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Synthesis of Novel Nucleoside Analogues Built on a Bicyclo[4.1.0]heptane Scaffold

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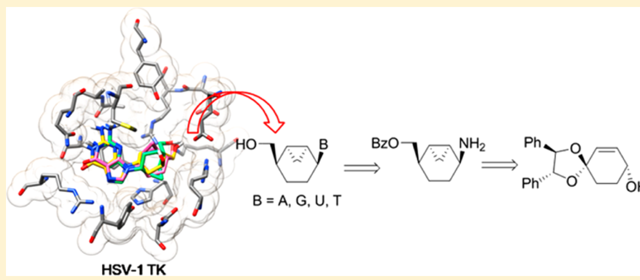
Ⓢ *Supporting Information*

ABSTRACT: A new class of carbocyclic nucleoside analogues built on a bicyclo[4.1.0]heptane scaffold, a perspective novel pseudosugar pattern, have been conceived as anti-HSV agents on the basis of initial protein–ligand docking studies. The asymmetric synthesis of a series of these compounds incorporating different nucleobases has been efficiently completed starting from 1,4-cyclohexanedione.



■ INTRODUCTION

Nucleoside analogues (NAs) constitute a prominent class of antiviral and anticancer prodrugs whose capacity to mimic the structural and functional features of natural nucleosides allows them to interact with viral and/or cellular enzymes and therefore inhibit critical processes in the metabolism of nucleic acids. Carbocyclic nucleoside analogues (CNAs) are an interesting family of NAs which have been extensively targeted in medicinal chemistry for the past few decades.[1] CNAs are more hydrolytically stable toward cellular phosphorylases and hydrolases, displaying enhanced biostability than their natural counterparts.[2] Since the discovery of abacavir (ABC)[3] and entecavir (ETC)[4] as effective antiviral agents (Figure 1), the search for new active CNAs has been primarily focused on cyclopentane derivatives. Examples of their six-membered counterparts are much more limited,[5] even though some of them have shown interesting biological properties. In particular, both enantiomers of cyclohexenyl G (DCG and LCG) were found to display antiviral activity against some herpes viruses (HSV-1, HSV-2, VZV, CMV).[5c] It was suggested that the replacement of the oxygen atom of the furanose ring by a double bond in the cyclohexenyl analogues induces annular flexibility similar to that of the regular nucleosides.[6] Many NAs currently used for the treatment of Herpes simplex virus (HSV) infections have limited oral bioavailability and can become ineffective due to the development of drug resistance. Thus, there is still a need for the development of new anti-HSV agents.

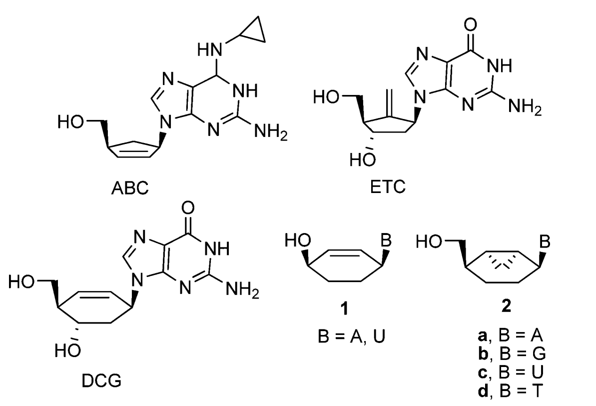


Figure 1. Selected biologically active carbocyclic nucleoside analogues, cyclohexene nucleosides **1** synthesized in our group, and targeted bicyclic analogues **2**.

Over the past few years, our research group has been involved in the enantioselective synthesis of bioactive products containing a cyclohexane unit in their structure.[7] Related to this research, we became interested in developing new strategies for the synthesis of cyclohexene nucleoside analogues as prodrug candidates. Thus, we recently reported an enantiodivergent synthesis of cyclohexene nucleoside analogues of type **1**.[5e] Turning to the leads provided by this work and considering the interesting anti-HSV activity of cyclohexenyl G, a series of enantiopure cyclohexane nucleoside analogues **2a–d** were designed, wherein the double bond is replaced by a fused cyclopropane, which was intended to mimic the cyclohexene conformations (Figure 1). Because of their unusual ring puckering, carbocyclic nucleosides might display structure–activity relationships (SARs) different from those of their

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natural nucleoside counterparts and can therefore display new biological properties. Introducing a conformational restriction by inclusion of a fused cyclopropane is a well-known approach to modulate the antiviral activity of a nucleoside. Thus, Marquez and co-workers[8] and more recently Jung and co-workers[9] have reported new families of conformationally NAs built on a bicyclo[3.1.0]hexyl scaffold that locks the conformation of the cyclopentane ring mimicking the North and South conformations of the natural furanose ring. These analogues have been successfully employed to discern the North/South conformational preferences of several nucleoside binding enzymes for their natural substrates.

The antiherpetic (HSV-1) activity of NAs is based upon serial intracellular phosphorylation that leads to their triphosphorylated forms (NAs-TP), which can interact with HSV-1 DNA polymerase, acting as competitive inhibitors or alternate substrates for the enzyme and usually preventing further viral nucleic acid chain elongation. For HSV-1, the first phosphorylation step is carried out by the thymidine kinase encoded by the virus itself (HSV-1 TK), which may enable the selective recognition of NAs by the viral enzyme but not by its human counterpart.[10] This feature has been exploited not only in antiviral therapy but also in suicide gene therapy protocols.[11] Moreover, in contrast to other thymidine kinases that are highly specific, HSV-1 TK is able to phosphorylate both pyrimidine[12] and purine nucleoside analogues.[13]

The first phosphorylation reaction in the virus-infected cells is often postulated to be the rate-limiting step in the enzymatic activation of the nucleosides; hence, in addition to the final interaction with HSV-1 DNA polymerase, phosphorylation of the hydroxyl analogues **2a−d** by HSV-1 TK may be a prerequisite for antiviral activity. Therefore, prior to carrying out the chemical synthesis of **2a−d**, we decided to evaluate whether imposing rigidity with a cyclopropane could affect their binding to the HSV-1 TK, by protein−ligand docking the proposed compounds into the known active site of the kinase. The effectiveness of compounds **2a−d** to act as a substrate would depend on the ability of the carbocycle to mimic the interaction of the sugar moiety of the natural substrate with the kinase. In parallel, the binding modes of thymidine (dT), acyclovir (ACV), and cyclohexenyl-G (DCG) to HSV-1 TK was also achieved to provide structural and energetic benchmarks.

In this work, we describe the molecular modeling study of carbocyclic nucleoside analogues built on a bicyclo[4.1.0]-heptane scaffold **2a−d** on the active site of the HSV-1 TK and the subsequent synthesis and antiviral testing of these compounds.

■ RESULTS AND DISCUSSION

Protein−ligand docking calculations on HSV-1 TK were performed with the docking program GOLD (version 5.2).[14] Calculations were performed using the crystallographic structures available that have been solved with dT (PDB entry code: 1KIM)[15] or ACV (PDB entry code: 2KI5)[16] in its binding site. The docking results were analyzed in structural and energetic terms considering binding and catalytic activity. The main criterion used to analyze the docking outcomes was to check that at least several low-energy binding modes were consistent with precatalytic orientations and that their corresponding binding energies were similar to those of the reference compounds. The docking protocol was validated by carrying out docking calculations of the crystallized ligands dT, ACV, and DCG into the corresponding HSV-1 TK X-ray structures. The lowest energy poses were perfectly overlapped with the ligand poses in the crystallographic structures, and thus dT, ACV, and DCG were used as benchmarks for pyrimidine and purine analogues.

Most of the predicted complexes of **2a−d** closely match the experimental and computed structures of the benchmark compounds at the active site of HSV-1 TK with binding energies being similar to or even lower (Supporting Information). Furthermore, these modes are properly posed for the catalytic activity of the enzyme. For example, for **2b** and **DCG** the nucleobase moiety is sandwiched between Met-128 and Tyr-172, and it is stabilized by pairwise hydrogen bond interactions with Gln-125 as well as with the side chain of Arg-176 (Figure 2). The 5′-OH is hydrogen bonded to Arg-163 and

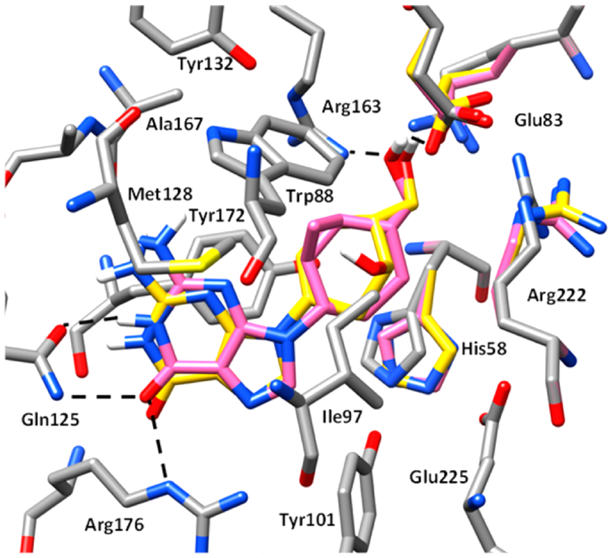

Figure 2. Compound **2b** (pink) superimposed with DCG (gold) in HSV-1 TK (PDB 2KI5; X-ray residues shown in gray). Hydrogen bonds are depicted as dotted lines. For the sake of clarity, hydrogen atoms are only shown when they are bound to a heteroatom of the ligand.

Glu-83, which is responsible for deprotonating the alcohol to be phosphorylated. The bicyclic scaffold provides favorable van der Waals interactions with the hydrophobic pocket of HSV-1 TK shaped by the side chain of tryptophan (Trp88), isoleucine (Ile97), and histidine (His-58). These results suggested that the replacement of the double bond for a fused cyclopropane ring does not alter the binding mode of the nucleosides in this kinase and, as a consequence, the synthetic analogues envisaged in this work should be correctly activated at the first phosphorylation step.

Having demonstrated the capability of **2a−d** to interact properly with the binding site of the HSV-1 TK, we then focused on their synthesis. Enantiomerically pure cyclohexenol **3** bearing a hydrobenzoin monoketal as a chiral auxiliary was visualized as an appropriate starting material to undertake the synthesis of the target nucleoside analogues (Scheme 1). Our synthetic plan involved three main transformations: (i) stereoselective Simmons−Smith cyclopropanation, (ii) regio- and stereoselective olefin hydration, and (iii) stepwise construction of the selected nucleobases from the common intermediate cyclohexylamine **6**.

