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude product was purified by chromatography on a chromatotron (MeOH in CH_2Cl_2, 0−5%) to yield the title compound **32** (84.4 mg, 95%) as a colorless foam: $[\alpha]^{20}_D$ = 23.20 (*c* 1.0, $CHCl_3$); IR (neat) 3074, 2931, 2865, 1696, 1630, 1540, 1507, 1464, 1401, 1303, 1109, 954, 781 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1 H), 8.05 (s, 1 H), 7.79 (d, 1 H, *J* = 7.2 Hz), 7.64−7.59 (m, 4 H), 7.40−7.30 (m, 6 H), 6.81 (d, 1 H, *J* = 7.2 Hz), 4.21 (dd, 1 H, *J* = 9.3, 3.8 Hz), 3.95 (dd, 1 H, *J* = 10.1, 7.4 Hz), 3.88 (dd, 1 H, *J* = 10.1, 7.0 Hz), 3.79 (dd, 1 H, *J* = 9.3, 7.6 Hz), 2.56 (dddd, 1 H, *J* = 7.3, 7.3, 7.3, 3.8 Hz), 1.93 (dd, 1 H, *J* = 10.1, 5.4 Hz), 1.49 (dd, 1 H, *J* = 7.0, 5.4 Hz), 1.31 (dd, 1 H, *J* = 10.1, 7.0 Hz), 1.02 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5 (C-4); 154.1 (C-2); 154.0 (C-5, triazole); 151.1 (C-3, triazole); 143.4, 135.5, 135.5, 133.5, 129.8, 129.8, 127.8, 94.9, 81.4, 72.5, 65.1, 45.2, 26.9, 25.0, 19.1, 18.4; APCI-MS *m*/*z* 514.2 (M + H^+); 436.1 ((M − C_6H_6)$^+$); HRFAB-MS *m*/*z* calcd for $C_{28}H_{32}N_5O_3Si$ (M + H^+) 514.2274, found 514.2252.

4-Amino-1-((1*R*,4*S*,5*R*)-4-hydroxymethyl-2-oxabicyclo-[3.1.0]hexan-1-yl)pyrimidin-2(1*H*)-one (34). Compound **32** (75.0 mg, 0.146 mmol) was dissolved in dioxane (4.0 mL), and concd aqueous ammonium hydroxide solution (1.0 mL) was added at room temperature. The solution was stirred at room temperature overnight. The solvent was evaporated, and the residue was dried under high vacuum. Subsequently, the crude cytidine analogue (67.5 mg, 0.146 mmol) was dissolved in THF (3.0 mL) at 0 °C, and a 1 M solution of tetrabutylammonium fluoride (TBAF, 292 μL, 0.292 mmol) was added dropwise. The cooling bath was removed, and the mixture was stirred at room temperature overnight. The solvent was evaporated and the crude nucleoside was purified by chromatography on a chromatotron (MeOH in CH_2Cl_2 0−15%) to yield the title compound **34** (25.0 mg, 77%) as a colorless foam: $[\alpha]^{20}_D$ = 48.68 (*c* 1.0, MeOH); IR (neat) 3295, 2957, 1645, 1488, 1379, 1045, 865, 786, 715 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.63 (d, 1 H, *J* = 7.4 Hz), 5.85 (d, 1 H, *J* = 7.4 Hz), 4.09 (dd, 1 H, *J* = 9.2, 2.8 Hz) 3.79 (dd, 1 H, *J* = 10.9, 5.4 Hz), 3.73−3.67 (m, 2 H), 2.48 (dddd, 1 H, *J* = 8.0, 5.5, 5.5, 2.8 Hz), 1.88 (dd, 1 H, *J* = 10.0, 5.2 Hz), 1.41 (dd, 1 H, *J* = 6.7, 5.2 Hz), 1.20 (dd, 1 H, *J* = 10.0, 6.7 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 166.5, 157.2, 146.2, 95.3, 80.4, 70.0, 63.4, 44.4, 24.7, 15.8; APCI-MS *m*/*z* 224.1 (M + H^+); HRFAB-MS *m*/*z* calcd for $C_{10}H_{14}N_3O_3$ (M + H^+) 224.1035, found 224.1029.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org/.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: marquezv@mail.nih.gov.

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