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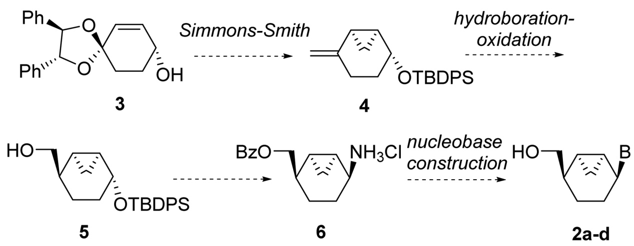
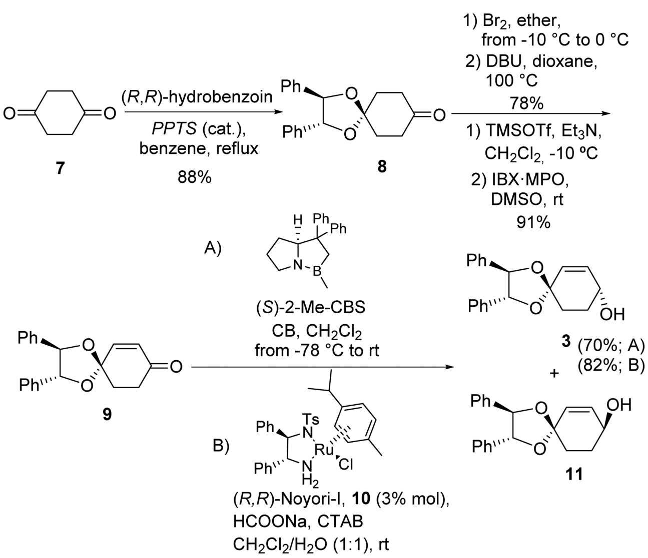
Scheme 1. Synthetic Strategy toward Bicyclic Nucleoside Analogues 2a–d



Initially, work was focused on improving our precedented synthesis of allylic alcohol **3** from the commercially available 1,4-cyclohexanedione **7** (Scheme 2), which included chemo-

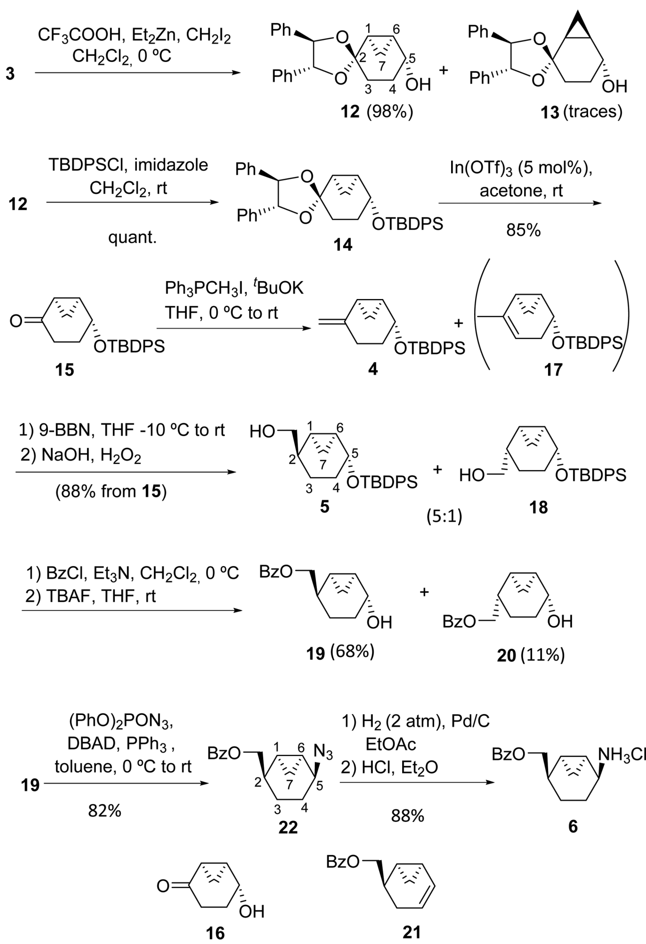
Scheme 2. Synthesis of Enantiomerically Pure Cyclohexenol 3



selective ketalization with (*R*,*R*)-hydrobenzoin (82% yield), enone formation by sequential bromination/dehydrobromination (78%), and stereoselective reduction using catecholborane (CB) paired with (*S*)-2-Me-CBS that provided a 8/1 mixture of allylic alcohols **3** and **11**, which after crystallization delivered the major diastereomer in 70% yield.[5e] However, the yields of the dehydrogenation of ketal **8** were barely reproducible on a multigram scale and an alternative methodology following Nicolaou's IBX-mediated dehydrogenation[17] to prepare the enone **9** was considered. Thus, the reaction of **8** with Et_3N in CH_2Cl_2 and successive addition of TMSOTf provided the corresponding silyl enol ether, which was treated with the IBX·MPO complex to furnish the enone **9** in 91% reproducible yield. Next, to enhance the stereoselectivity of the reduction step, a Noyori asymmetric transfer hydrogenation (ATH) was attempted.[18] In this double stereodifferentiating reaction, by employing a chiral catalyst on a chiral substrate, the stereochemical control can be exerted either internally from the substrate or/and externally from the catalyst.[19] The reduction of **9** was achieved under nonclassical phase-transfer conditions, using the (*R*,*R*)-Noyori-I catalyst **10**, HCOONa, cetyltrimethylammonium bromide (CTAB), and CH_2Cl_2/H_2O (1/1),[20,21] delivering a 24/1 mixture of allylic alcohols **3** and **11**, from which the major isomer was isolated in 82% yield. Remarkably, reduction with the enantiomeric (*S*,*S*)-ruthenium catalyst gave a 1/20 mixture of **3** and **11.** Thus, the carbonyl diastereofaces are efficiently differentiated by the chirality of the catalyst, while the chiral auxiliary does not play any significant role.

With **3** in hand, we assayed the diastereoselective construction of the cyclopropane by using Shi's carbenoid ($CF_3COOZnCH_2I$), generated in situ from Et_2Zn, CH_2I_2, and CF_3COOH,[22] which provided the expected cyclopropane-fused derivative **12** in 98% yield (Scheme 3), indicating that the

Scheme 3. Synthesis of Key Intermediate 6



hydroxyl group directs the incoming carbenoid to the syn face of the double bond. Traces of the corresponding anti isomer **13** were also detected in the crude reaction product. Other attempted cyclopropanation methodologies, including Et_2Zn and CH_2I_2 in diethyl ether or CH_2Cl_2, Et_2Zn and ICH_2Cl in CH_2Cl_2 or DCE[23] following Furukawa's procedure, and samarium-based carbenoids (Sm, CH_2I_2 in THF),[24] proved to be less efficient for this transformation, affording either lower yield and/or worse diastereoselectivity. The relative configuration of the products was assigned on the basis of NOESY experiments. For the minor compound **13**, a strong correlation was observed between H-5 and H-7endo protons, which was absent for the major isomer **12**. Protection of the free hydroxyl group as a silyl ether to render **14** was followed by removal of the chiral auxiliary under mild neutral conditions via transacetalization with acetone and indium(III) trifluoromethanesulfonate as the catalyst.[25] Under these conditions, ketone **15** was obtained in 85% yield for the two steps. Attempts to carry out

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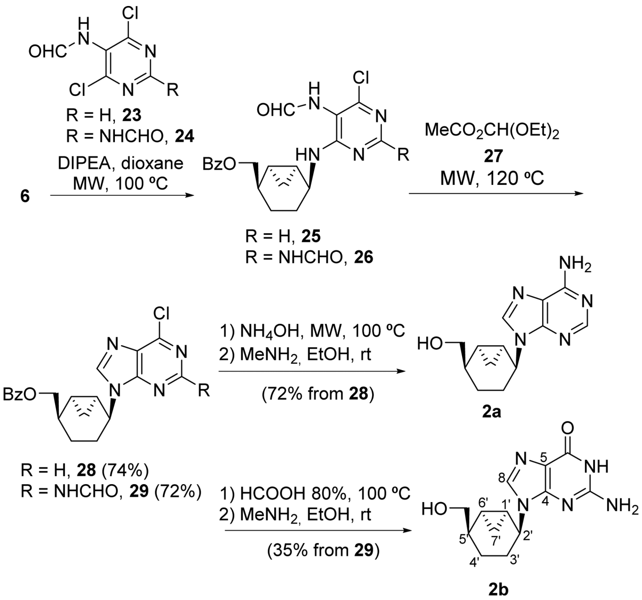
the hydrolysis using montmorillonite K-10[26] in CH_2Cl_2 gave a lower yield, due to the concomitant removal of the silyl protecting group to afford the highly volatile hydroxy ketone **16**.

The preparation of alcohol **5** was envisaged through olefination of ketone **15** followed by hydroboration−oxidation of the alkene **4**. Obviously, the feasibility of this protocol would be largely dependent on the success of the regio- and stereoselective transformation of the exocyclic double bond at C2 of **4** into a *β*-hydroxymethyl group. In the event, treatment of ketone **15** with methyltriphenylphosphonium iodide and *t*-BuOK in THF furnished alkene **4** in 92% yield. Nevertheless, the exocyclic alkene was unstable and rapidly isomerized to the endocyclic isomer **17**. In order to avoid this isomerization, alkene **4** was submitted immediately to hydroboration with 9-borabicyclo[3.3.1]nonane (9-BBN) in anhydrous THF at −10 °C, followed by standard oxidative workup, to provide a chromatographically unseparable 5/1 mixture of alcohols **5** and **18** in 88% combined yield over the two steps. The anti relative configuration of the main product was determined with the aid of a NOESY experiment, which showed cross peaks between H-7endo and H-2, evidencing that the addition of the borane took place preferentially by the syn face. Although the *β* side is more accessible, the four-center transition state toward the all-cis-substituted derivative is unfavored due to steric repulsion between the new alkylborane and the cyclopropane. Thus, hydroboration proceeded preferentially through the attack of the borane from the *α*-side, leading mainly to the isomer with the hydroxymethyl substituent in the *β* face.

Benzoyl protection and subsequent desilylation afforded, after purification by column chromatography, the desired alcohol **19** in 68% yield and its diastereomer **20** in 11% yield. Then, we planned to exploit alcohol **19** to prepare the key amine **6** via formation of the azide with inversion of configuration and subsequent reduction. However, the initial attempts to assemble the azide using a sulfonate derivative of alcohol **19** were abandoned when it became obvious that the activated alcohol underwent elimination to the cyclohexene **21** under all of the reaction conditions assayed before the azide displacement step could occur. Faced with these difficulties, we opted for introducing the azide though a Mitsunobu protocol using diphenylphosphoryl azide (DPPA).[27] Thus, treatment of alcohol **19** with DPPA in the presence of DBAD and PPh_3 in toluene at 0 °C led to the azide **22** in 82% yield. The configuration of C-5 was assessed by the presence of cross peaks between proton H-5 and protons H-2 and H-7endo in the NOESY spectrum. Finally, catalytic hydrogenation afforded the primary amine, which was isolated as the hydrochloride salt **6** in 88% yield. With an efficient source of this key intermediate, the remaining endeavor leading to the targeted compounds was the stepwise construction of the selected purine and pyrimidine nucleobases.

The formation of the chloropurine derivative **28** was first attempted following the original Harnden procedure.[28] However, treatment of **6** with *N*-(4,6-dichloropyrimidin-5-yl)formamide (**23**) and Et_3N in dioxane at 110 °C and subsequent reaction with triethyl orthoformate and concentrated HCl in DMF met with failure, leading to decomposition products. Recently, there has been described a one-pot microwave-assisted procedure to afford purine-based nucleoside analogues in good yields.[29] Thus, coupling of **6** and **23** in dioxane at 110 °C to render intermediate **25**, followed by closure of the imidazole ring using diethoxymethyl acetate (**27**) at 120 °C, under microwave irradiation in both sequential transformations, furnished the chloropurine derivative **28** in 74% yield (Scheme 4). Then, ammonolysis of **28** with NH_4OH

Scheme 4. Synthesis of the Purine Nucleosides

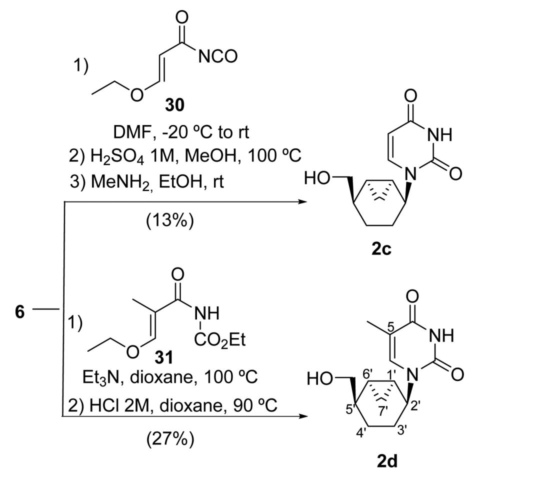


in 1,4-dioxane at 100 °C under microwave irradiation and successive exposure to a 33% solution of $MeNH_2$ in EtOH[30] delivered the expected adenine nucleoside analogue **2a** in 72% yield over the two steps.

The guanine nucleoside **2b** was synthesized by following the same procedure. Accordingly, **6** was coupled with the formyl derivative of 2,5-diamino-4,6-dichloropyrimidine, **24**, followed by ring closure to afford the chloropurine derivative **29** in 72% yield. A subsequent hydrolysis with 80% formic acid at 100 °C and reaction with a 33% solution of $MeNH_2$ in EtOH provided the desired nucleoside analogue **2b** in 35% global yield.

The synthesis of the uracil analogue was performed according to the conditions described by Shaw and Warrener, which involved a two-stage reaction consisting of the aminolysis of a carbamate followed by cyclization (Scheme 5).[31] The reaction of **6** with freshly prepared 3-ethoxy-2-propenoyl isocyanate (**30**)[32] gave the intermediate urea, which was

Scheme 5. Synthesis of the Pyrimidine Nucleosides



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subjected to acidic cyclization and posterior debenzoylation (using a 33% solution of $MeNH_2$ in EtOH) to furnish the expected nucleoside analogue **2c** in 13% overall yield. The preparation of the thymine nucleoside **2d** was accomplished using the acyl carbamate **31** prepared in situ from ethyl propenyl ether following Wyatt's methodology.[33] Thus, the reaction of **6** with acyl carbamate **31** and Et_3N in 1,4-dioxane at 100 °C followed by acid promoting cyclization and benzoyl deprotection furnished **2d** in 27% overall yield.

The reported conformational analysis of cyclohexenyl nucleosides has shown that, at the molecular level, they exist in an equilibrium between two half-chair conformations ($^2H_3$ and $^3H_2$) mimicking the 2′-endo and 3′-endo sugar conformations, respectively (Figure 3).[6] The conformation of the bicyclic compounds **2a−d** was investigated by 1D and 2D NMR studies.[34] As an example, in the ^{1}H NMR spectrum of **2b**, H-1′ resonates at δ 4.86 and appears as a triplet with small coupling constants ($J_{1',2'ax} = J_{1',2'eq}$ = 3.8 Hz), while H-4′ displays a doublet of quartets at δ 1.89 with a large diaxial coupling constant, $J_{4',3'ax}$ = 10.7 Hz, and three smaller coupling constants, $J_{4',1''} = J_{4',1''} = J_{4',3'eq}$ = 6.1 Hz. Moreover, for H-3′ax (δ 1.06) the three large coupling constants 13.8, 13.8, and 10.7 Hz with H3′eq, H-2′ax, and H-4′, respectively, were detected. These data suggest that **2b** exists predominantly in the pseudochair conformation $^3H_2$ with the base in a pseudoaxial position and the hydroxymethyl group in a pseudoequatorial orientation. These conclusions have been further supported by examination of 2D NOESY spectra, wherein NOE interactions were observed between purine H-8 and H-3ax. In addition, correlations from H-4′ to H-2′ax and to one of the methylene protons of the cyclopropane were observed. Similar analyses performed with the rest of the synthesized analogues allowed us to conclude that they occur predominantly in a $^3H_2$ conformation similar to that reported for the deoxycyclohexenyl nucleosides.[35]

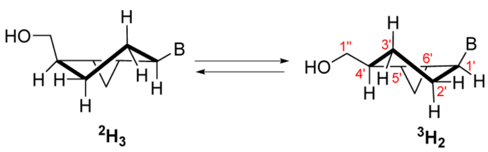

Figure 3. Conformational equilibrium of the nucleoside analogues **2a−d** built on a bicyclo[4.1.0]heptane scaffold.

Compounds **2a−d** have been subject to comprehensive screening for antiviral activity. In particular the compounds were examined for antiherpetic activity (herpes simplex virus-1 (HSV-1; strain KOS), herpes simplex virus-2 (G), and herpes simplex virus-1 (KOS thymidine kinase-deficient acyclovir resistant)) in human embryonic lung (HEL) cell cultures. Unfortunately, none of the compounds showed significant antiviral activity at subtoxic concentrations (∼250 μM) (Table 1).

The lack of inhibitory activity of compounds **2a−d** against herpes simplex virus replication in cell culture may be explained by poor cellular uptake, lack of sufficient affinity or substrate activity for HSV-encoded or cellular nucleoside kinases as the activating enzymes, lack of substrate activity for one of the cellular nucleotide kinases to further convert the compounds to their 5′-triphosphate metabolites, and/or lack of sufficient substrate activity of the 5′-triphosphate metabolites against the virus-encoded DNA polymerases. Further studies are required to reveal the molecular basis of the antiherpetic inactivity of the test compounds.

Table 1. Cytotoxicity and Anti Herpes Simplex Virus Activity of the Synthesized Cyclohexanyl Nucleosides in HEL Cell Cultures

		EC_{50}[b] (μM)		
compd	CC_{50}[a]	herpes simplex virus-1 (KOS)	herpes simplex virus-2 (G)	herpes simplex virus-1 TK^- KOS ACV^r
2a	≥250	>250	>250	>250
2b	>250	>250	>250	>250
2c	250	>250	>250	>250
2d	>250	>250	>250	>250
brivudin	>250	0.06	250	250
cidofovir	>250	2.0	2.0	2.0
acyclovir	>250	0.8	0.8	50
ganciclovir	>100	0.03	0.08	4.0

[a]Minimum cytotoxic concentration required to cause a microscopically detectable alteration of normal cell morphology. [b]Required to reduce virus-induced cytopathogenicity by 50%.

CONCLUSIONS

In summary, we have carried out a molecular modeling study of several nucleoside analogues built on a bicyclo[4.1.0]heptane scaffold considered as potential prodrugs in the HSV-1 TK active site in order to test the suitability of these compounds to pass the usual rate-limiting first phosphorylation step. Considering the positive outcomes of the theoretical results, we have developed an efficient approach for the preparation of enantiomerically pure nucleosides **2a−d** from the pivotal cyclohexenol **3** bearing a dihydrobenzoin moiety as chiral auxiliary. First, we have set up a more practical and multigram preparation of enantiopure **3** starting from 1,4-cyclohexanedione. Key steps of the synthesis of the nucleoside analogues **2a−d** are highly diastereoselective Simmons−Smith cyclopropanation and hydroboration reactions and the stepwise construction of the nucleobase from the key cyclohexyl amine **6**. Anti-HSV-1 and -HSV-2 activity was evaluated in cell culture, and the nucleosides **2a−d** were found to be inactive at 250 μM. The lack of activity indicates that these functionalized NAs built on a bicyclo[4.1.0]heptane scaffold might eventually not reach the HSV DNA incorporation step catalyzed by the HSV-encoded DNA polymerases. Work is in progress to study the final interactions by molecular docking and will be reported elsewhere.

EXPERIMENTAL SECTION

General Methods. Commercially available reagents were used as received. The solvents were dried by distillation over the appropriate drying agents. All reactions were performed with the exclusion of moisture by standard procedures and under a nitrogen atmosphere. Flash column chromatography was performed using silica gel (230−400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded at 250 and 62.5 MHz, 360 and 90 MHz, or 400 and 100 MHz. Proton chemical shifts are reported in ppm (δ) ($CDCl_3$ δ 7.26 or acetone-d_6 δ 2.05). Carbon chemical shifts are reported in ppm (δ) ($CDCl_3$ δ 77.2). NMR signals were assigned with the help of COSY, HSQC, HMBC, and NOESY experiments. Melting points were determined on a hot stage and are uncorrected. Optical rotations were measured at 22 ± 2 °C.

Microwave reactions were conducted on a CEM Discover Microwave synthesizer. The machine consists of a continuous focused microwave-power delivery system with operator-selectable power output from 0 to 300 W. The temperature of the contents of the

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vessel was monitored using a calibrated infrared temperature control mounted under the reaction vessel. All experiments were performed using a stirring option whereby the contents of the vessel were stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel.

Antiviral Activity Assays. The compounds were evaluated for their inhibitory activity against herpes simplex virus type 1 (HSV-1) strain KOS, thymidine kinase-deficient (TK) HSV-1 strain KOS resistant to ACV (ACVr), and herpes simplex virus type 2 (HSV-2) strain G. The antiviral assays were based on the inhibition of virus-induced cytopathicity in human embryonic lung (HEL) fibroblasts.

Confluent cell cultures in microtiter 96-well plates were inoculated with 100 CCID50 of the virus (1 CCID50 being the dose of the virus sufficient to infect 50% of the cell cultures) in the presence of varying concentrations of the test compounds. Viral cytopathicity was recorded as soon as it reached completion in the control virus-infected cell cultures that had not been treated with the test compounds. Antiviral activity is expressed as EC50: i.e., the compound concentration required to suppress virus-induced cytopathogenicity by 50%.

(2*R*,3*R*)-2,3-Diphenyl-1,4-dioxaspiro[4.5]decan-8-one (8).[7b] A solution of 1,4-cyclohexanedione **7** (17.6 g, 153 mmol), (*R*,*R*)-hydrobenzoin (16.4 g, 76.6 mmol), and PPTS (1.92 g, 7.66 mmol) in benzene (300 mL) was stirred at reflux temperature for 5 h in a Dean–Stark apparatus. The reaction mixture was cooled to room temperature and concentrated under vacuum, and the resulting oil was purified by column chromatography (hexanes/EtOAc, 8/1) to provide the monoketal **8** (16.1 g, 52.1 mmol, 68% yield) and the corresponding bisketal (6.18 g, 12.3 mmol, 32% yield), both as white solids. The bisketal can be partially monohydrolyzed by dissolving it in a 5/1 acetic acid/water mixture and stirring at the reflux temperature for 6 h. The same workup as above afforded an extra amount of the monoketal **8** (2.31 g, 7.47 mmol, 61% yield). Thus, the monoketal **8** was obtained in 88% overall yield: $[\alpha]_D^{20}$ = +62.6 (*c* 2.3, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.38–7.28 (m, 6H, Ph), 7.28–7.18 (m, 4H, Ph), 4.87 (s, 2H, H-2, H-3), 2.69 (t br, $J_{7/9,6/10}$ = 7.0 Hz, 4H, H-7, H-9), 2.39–2.27 (m, 4H, H-6, H-10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.2 (C-8), 136.2/128.6/126.8 (C-Ph), 107.9 (C-5), 85.6 (C-2, C-3), 38.2 (C-7, C-9), 35.4 (C-6, C-10).

(2*R*,3*R*)-2,3-Diphenyl-1,4-dioxaspiro[4.5]dec-6-en-8-one (9).[7a] To a stirred solution of monoketal **8** (6.70 g, 21.7 mmol) and Et_3N (4.50 mL, 32.6 mmol) in anhydrous CH_2Cl_2 (145 mL) at −10 °C, under a nitrogen atmosphere, was added dropwise TMSOTf (5.90 mL, 32.6 mmol), and the reaction mixture was stirred for 2 h. A solution of IBX (10.2 g, 36.3 mmol) and MPO (4.21 g, 32.6 mmol) in DMSO (145 mL) was stirred for 1 h until it became clearly yellow, and then, it was poured onto the reaction mixture. After 1 h of stirring at room temperature, a saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$ solution (100 mL) was added and stirred for 30 min. Then, diethyl ether (100 mL) was added, and the aqueous layer was extracted with additional diethyl ether (2 × 100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum to provide enone **9** (6.08 g, 19.8 mmol, 91% yield) as a pale yellow solid: $[\alpha]_D^{20}$ = +48.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40–7.25 (m, 6H, Ph), 7.25–7.10 (m, 4H, Ph), 6.93 (ddd, $J_{6,7}$ = 10.2 Hz, $J_{6,10}$ = 1.4 Hz, $J_{6,10}$ = 0.5 Hz, 1H, H-6), 6.13 (dd, $J_{7,6}$ = 10.2 Hz, $J_{7,9}$ = 0.8 Hz, 1H, H-7), 4.88 (d, $J_{3,2}$ = 8.5 Hz, 1H, H-3), 4.80 (d, $J_{2,3}$ = 8.5 Hz, 1H, H-2), 2.81 (ddt, *J* = 16.8 Hz, *J*′ = 9.3 Hz, *J*″ = 6.4 Hz, 1H, H-9/H-10), 2.68 (dt, *J* = 16.8 Hz, *J*′ = *J*″ = 5.5 Hz, 1H, H-9/H-10), 2.60–2.40 (m, 2H, H-9, H-10); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 198.6 (C-8), 146.7 (C-6), 135.6/135.4 (C-Ph), 130.8 (C-7), 128.7/128.6/126.6 (C-Ph), 104.5 (C-5), 85.8/85.2 (C-2, C-3), 35.2/34.0 (C-9, C-10).

(2*R*,3*R*,8*R*)-2,3-Diphenyl-1,4-dioxaspiro[4.5]dec-6-en-8-ol (3) and Its 2*R*,3*R*,8*S* Isomer (11). To a stirred solution of enone **9** (1.76 g, 5.75 mmol) in a biphasic media of CH_2Cl_2 (10 mL) and water (10 mL), hexadecyltrimethylammonium bromide (CTAB) (628 mg, 1.72 mmol), sodium formate (589 mg, 8.62 mmol) and (*R*,*R*)-Noyori-I catalyst **10** (109 mg, 0.17 mmol) were sequentially added at room temperature. The reaction mixture was stirred for 24 h. Then, the layers were separated and the volatiles of the organic phase were removed under reduced pressure affording a yellow oil, which was further purified by column chromatography (hexanes/EtOAc, 9/1 to 3/1) to deliver allylic alcohols **3** and **11** in a 24/1 ratio (1.53 g, 4.95 mmol, 86% yield) as a white solid. Recrystallization in diethyl ether/pentane furnished pure alcohol **3** (1.46 g, 4.72 mmol, 82% yield).

When the reaction was carried out with the (*S*,*S*)-Noyori-I catalyst, from enone **9** (102 mg, 0.33 mmol) a mixture of allylic alcohols **3** and **11** in a 1/20 ratio (90 mg, 0.29 mmol, 88% yield) was obtained.

3: $[\alpha]_D^{20}$ = +55.0 (*c* 0.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.26 (m, 6H, Ph), 7.26–7.17 (m, 4H, Ph), 6.05 (ddd, $J_{7,6}$ = 10.1 Hz, $J_{7,8}$ = 2.0 Hz, $J_{7,9}$ = 1.2 Hz, 1H, H-7), 5.92 (dt, $J_{6,7}$ = 10.1 Hz, $J_{6,8}$ = $J_{6,10}$ = 1.9 Hz, 1H, H-6), 4.79 (d, $J_{3,2}$ = 8.5 Hz, 1H, H-3), 4.69 (d, $J_{2,3}$ = 8.5 Hz, 1H, H-2), 4.29 (ddt, $J_{8,9ax}$ = 9.0 Hz, $J_{8,9eq}$ = 4.3 Hz, $J_{8,7}$ = $J_{8,6}$ = 2.0 Hz, 1H, H-8), 2.29–2.18 (m, 2H, H-9, H-10), 2.11–2.01 (m, 1H, H-9/H-10), 1.93–1.80 (m, 1H, H-9/H-10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3/136.2 (C-Ph), 135.7 (C-7), 129.5 (C-6), 128.5/128.4/128.3/126.8/126.6 (C-Ph), 105.7 (C-5), 85.5/85.1 (C-2, C-3), 66.6 (C-8), 32.8 (C-10), 31.0 (C-9).

11: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.30 (m, 6H, Ph), 7.25–7.20 (m, 4H, Ph), 6.08 (dd, $J_{7,6}$ = 10.1 Hz, $J_{7,8}$ = 3.2 Hz, 1H, H-7), 5.99 (d, $J_{6,7}$ = 10.1 Hz, 1H, H-6), 4.82 (d, $J_{3,2}$ = 8.5 Hz, 1H, H-3), 4.77 (d, $J_{2,3}$ = 8.5 Hz, 1H, H-2), 4.30 (br s, 1H, H-8), 2.42–2.31 (ddd, *J* = 13.0 Hz, *J*′ = 9.1 Hz, *J*″ = 3.0 Hz, 1H, H-9/10), 2.30–2.17 (m, 1H, H-9/10), 2.12–2.01 (m, 1H, H-9/10), 1.95 (dtd, *J* = 13.0 Hz, *J*′ = 6.4 Hz, *J*″ = 3.0 Hz, 1H, H-9/10).

(1*R*,4′*R*,5*R*,5′*R*,6*S*)-4′,5′-Diphenylspiro[bicyclo[4.1.0]-heptane-2,2′-[1,3]dioxolan]-5-ol (12). An ice-cooled solution of Et_2Zn (6.48 mL, 6.480 mmol, 1.0 M in hexanes) in CH_2Cl_2 (45 mL) was stirred for 15 min under a nitrogen atmosphere. Trifluoroacetic acid (504 μL, 6.480 mmol) was added dropwise, and the mixture was stirred for another 20 min. Then, diiodomethane (523 μL, 6.480 mmol) was added dropwise and stirring was continued for 20 min. After that time, a solution of alcohol **3** (1.0 g, 3.240 mmol) in CH_2Cl_2 (20 mL) was introduced at 0 °C. The resulting mixture was stirred for 2 h and then quenched by the addition of saturated aqueous Na_2EDTA solution (80 mL) and extracted with CH_2Cl_2 (2 × 60 mL). The organic layers were dried (Na_2SO_4), concentrated under reduced pressure, and purified by column chromatography (hexanes/EtOAc, 4/1) to provide cyclohexanol **12** (1.126 g, 3.492 mmol, 98% yield) as a white solid: mp 103–105 °C (diethyl ether); $[\alpha]_D^{20}$ = +25.5 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.28 (m, 8H, Ph), 7.23–7.19 (m, 2H, Ph), 4.83 (d, $J_{5',4'}$ = 9.0 Hz, 1H, H-5′), 4.70 (d, $J_{4',5'}$ = 9.0 Hz, 1H, H-4′), 4.35 (q, $J_{5,4ax}$ = $J_{5,4eq}$ = $J_{5,6}$ = 5.5 Hz, 1H, H-5), 1.94–1.81 (m, 3H, 2H-3, H-4eq), 1.70–1.55 (m, 2H, H-1, H-6), 1.56–1.41 (m, 1H, H-4ax), 0.96 (q, $J_{7endo,1}$ = $J_{7endo,6}$ = J_{gem} = 5.7 Hz, 1H, H-7endo), 0.83 (td, $J_{7exo,1}$ = $J_{7exo,6}$ = 9.4 Hz, J_{gem} = 5.7 Hz, 1H, H-7exo); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9/136.6 (C-Ph), 128.5/128.5/128.4 (C-Ph), 127.0/126.7 (C-Ph), 108.7 (C-2), 85.5/85.2 (C-4′,C-5′), 65.4 (C-5), 31.8 (C-3), 27.5 (C-4), 23.4 (C-1), 19.4 (C-6), 4.2 (C-7); IR (ATR) 3496, 2930, 1454, 1258, 1086, 1062 cm^{-1}; HRMS (ESI+) calcd for $[C_{21}H_{22}O_3 + Na]^+$ 345.1461, found 345.1448.

Traces of the 1*S*,4′*R*,5*R*,5′*R*,6*R* isomer **13** were also obtained: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.32 (m, 8H, H-Ar), 7.23 (m, 2H, H-Ar), 4.88 (d, $J_{5',4'}$ = 8.5 Hz, 1H, H-5′), 4.77 (d, $J_{4',5'}$ = 8.5 Hz, 1H, H-4′), 4.10 (s br, 1H, H-5), 2.02 (m, 2H, H-3), 1.79 (m, 2H, H-4a, H-6), 1.67 (td, $J_{1,6}$ = $J_{1,7b}$ = 8.5 Hz, $J_{1,7a}$ = 5.8 Hz, 1H, H-1), 1.49 (tdd, $J_{4b,3ax}$ = $J_{4b,3eq}$ = 8.5 Hz, $J_{4b,5}$ = 5.8 Hz, $J_{4b,6}$ = 2.1 Hz, 1H, H-4b), 0.87 (td, $J_{7b,1}$ = $J_{7b,6}$ = 9.0 Hz, $J_{7b,7a}$ = 5.8 Hz, 1H, H-7b), 0.57 (q, $J_{7a,1}$ = $J_{7a,6}$ = $J_{7a,7b}$ = 5.8 Hz, 1H, H-7a); ^{13}C NMR (90 MHz, $CDCl_3$) δ 136.6/136.6 (C-Ar), 128.5/128.4/128.4 (C-Ar), 126.9/126.8 (C-Ar), 109.9 (C-2), 85.4/85.3 (C-4′,C-5′), 66.2 (C-5), 28.6 (C-3), 27.9 (C-4), 21.0 (C-1), 20.6 (C-6), 7.6 (C-7).

(1*R*,4′*R*,5*R*,5′*R*,6*S*)-5-(*tert*-Butyldiphenylsilyloxy)-4′,5′-diphenylspirobicyclo[4.1.0]heptane-2,2′-[1,3]dioxolane (14). To a stirred solution of **12** (1.55 g, 4.81 mmol) in CH_2Cl_2 (32 mL) were added imidazole (360 mg, 5.290 mmol) and TBDPSCl (1.3 mL, 5.05 mmol) at room temperature, and the mixture was stirred overnight. After this time, the volatiles were removed under vacuum and the resulting crude reaction product was purified by column chromatography (hexanes/EtOAc, 5/1) to furnish the silyl derivate **14**

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(2.70 g, 4.81 mmol, quantitative yield) as a colorless syrup: $[\alpha]_D^{20}$ = +38.1 (*c* 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 7.3 Hz, *J* = 5.8 Hz, 4H, Ph), 7.50−7.37 (m, 6H, Ph), 7.37−7.28 (m, 8H, Ph), 7.21 (dd, *J* = 6.8 Hz, *J* = 2.9 Hz, 2H, Ph), 4.84 (d, $J_{5',4'}$ = 8.5 Hz, 1H, H-5′), 4.74 (d, $J_{4',5'}$ = 8.5 Hz, 1H, H-4′), 4.40 (q, $J_{5,4ax}$ = $J_{5,4eq}$ = $J_{5,6}$ = 5.8 Hz, 1H, H-5), 1.98 (t, J_{gem} = $J_{3eq,4ax}$ = $J_{3eq,4eq}$ = 10.8 Hz, 1H, H-3eq), 1.86−1.72 (m, 2H, H-3ax, H-4eq), 1.70−1.62 (m, 1H, H-4ax), 1.49 (td, $J_{1,6}$ = $J_{1,7exo}$ = 9.3 Hz, $J_{1,7endo}$ = 5.8 Hz 1H, H-1), 1.32 (tt, $J_{6,7exo}$ = $J_{6,1}$= 9.3 Hz, $J_{6,7endo}$ = $J_{6,5}$ = 5.8 Hz, 1H, H-6), 1.19 (q, $J_{7endo,1}$ = $J_{7endo,6}$ = J_{gem} = 5.8 Hz, 1H, H-7endo), 1.13 (s, 9H, H-*t*Bu), 0.83 (td, $J_{7exo,1}$ = $J_{7exo,6}$ = 9.3 Hz, J_{gem} = 5.8 Hz, 1H, H-7exo); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2/136.9 (C-Ph), 136.0/135.9 (C-Ph), 135.3/134.9/134.8/134.7 (C-Ph), 129.8/129.7 (C-Ph), 128.6/128.5/128.4 (C-Ph), 127.8/127.7/127.6/127.0/126.7 (C-Ph), 109.6 (C-2), 85.5/85.3 (C-4′,C-5′), 66.2 (C-5), 30.7 (C-3), 28.9 (C-4), 27.1 ($C(CH_3)_3$), 23.1 (C-1), 19.4 (C-6), 19.1 ($C(CH_3)_3$), 5.7 (C-7); IR (ATR) 3068, 2930, 1695, 1427, 1104 cm^{-1}; HRMS (ESI+) calcd for $[C_{37}H_{40}O_3Si + Na]^+$ 583.2639, found 583.2636.

(1*R*,5*R*,6*S*)-5-(*tert*-Butyldiphenylsilyloxy)bicyclo[4.1.0]-heptan-2-one (15). To a solution of **14** (6.01 g, 10.7 mmol) in acetone (228 mL) was added $In(OTf)_3$ (258 mg, 0.459 mmol) and the mixture was stirred at room temperature for 16 h. Then, the acetone was removed under vacuum and the residue was purified by column chromatography (hexanes/EtOAc, 8/1) to afford ketone **15** (3.33 mg, 9.13 mmol, 85% yield) as a white solid: mp 49−51 °C (diethyl ether); $[\alpha]_D^{20}$ = +136.7 (*c* 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 14.1 Hz, *J* = 6.9 Hz, 4H, Ph), 7.41 (dd, *J* = 13.7 Hz, *J* = 7.0 Hz, 6H, Ph), 4.39 (q, $J_{5,4ax}$ = $J_{5,4eq}$ = $J_{5,6}$ = 6.9 Hz, 1H, H-5), 2.32 (dt, J_{gem} = 17.6 Hz, $J_{3eq,4ax}$ = $J_{3eq,4eq}$ = 5.2 Hz, 1H, H-3eq), 1.98 (dt, J_{gem} = 17.6 Hz, $J_{3ax,4ax}$ = $J_{3ax,4eq}$ = 8.6 Hz, 1H, H-3ax), 1.82−1.72 (m, 2H, H-4), 1.72−1.62 (m, 2H, H-1, H-6), 1.52 (q, $J_{7endo,1}$ = $J_{7endo,6}$ = J_{gem} = 5.5 Hz, 1H, H-7endo), 1.10 (s, 10H, 9H-*t*Bu, H-7exo); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.0 (C-2), 135.8/135.8 (C-Ph), 134.2/134.0 (C-Ph), 129.9/129.8 (C-Ph), 127.8/127.7 (C-Ph), 66.4 (C-5), 34.5 (C-3), 27.8 (C-4), 27.0 ($C(CH_3)_3$), 27.0 (C-1), 23.9 (C-6), 19.3 ($C(CH_3)_3$), 9.2 (C-7); IR (ATR) 3069, 2927, 1689, 1427, 1080 cm^{-1}; HRMS (ESI+) calcd for $[C_{23}H_{28}O_2Si+Na]^+$ 387.1751, found 387.1744.

Traces of (1*R*,5*R*,6*S*)-5-Hydroxybicyclo[4.1.0]heptan-2-one (**16**) were also obtained: $[\alpha]_D^{20}$ = +78.5 (*c* 0.65, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 (dddd, $J_{5,4ax}$ = 10.1 Hz, $J_{5,6}$ = 5.2 Hz, $J_{5,4eq}$ = 4.1 Hz, $J_{5,3ax}$ = 0.8 Hz, 1H, H-5), 2.37 (ddd, J_{gem} = 18.4 Hz, $J_{3eq,4ax}$ = 5.6 Hz, $J_{3eq,4eq}$ = 3.6 Hz, 1H, H-3eq), 2.15 (dddd, J_{gem} = 18.4 Hz, $J_{3ax,4ax}$ = 12.1 Hz, $J_{3ax,4eq}$ = 6.6 Hz, $J_{3ax,5}$ = 0.8 Hz, 1H, H-3ax), 1.98−1.83 (m, 3H, H-1, H-6, H-4eq), 1.63 (dddd, J_{gem} = 13.8 Hz, $J_{4ax,3ax}$ = 12.1 Hz, $J_{4ax,5}$ = 10.3 Hz, $J_{4ax,3eq}$ = 5.6 Hz, 1H, H-4ax), 1.44 (q, J_{gem} = $J_{7endo,1}$ = $J_{7endo,6}$ = 5.4 Hz, 1H, H-7endo), 1.14 (ddd, $J_{7exo,1/6}$ = 9.8 Hz, $J_{7exo,1/6}$ = 7.7 Hz, J_{gem} = 5.4 Hz, 1H, H-7exo); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.5 (C-2), 65.3 (C-5), 34.8 (C-3), 26.8 (C-1), 26.7 (C-4), 23.3 (C-6), 8.0 (C-7); IR (ATR) 3359, 2919, 2850, 1659, 1345, 1066 cm^{-1}; HRMS (ESI+) calcd for $[C_7H_{10}O_2 + Na]^+$ 149.0573, found 149.0576.

((1′*S*,2′*R*,5′*R*,6′*S*)-5′-(*tert*-Butyldiphenylsilyloxy)bicyclo-[4.1.0]hept-2′-yl)methanol (5) and Its 2′*S* Diastereomer (18). To a stirred solution of Ph_3PCH_3I (587 mg, 1.41 mmol) in anhydrous THF (1.6 mL) at 0 °C was added *t*BuOK (160 mg, 1.36 mmol) under a nitrogen atmosphere, and the resulting yellow mixture was allowed to react for 1 h. After this time, a solution of ketone **15** (102 mg, 0.28 mmol) in THF (1.6 mL) was added and the mixture was stirred for 3 h. Then, diethyl ether (3 mL) was added and the solution was filtered through a thin pad of silica and Celite, using more diethyl ether (15 mL) as eluent. The volatiles were removed under vacuum to furnish an orange oil identified as alkene **4**, which was directly used for the next step without further purification. Alkene **4** is unstable and rapidly isomerizes to the endocyclic isomer **17**. In order to avoid the isomerization process, crude alkene **4** was rapidly dissolved in anhydrous THF (2.9 mL) and 9-BBN (1.68 mL, 0.84 mmol, 0.5 M in THF) was added at −10 °C. The mixture was stirred overnight, and then water (0.6 mL), NaOH (1.1 mL, 3 M in water) and H_2O_2 (1 mL, 30% in water) were added at 0 °C. After the mixture was stirred for 15 min, brine (10 mL) and CH_2Cl_2 (10 mL) were added. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by column chromatography (hexanes/EtOAc, 4/1 to 2/1) to provide a 5/1 mixture of alcohols **5** and **18** (94 mg, 0.25 mmol, 88% yield).

4: $[\alpha]_D^{20}$ = +22.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 18.0 Hz, *J* = 7.2 Hz, 4H, Ph), 7.41 (dd, *J* = 11.4 Hz, *J* = 6.9 Hz, 6H, Ph), 4.84 (s, 1H, H-1′), 4.75 (s, 1H, H-1′), 4.34 (q, $J_{5,4ax}$ = $J_{5,4eq}$ = $J_{5,6}$ = 6.1 Hz, 1H, H-5), 2.21 (dt, J_{gem} = 14.8 Hz, $J_{3eq,4ax}$ = $J_{3eq,4eq}$ = 6.0 Hz, 1H, H-3eq), 1.95 (dt, J_{gem} = 14.8 Hz, $J_{3ax,4ax}$ = $J_{3ax,4eq}$ = 7.2 Hz, 1H, H-3ax), 1.66 (td, $J_{1,6}$ = $J_{1,7exo}$ = 8.7 Hz, $J_{1,7endo}$ = 5.0 Hz, 1H, H-1), 1.56−1.46 (m, 2H, H-4), 1.35−1.21 (m, 1H, H-6), 1.12 (s, 9H, H-*t*Bu), 0.94 (q, $J_{7endo,1}$ = $J_{7endo,6}$ = J_{gem} = 5.0 Hz, 1H, H-7endo), 0.75 (td, $J_{7exo,1}$ = $J_{7exo,6}$ = 8.7 Hz, J_{gem} = 5.0 Hz, 1H, H-7exo); ^{13}C NMR (90 MHz, $CDCl_3$) δ 146.4 (C-2), 136.0/135.9 (C-Ph) 134.9/134.8 (C-Ph), 129.6/129.6/127.6/127.5 (C-Ph), 108.2 (C-1′), 67.4 (C-5), 31.1 (C-4), 27.9 (C-3), 27.1 ($C(CH_3)_3$), 20.3 (C-6), 20.2 (C-1), 19.4 ($C(CH_3)_3$), 9.1 (C-7); IR (ATR) 3070, 2930, 1471, 1427, 1106 cm^{-1}. HRMS (ESI+) calcd for $[C_{24}H_{30}OSi + Na]^+$ 385.1958, found 385.1950.

17: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.89−7.55 (m, 4H, Ph), 7.49−7.27 (m, 6H, Ph), 4.89 (dq, $J_{3,4}$ = 6.7 Hz, $J_{3,4}$ = $J_{3,1'}$ = $J_{3,1'}$ = 1.6 Hz, 1H, H-3), 4.25 (ddd, $J_{5,4}$ = 9.8 Hz, $J_{5,4}$ = 6.8 Hz, $J_{5,6}$ = 4.2 Hz, 1H, H-5), 2.18−2.04 (m, 1H, H-4eq), 1.99−1.78 (m, 1H, H-4ax), 1.74 (t, $J_{1',3}$ = $J_{1',1}$ = 1.6 Hz, 3H, H-1′), 1.41−1.17 (m, 2H, H-6, H-1), 1.08 (s, 9H, H-*t*Bu), 0.90 (q, $J_{7endo,1}$ = $J_{7endo,6}$ = J_{gem} = 4.8 Hz, 1H, H-7endo), 0.77 (td, $J_{7exo,1}$ = $J_{7exo,6}$ = 8.2 Hz, J_{gem} = 4.4 Hz, 1H, H-7exo); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 136.1 (C-2), 136.0/135.9/135.1/134.8/129.6/129.5/127.7/127.6/127.5 (C-Ph), 114.4 (C-3), 68.1 (C-5), 30.7 (C-4), 27.2 ($C(CH_3)_3$), 23.1 (C-1′), 20.6 (C-1), 19.4 ($C(CH_3)_3$), 18.0 (C-6), 9.6 (C-7).

5 and **18** mixture: ^{1}H NMR (400 MHz, $CDCl_3$) (ca. 83% **5**) δ 7.78−7.64 (m, 4H, Ph), 7.46−7.31 (m, 6H, Ph), 4.26−4.13 (m, 1H, H-5′), 3.51 (d, $J_{1,2'}$ = 6.6 Hz, 2H, H-1), 1.73−1.58 (m, 2H, H-2′, H-4′eq), 1.57−1.39 (m, 1H, H-3′eq), 1.07 (s, 10H, $C(CH_3)_3$, H-4′eq), 0.96 (ddd, $J_{6',7'exo}$ = 8.8 Hz, $J_{6',7'endo}$ = 5.3 Hz, $J_{6',1'}$ = 3.0 Hz, 1H, H-6′), 0.82−0.69 (m, 2H, H-1′, H-3′ax), 0.65 (td, $J_{7'exo,1'}$ = $J_{7'exo,6'}$ = 8.8, J_{gem} = 5.3 Hz, 1H, H-7′exo), 0.50 (q, J_{gem} = $J_{7'endo,1'}$ = $J_{7'endo,6'}$= 5.3 Hz, 1H, H-7′endo); (ca. 17% **18**, observable signals) δ 7.78−7.64 (m, 4H, Ph), 7.46−7.31 (m, 6H, Ph), 4.31 (dt, $J_{5',6'}$ = 6.5 Hz, $J_{5',4'ax}$ = $J_{5',4'eq}$ = 4.5 Hz, 1H, H-5′), 3.61−3.46 (m, 2H, H-1), 2.04−1.94 (m, 1H, H-2′), 1.88−1.78 (m, 1H, H-4′), 0.38 (td, $J_{7'exo,1'}$ = $J_{7'exo,6'}$ = 9.0 Hz, J_{gem} = 4.9 Hz, 1H, H-7′exo); ^{13}C NMR (100 MHz, $CDCl_3$) (ca. 83% **5**) δ 136.0/135.9 (C-Ph), 135.2/135.0 (C-Ph), 129.6/129.5/127.6/127.5 (C-Ph), 69.8 (C-5), 68.2 (C-1), 38.1 (C-2′), 28.4 (C-4′), 27.2 ($C(CH_3)_3$), 25.7 (C-3′), 19.4 ($C(CH_3)_3$), 18.2(C-6′), 16.4 (C-1′), 8.6 (C-7′); (ca. 17% **18**, observable signals) δ 136.0/135.9 (C-Ph), 135.0/134.9 (C-Ph), 129.8/129.6/127.9/127.7 (C-Ph), 67.7 (C-1), 66.4 (C-5′), 35.1 (C-2′), 30.9 (C-4′), 27.2 ($C(CH_3)_3$), 22.8 (C-3′), 19.4 ($C(CH_3)_3$), 17.2 (C-6′), 14.5 (C-1′), 2.5(C-7′); IR (ATR) 3358, 3070, 2930, 2856, 1427, 1109 cm^{-1}; HRMS (EI) calcd for $[C_{24}H_{32}O_2Si - C_4H_9]^+$ 323.1467, found 323.1469.

((1′*S*,2′*R*,5′*R*,6′*S*)-5′-Hydroxybicyclo[4.1.0]heptan-2′-yl)-methyl Benzoate (19). To a stirred solution of a 5/1 mixture of **5** and **18** (1.00 g, 2.63 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C were sequentially added anhydrous Et_3N (310 mL, 2.68 mmol) and benzoyl chloride (0.38 mL, 2.68 mmol) under an argon atmosphere, and the mixture was stirred overnight. Then, HCl (10% solution, 30 mL) and CH_2Cl_2 (30 mL) were added, the two phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude reaction product was dissolved in THF (44 mL), TBAF (6.6 mL, 6.57 mmol, 1 M in THF) was added, and the mixture was stirred at room temperature overnight. Then, the solvent was removed and the residue was purified by column chromatography (hexanes/EtOAc, 10/1) to afford alcohol **19** (369 mg, 1.50 mmol, 68% yield) as a colorless syrup and its isomer **20** (60 mg, 0.24 mmol, 11% yield) also as a colorless syrup.

19: $[\alpha]_D^{20}$ = +44.9 (*c* 0.88, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 8.3 Hz, *J* = 1.3 Hz, 2H, Ph), 7.61−7.51 (m, 1H, Ph), 7.44

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(t, J = 7.6 Hz, 2H, Ph), 4.28 (dd, $J_{1,2'}$ = 6.8 Hz, $J_{1,1'}$ = 2.0 Hz, 2H, H-1), 4.20 (dt, $J_{5',6'}$ = 8.8 Hz, $J_{5',4'ax}$ = $J_{5',4'eq}$ = 6.9 Hz, 1H, H-5′), 2.05−1.91 (m, 1H, H-2′), 1.86−1.72 (m, 1H, H-4′eq), 1.70−1.61 (m, 2H, H-3′), 1.33 (tt, $J_{6',5'}$ = $J_{6',7'exo}$ = 8.8 Hz, $J_{6',1'}$ = $J_{6',7'endo}$ = 5.3 Hz, 1H, H-6′), 1.13−0.87 (m, 2H, H-1′, H-4′ax), 0.71 (td, $J_{7'exo,1'}$ = $J_{7'exo,6'}$ = 8.8 Hz, J_{gem} = 5.3 Hz, 1H, H-7′exo), 0.40 (q, $J_{7'endo,1'}$ = $J_{7'endo,6'}$ = J_{gem} = 5.3 Hz, 1H, H-7′endo); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8 (C═O), 133.1/130.4/129.7/128.5 (C-Ph), 69.4 (C-1), 68.0 (C-5′), 34.5 (C-2′), 28.0 (C-4′), 26.0 (C-3′), 18.1 (C-6′), 16.2 (C-1′), 7.6 (C-7′); IR (ATR) 3366, 3066, 3003, 2937, 2869, 1715, 1269, 1110 cm^{-1}; HRMS (EI) calcd for $[C_{15}H_{18}O_3]^+$ 246.1256, found 246.1258.

20: $[\alpha]_D^{20}$ = −7.2 (c 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.2 Hz, 2H, Ph), 7.56 (t, J = 7.4 Hz, 1H, Ph), 7.44 (t, J = 7.6 Hz, 2H, Ph), 4.34 (dt, $J_{5',4'ax}$ = 7.3 Hz, $J_{5',4'eq}$ = $J_{5',6'}$ = 4.7 Hz, 1H, H-5′), 4.29 (dd, J_{gem} = 10.7 Hz, $J_{1,2'}$ = 6.9 Hz, 1H, H-1), 4.18 (dd, J_{gem} = 10.7 Hz, $J_{1,2'}$ = 6.9 Hz, 1H, H-1), 2.36 (dq, $J_{2',3'ax}$ = 12.6 Hz, $J_{2',1}$ = $J_{2',1}$ = $J_{2',3'eq}$ = 6.9 Hz, 1H, H-2′), 1.51−1.37 (m, 4H, H-6′, 2H-4′, H-3′eq), 1.27 (tt, $J_{1',2'}$ = $J_{1',7'exo}$ = 8.9 Hz, $J_{1',7'endo}$ = $J_{1',6'}$ = 5.3 Hz, 1H, H-1′), 1.23−1.13 (m, 1H, H-3′ax), 0.57 (q, J_{gem} = $J_{7'endo,6'}$ = $J_{7'endo,1'}$ = 5.3 Hz, 1H, H-7′endo), 0.46 (td, $J_{7'exo,1'}$ = $J_{7'exo,6'}$ = 8.9 Hz, J_{gem} = 5.3 Hz, 1H, H-7′exo); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8 (C═O), 133.0/130.6/129.7/128.5 (C-Ph), 68.9 (C-1), 64.7 (C-5′), 31.7 (C-2′), 29.9 (C-4′), 19.4 (C-3′), 17.1 (C-1′), 14.7 (C-6′), 1.7 (C-7′); IR (ATR) 3410, 3069, 3009, 2938, 1715, 1273, 1114 cm^{-1}; HRMS (EI) calcd. for $[C_{15}H_{18}O_3]^+$ 246.1256, found 246.1252.

((1′*R*,2′*R*,6′*R*)-Bicyclo[4.1.0]hept-4′-en-2′-yl)methyl Benzoate (21). To a solution of **19** (33 mg, 0.13 mmol) in dry CH_2Cl_2 (1.5 mL) were sequentially added anhydrous Et_3N (37 μL, 0.27 mmol) and mesyl chloride (17 μL, 0.23 mmol) at 0 °C, under an argon atmosphere, and stirred overnight. Then, aqueous HCl (5%, 2 mL) and CH_2Cl_2 (0.5 mL) were added. The two layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 2 mL). The organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and purified by column chromatography (hexanes/EtOAc, 20/1) to afford **21** (11 mg, 0.048 mmol, 37% yield) as a colorless syrup: $[\alpha]_D^{20}$ = −21.7 (c 0.17, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, J = 8.5 Hz, J = 1.3 Hz, 2H, H-Ar), 7.62−7.53 (m, 1H, H-Ar), 7.47 (tt, J = 6.8 Hz, J = 1.3 Hz, 2H, H-Ar), 6.08 (dddd, $J_{5',4'}$ = 9.9 Hz, $J_{5',6'}$ = 5.1 Hz, $J_{5',3'ax}$ = 2.7 Hz, $J_{5',3'eq}$ = 1.8 Hz, 1H, H-5′), 5.33 (ddd, $J_{4',5'}$ = 9.9 Hz, $J_{4',3'eq}$ = 6.6 Hz, $J_{4',3'ax}$ = 2.7 Hz, 1H, H-4′), 4.30 (dd, J_{gem} = 10.6 Hz, $J_{1,2'}$ = 6.4 Hz, 1H, H-1), 4.20 (dd, J_{gem} = 10.6 Hz, $J_{1,2'}$ = 8.3 Hz, 1H, H-1), 2.68−2.53 (m, 1H, H-2′), 2.11 (ddt, J_{gem} = 17.3 Hz, $J_{3'eq,4'}$ = 6.6 Hz, $J_{3'eq,2'}$ = $J_{3'eq,5'}$ = 1.8 Hz, 1H, H-3′eq), 2.00 (ddt, J_{gem} = 17.3 Hz, $J_{3'ax,2'}$ = 6.9 Hz, $J_{3'ax,5'}$ = $J_{3'ax,4'}$ = 2.7 Hz, 1H, H-3′ax), 1.33−1.23 (m, 2H, H-1′, H-6′), 0.92 (td, $J_{7'exo,1'}$ = $J_{7'exo,6'}$ = 8.5 Hz, J_{gem} = 5.7 Hz, 1H, H-7′exo), 0.75 (dt, $J_{7'endo,6'}$ = $J_{7'endo,1'}$ = 5.7 Hz, J_{gem} = 4.4 Hz, 1H, 1H, H-7′endo); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8 (C═O), 133.0/130.7/129.7 (C-Ar), 129.4 (C-5′), 128.5 (C-Ar), 119.8 (C-4′), 68.1 (C-1), 29.0 (C-2′), 23.4 (C-3′), 16.1 (C-6′), 15.4 (C-1′), 11.2 (C-7′); IR (ATR) 3031, 2924, 2852, 2363, 1720, 1270, 1114 cm^{-1}; HRMS (ESI+) calcd. for $[C_{15}H_{16}O_2 + Na]^+$ 251.1046, found 251.1043.

((1′*R*,2′*R*,5′*S*,6′*S*)-5′-Azidobicyclo[4.1.0]hept-2′-yl)methyl Benzoate (22). To a stirred suspension of Ph_3P (360 mg, 1.36 mmol) in dry toluene (9 mL) was slowly added DBAD (313 mg, 1.36 mmol) under an argon atmosphere, and the mixture was stirred for 45 min at 0 °C. After 15 min, a suspension appeared. Then, diphenylphosphoryl azide (216 μL, 0.97 mmol) and a solution of **19** (223 mg, 0.91 mmol) in dry toluene (2 mL) were sequentially added. The mixture was warmed to room temperature and stirred overnight. Then, the solvent was removed and the crude reaction product was purified by column chromatography (hexanes/EtOAc, 20/1) to furnish azide **22** (201 mg, 0.74 mmol, 82% yield) as a yellowish syrup: $[\alpha]_D^{20}$ = −36.2 (c 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 7.0 Hz, 2H, Ph), 7.56 (t, J = 7.5 Hz, 1H, Ph), 7.45 (t, J = 7.9 Hz, 2H, Ph), 4.32 (d, $J_{1,2'}$ = 6.8 Hz, 2H, H-1), 4.01 (br s, 1H, H-5′), 2.19−2.00 (m, 1H, H-2′), 1.70−1.58 (m, 1H, H-4′), 1.45−1.31 (m, 3H, 2H-3′, H-4′), 1.21−1.12 (m, 1H, H-6′), 0.99 (dddd, $J_{1',7'exo}$ = 9.3 Hz, $J_{1',6'}$ = 7.5 Hz, $J_{1',7'endo}$ = 5.4 Hz, $J_{1',2'}$ = 1.3 Hz, 1H, H-1′), 0.85 (td, $J_{7'exo,1'}$ = $J_{7'exo,6'}$ = 9.3 Hz, J_{gem} = 5.4 Hz, 1H, H-7′exo), 0.15 (q, J_{gem} = $J_{7'endo,1'}$ = $J_{7'endo,6'}$ = 5.4 Hz, 1H, H-7′endo); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8 (C = O), 133.1/130.5/129.7/128.5 (C-Ph), 69.4 (C-1), 57.0 (C-5′), 34.0 (C-2′), 24.5 (C-4′), 20.2 (C-3′), 14.7 (C-6′), 12.6 (C-1′), 9.9 (C-7′); IR (ATR) 2925, 2089, 1716, 1270, 1110 cm^{-1}; HRMS (EI) calcd for $[C_{15}H_{17}N_3O_2]^+$ 271.1321, found 271.1324.

(1*S*,2*S*,5*R*,6*R*)-5-(Benzoyloxymethyl)bicyclo[4.1.0]heptan-2-ylammonium Chloride (6). A stirred solution of azide **22** (200 mg, 0.74 mmol) in EtOAc (2.5 mL) at room temperature was hydrogenated in the presence of 10% Pd/C (20 mg) at 2 atm for 24 h. Then, the mixture was filtered through a short pad of Celite and washed with EtOAc. The solvent was evaporated under reduced pressure, and the crude product was treated with a 2 M solution of HCl in Et_2O (1 mL, 2 mmol); the mixture was then stirred for 2 h and filtered to furnish the ammonium salt **6** (184 mg, 0.65 mmol, 88% yield) as a brown solid: mp 130−132 °C (diethyl ether); $[\alpha]_D^{20}$ = +14.6 (c 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 3H, NH_3), 8.08−7.97 (m, 2H, Ph), 7.56−7.50 (m, 1H, Ph), 7.44−7.36 (m, 2H, Ph), 4.45 (d, $J_{1',2}$ = 7.7 Hz, 2H, H-1′), 3.84 (br s, 1H, H-2), 2.15−1.89 (m, 2H, H-5, H-4), 1.60−1.46 (m, J = 7.8 Hz, 3H, 2H-3, H-4), 1.31−1.22 (m, 1H, H-1), 1.12−1.02 (m, 1H, H-6), 0.91 (td, $J_{7exo,1}$ = $J_{7exo,6}$ = 9.1 Hz, J_{gem} = 5.5 Hz, 1H, H-7exo), 0.19 (q, J_{gem} = $J_{7endo,1}$ = $J_{7endo,6}$ = 5.5 Hz, 1H, H-7endo); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6 (C = O), 133.0/130.4/129.7/128.5 (C-Ph), 69.0 (C-1′), 47.1 (C-2), 33.9 (C-5), 23.2 (C-4), 19.4 (C-3), 14.0 (C-1), 12.5 (C-6), 10.4 (C-7); IR (ATR) 3404, 2929, 1712, 1273, 1113 cm^{-1}; HRMS (EI) calcd for $[C_{15}H_{18}NO_2]^+$ 244.1338, found 244.1335.

6-Chloro-9-((1′*S*,2′*S*,5′*R*,6′*R*)-5′-(benzoyloxymethyl)bicyclo-[4.1.0]heptan-2′-yl)-9*H*-purine (28). To a solution of compound **6** (32 mg, 0.11 mmol) and *N*-(4,6-dichloropyrimidin-5-yl)formamide (**23**; 34 mg, 0.18 mmol) in 1,4-dioxane (0.8 mL) was added *i*-Pr_2NEt (110 μL, 0.64 mmol), and the mixture was heated in a microwave reactor at 100 °C for 40 min. The solvent was evaporated under vacuum, and the resulting residue was taken up with EtOAc (2 mL), washed with brine, and dried (Na_2SO_4). Evaporation of the solvent gave crude **25**, which was dissolved in diethoxymethyl acetate (**27**; 0.8 mL). and the mixture was heated in a microwave reactor at 120 °C for 2 h. After the volatiles were removed under reduced pressure, the residue was purified by column chromatography (hexanes/EtOAc, 1/1) to afford **28** (32 mg, 0.084 mmol, 74% yield) as a white solid: mp 210−213 °C (EtOAc); $[\alpha]_D^{20}$ = +53.1 (c 0.39, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H, H-2), 8.50 (s, 1H, H-8), 8.06 (dd, J = 8.3 Hz, J = 1.4 Hz, 2H, Ph), 7.58 (ddt, J = 8.7 Hz, J = 2.6 Hz, J = 1.3 Hz, 1H, Ph), 7.48 (t, J = 7.6 Hz, 2H, Ph), 5.24 (t, $J_{2',3'ax}$ = $J_{2',3'eq}$ = 3.4 Hz, 1H, H-2′), 4.46 (dd, J_{gem} = 11.8 Hz, $J_{1'',5'}$ = 7.5 Hz, 1H, H-1″), 4.42 (dd, J_{gem} = 11.8 Hz, $J_{1'',5'}$ = 7.5 Hz, 1H, H-1″), 2.30 (dtd, $J_{5',4'ax}$ = 12.0 Hz, $J_{5',1''}$ = $J_{5',1''}$ = 7.5 Hz, $J_{5',4'eq}$ = 5.7 Hz 1H, H-5′), 2.04−1.94 (m, 1H, H-3′eq), 1.71 (ddt, J_{gem} = 14.5 Hz, $J_{3'ax,4'ax}$ = 12.3 Hz, $J_{3'ax,2'}$ = $J_{3'ax,4'eq}$ = 3.4 Hz, 1H, H-3′ax), 1.49 (dtd, J_{gem} = 14.5 Hz, $J_{4'eq,3'eq}$= $J_{4'eq,5'}$ = 5.7 Hz, $J_{4'eq,3'ax}$ = 3.4 Hz, 1H, H-4′eq), 1.42−1.27 (m, 2H, H-1′, H-6′), 1.19−1.04 (m, 2H, H-4′ax, H-7′exo), 0.48 (q, J_{gem} = $J_{7'endo,1'}$ = $J_{7'endo,6'}$ = 5.3 Hz, 1H, H-7′endo); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8 (C═O), 152.0 (C-2), 151.6/151.2 (C-6, C-4), 144.4 (C-8), 133.3 (C-Ph), 132.0 (C-5), 130.1/129.7/128.7 (C-Ph), 67.0 (C-1″), 50.9 (C-2′), 33.7 (C-5′), 24.7 (C-3′), 19.8 (C-4′), 14.8 (C-1′), 12.9 (C-6′), 10.4 (C-7′); IR (ATR) 3064, 2931, 1716, 1590, 1560, 1272, 1115 cm^{-1}; HRMS (EI) calcd for $[C_{20}H_{19}N_4O_2Cl]^+$ 382.1197, found 382.1175.

6-Amino-9-((1′*S*,2′*S*,5′*R*,6′*R*)-5′-(hydroxymethyl)bicyclo-[4.1.0]heptan-2′-yl)-9*H*-purine (2a). Compound **28** (11 mg, 28 μmol) was dissolved in a mixture of 1,4-dioxane and NH_4OH (0.5 mL, 1/1, v/v), and the solution was heated in a microwave reactor at 100 °C for 40 min. After the volatiles were removed, the residue was dissolved in a 33% solution of methylamine in EtOH and stirred overnight. Then, the mixture was concentrated under reduced pressure and purified by column chromatography (CH_2Cl_2/MeOH, 15/1) to provide **2a** (5.3 mg, 20 μmol, 72% yield) as a white solid: mp 226−230 °C (MeOH); $[\alpha]_D^{20}$ = +73.9 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (s, 1H, H-2), 8.22 (s, 1H, H-8), 5.09 (br t, $J_{2',3'ax}$ = $J_{2',3'eq}$ = 3.5 Hz, 1H, H-2′), 3.68 (dd, J_{gem} = 10.7 Hz, $J_{1'',5'}$ = 5.7 Hz, 1H, H-1″), 3.63 (dd, J_{gem} = 10.7 Hz, $J_{1'',5'}$ = 5.7 Hz, 1H, H-1″), 1.92 (dq,

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$J_{5',4'ax}$ = 13.6 Hz, $J_{5',1''}$ = $J_{5',1''}$ = $J_{5',4'eq}$ = 5.7 Hz, 1H, H-5′), 1.83 (ddt, J_{gem} = 14.5 Hz, $J_{3'eq,4'eq}$ = 4.0 Hz, $J_{3'eq,2'}$ = $J_{3'eq,4'ax}$ = 3.5 Hz 1H, H-3′eq), 1.66 (ddt, J_{gem} = 14.5 Hz, $J_{3'ax,4'ax}$ = 11.0 Hz, $J_{3'ax,4'eq}$ = $J_{3'ax,2'}$ = 3.5 Hz, 1H, H-3′ax), 1.42−1.26 (m, 2H, H-4′eq, H-1′), 1.23 (dddd, $J_{6',7'exo}$ = 9.3 Hz, $J_{6',1'}$ = 7.3 Hz, $J_{6',7'endo}$ = 5.4 Hz, $J_{6',5'}$ = 1.5 Hz, 1H, H-6′), 1.06 (tdd, J_{gem} = $J_{4'ax,5'}$ = 13.6 Hz, $J_{4'ax,3'ax}$ = 11.0 Hz, $J_{4'ax,3'eq}$ = 3.5 Hz, 1H, H-4′ax), 0.98 (td, $J_{7'exo,1'}$ = $J_{7'exo,6'}$ = 9.3 Hz, J_{gem} = 5.4 Hz, 1H, H-7′exo), 0.43 (q, J_{gem} = $J_{7'endo,1'}$ = $J_{7'endo,6'}$ = 5.4 Hz, 1H, H-7′endo); ^{13}C NMR (100 MHz, CD_3OD) δ 157.1 (C-5), 153.1 (C-8), 150.5 (C-4), 142.4 (C-2), 120.5 (C-6), 67.9 (C-1″), 51.8 (C-2′), 37.9 (C-5′), 25.8 (C-3′), 20.3 (C-4′), 16.1 (C-1′), 14.3 (C-6′), 10.8 (C-7′); IR (ATR) 3273, 3102, 2930, 2882, 2362, 1675, 1601, 1334, 1312 cm^{-1}; HRMS (EI) calcd for $[C_{13}H_{17}N_5O]^+$ 259.1433, found 259.1430.

6-Chloro-2-formamido-9-((1′*S*,2′*S*,5′*R*,6′*R*)-5′-(benzoyloxymethyl)bicyclo[4.1.0]heptan-2′-yl)-9*H*-purine (29). To a solution of compound **6** (50 mg, 0.18 mmol) and *N*,*N*′-(4,6-dichloropyrimidine-2,5-diyl)diformamide (**24**; 46 mg, 0.20 mmol) in 1,4-dioxane (0.9 mL) was added *i*-Pr_2NEt (125 μL, 0.71 mmol), and the mixture was heated in a microwave reactor at 100 °C for 40 min. The mixture was evaporated in vacuo, the residue was extracted with EtOAc (2 mL), and the organic extracts were washed with brine, dried (Na_2SO_4), filtered, and evaporated in vacuo. The crude **26** was then dissolved in diethoxymethyl acetate (**27**; 0.9 mL) and heated in a microwave reactor at 120 °C for 2 h. After the volatiles were removed in vacuo, the residue was purified by column chromatography (CH_2Cl_2/MeOH, 15/1) to afford **29** (54 mg, 0.13 mmol, 72% yield) as a white solid: mp 240−243 °C (MeOH); $[\alpha]_D^{20}$ = +40.5 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (d, $J_{CHO,NH}$ = 10.5 Hz, 1H, CHO), 8.29 (s, 1H, H-8), 8.08 (dd, *J* = 8.3 Hz, *J* = 1.2 Hz, 2H, Ph), 7.65−7.55 (m, 1H, Ph), 7.48 (t, *J* = 7.6 Hz, 2H, Ph), 5.04 (t, $J_{2',3'ax}$ = $J_{2',3'eq}$ = 4.6 Hz, 1H, H-2′), 4.56 (dd, J_{gem} = 10.9 Hz, $J_{1'',5'}$ = 7.1 Hz, 1H, H-1″), 4.45 (dd, J_{gem} = 10.9 Hz, $J_{1'',5'}$ = 6.3 Hz, 1H, H-1″), 2.34 (dq, $J_{5',4'ax}$ = 12.7 Hz, $J_{5',4'eq}$ = $J_{5',1''}$ = $J_{5',1''}$ = 6.4 Hz, 1H, H-5′), 2.02−1.91 (m, 1H, H-3′eq), 1.75−1.60 (m, 1H, H-3′ax), 1.50 (dtd, J_{gem} = 14.9 Hz, $J_{4'eq,5'}$ = $J_{4'eq,3'eq}$ = 6.4 Hz, $J_{4'eq,3'ax}$ = 2.9 Hz, 1H, H-4′eq), 1.38−1.25 (m, 2H, H-6′, H-1′), 1.19 (tdd, J_{gem} = $J_{4'ax,3'ax}$ = 14.9 Hz, $J_{4'ax,5'}$ = 12.7 Hz, $J_{4'ax,3'eq}$ = 3.0 Hz, 1H, H-4′ax), 1.05 (td, $J_{7'exo,1'}$ = $J_{7'exo,6'}$ = 9.4 Hz, J_{gem} = 5.4 Hz, 1H, H-7′exo), 0.46 (q, J_{gem} = $J_{7'endo,1'}$ = $J_{7'endo,6'}$ = 5.4 Hz, 1H, H-7′endo); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9 (C═O), 162.7 (−NHCHO), 152.5 (C-6), 151.9 (C-2), 151.8 (C-4), 143.8 (C-8), 133.4 (C-Ph), 130.1 (C-5), 129.8/129.4/128.7 (C-Ph), 68.9 (C-1″), 51.1 (C-2′), 33.2 (C-5′), 24.3 (C-3′), 19.7 (C-4′), 14.7 (C-1′), 13.0 (C-6′), 10.2 (C-7′); IR (ATR) 3214, 3111, 2922, 1714, 1695, 1262, 1236, 1202 cm^{-1}; HRMS (EI) calcd for $[C_{21}H_{20}N_5O_3Cl]^+$ 425.1255, found 425.1235.

2-Amino-9-((1′*S*,2′*S*,5′*R*,6′*R*)-5′-(hydroxymethyl)bicyclo-[4.1.0]heptan-2′-yl)-1,9-dihydro-6*H*-purin-6-one (2b). A solution of **29** (10 mg, 24 μmol) in 80% HCOOH (0.5 mL) was stirred at 100 °C for 1 h. The solution was cooled and the solvent removed. The residue was dissolved in concentrated aqueous ammonia (0.5 mL) and the mixture stirred at room temperature for 1 h. The solvent was removed in vacuo and the residue coevaporated with toluene. The residue was dissolved in a 33% solution of methylamine in EtOH (6 mL) and the mixture stirred overnight. Then, the mixture was concentrated under reduced pressure and purified by column chromatography (CH_2Cl_2/MeOH, 15/1) to provide **2b** (2.3 mg, 8.4 μmol, 35% yield) as a brown solid: mp 233−236 °C (MeOH); $[\alpha]_D^{20}$ = +65.6 (*c* 0.89, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (s, 1H, H-8), 4.86 (t, $J_{2',3'ax}$ = $J_{2',3'eq}$ = 3.8 Hz, 1H, H-2′), 3.65 (dd, J_{gem} = 10.7 Hz, $J_{1'',5'}$ = 5.9 Hz, 1H, H-1″), 3.61 (dd, J_{gem} = 10.7 Hz, $J_{1'',5'}$ = 6.0 Hz, 1H, H-1″), 1.89 (dq, $J_{5',4'ax}$ = 10.7 Hz, $J_{5',1''}$ = $J_{5',1''}$ = $J_{5',4'eq}$ = 6.1 Hz, 1H, H-5′), 1.81 (dq, J_{gem} = 13.8 Hz, $J_{3'eq,2'}$ = $J_{3'eq,4'ax}$ = $J_{3'eq,4'ax}$ = 3.8 Hz, 1H, H-3′eq), 1.57 (tt, J_{gem} = $J_{3'ax,4'ax}$ = 13.8 Hz, $J_{3'ax,4'eq}$ = $J_{3'ax,2'}$ = 3.4 Hz, 1H, H-3′ax), 1.40−1.22 (m, 2H, H-1′, H-4′eq), 1.18 (dddd, $J_{6',7'exo}$ = 9.3 Hz, $J_{6',1'}$ = 7.6 Hz, $J_{6',7'endo}$ = 5.4 Hz, $J_{6',5'}$ = 1.6 Hz, 1H, H-6′), 1.06 (tdd, J_{gem} = $J_{4'ax,3'ax}$ = 13.8 Hz, $J_{4'ax,5'}$ = 10.7 Hz, $J_{4'ax,3'eq}$ = 3.1 Hz, 1H, H-4′ax), 0.94 (td, $J_{7'exo,1'}$ = $J_{7'exo,6'}$ = 9.3 Hz, J_{gem} = 5.4 Hz, 1H, H-7′exo), 0.36 (q, J_{gem} = $J_{7'endo,1'}$ = $J_{7'endo,6'}$ = 5.4 Hz, 1H, H-7′endo); ^{13}C NMR (100 MHz, CD_3OD) δ 159.5 (C-6), 155.1 (C-2), 152.7 (C-4), 138.8 (C-8), 117.7 (C-5), 67.8 (C-1″), 51.0 (C-2′), 37.7 (C-5′), 25.4 (C-3′), 20.1 (C-4′), 15.8 (C-1′), 13.9 (C-6′), 10.5 (C-7′); IR (ATR) 3400, 3098, 2361, 2341, 1680, 1648, 1600 cm^{-1}. HRMS (ESI +) calcd for $[C_{13}H_{17}N_5O_2 + H]^+$ 276.1455, found 276.1455.

1-((1′*S*,2′*S*,5′*R*,6′*R*)-5′-(Hydroxymethyl)bicyclo[4.1.0]heptan-2′-yl)pyrimidine-2,4(1*H*,3*H*)-dione (2c). Silver cyanate (86 mg, 0.57 mmol), previously dried over phosphorus pentoxide at 80 °C for 3 h, in dry benzene (2 mL) was heated to reflux temperature for 30 min and then a solution of (2*E*)-3-ethoxyacryloyl chloride (39 mg, 0.28 mmol) in dry benzene (0.8 mL) was added dropwise. The mixture was stirred for 30 min before the solid was allowed to settle out. The supernatant, which was a solution of isocyanate **30**, was then decanted and used directly in the next reaction without further purification. The ammonium chloride **6** (50 mg, 0.18) was dissolved in dry DMF (1.8 mL), and Et_3N (25 μL, 0.18 mmol) was added. The mixture was cooled to −20 °C, and the solution of isocyanate **30** was added slowly enough to avoid an increase in the temperature. The reaction mixture was stirred overnight at room temperature. The solvent was evaporated, water (2 mL) was added, and the residue was extracted with EtOAc (2 × 2 mL), washed with brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was dissolved in MeOH (0.42 mL), H_2SO_4 (1 M, 0.76 mL) was added, and the mixture was heated to reflux for 3 h. After the volatiles were removed in vacuo, the residue was dissolved in a 33% solution of methylamine in EtOH (27 mL) and stirred overnight. Then, the mixture was concentrated under reduced pressure and the residue was purified by column chromatography (CH_2Cl_2/MeOH, 15/1) to provide compound **2c** (5.4 mg, 23 μmol, 13% yield) as a yellowish solid: mp 228−231 °C (MeOH); $[\alpha]_D^{20}$ = +23.4 (*c* 0.13, CD_3OD); ^{1}H NMR (400 MHz, CD_3OD) δ 8.05 (d, $J_{6,5}$ = 8.0 Hz, 1H, H-6), 5.69 (d, $J_{5,6}$ = 8.0 Hz, 1H, H-5), 4.86−4.79 (m, 1H, H-2′), 3.65 (dd, J_{gem} = 10.7 Hz, $J_{1'',5'}$ = 5.8 Hz, 1H, H-1″), 3.60 (dd, J_{gem} = 10.7 Hz, $J_{1'',5'}$ = 5.8 Hz, 1H, H-1″), 1.86 (dq, $J_{5',4'ax}$ = 11.3 Hz, $J_{5',1''}$ = $J_{5',1''}$ = $J_{5',4'eq}$ = 5.9 Hz, 1H, H-5′), 1.73−1.62 (m, 1H, H-3′eq), 1.56−1.42 (dddd, J_{gem} = 14.5 Hz, $J_{3'ax,4'ax}$ = 12.3 Hz, $J_{3'ax,4'eq}$ = 4.1 Hz, $J_{3'ax,2'}$ = 3.2 Hz, 1H, H-3′ax), 1.38−1.30 (m, 1H, H-4′eq), 1.25−1.10 (m, 2H, H-4′ax, H-1′), 1.07−0.96 (m, 1H, H-6′), 0.89 (dt, $J_{7'exo,6'}$ = $J_{7'exo,1'}$ = 9.3 Hz, J_{gem} = 5.2 Hz, 1H, H-7′exo), 0.31 (q, J_{gem} = $J_{7'endo,1'}$ = $J_{7'endo,6'}$ = 5.2 Hz, 1H, H-7′endo); ^{13}C NMR (100 MHz, CD_3OD) δ 165.0 (C-4), 151.4 (C-2), 144.0 (C-6), 99.9 (C-5), 66.0 (C-1″), 51.1 (C-2′), 35.8 (C-5′), 23.1 (C-3′), 18.2 (C-4′), 13.8 (C-1′), 12.4 (C-6′), 8.8 (C-7′); IR (ATR) 3393, 2925, 2361, 2341, 1678, 1260 cm^{-1}; HRMS (ESI+) calcd for $[C_{12}H_{16}N_2O_3 + Na]^+$ 259.1053, found 259.1074.

1-((1′*S*,2′*S*,5′*R*,6′*R*)-5′-(Hydroxymethyl)bicyclo[4.1.0]heptan-2′-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (2d). A solution of ammonium chloride **6** (50 mg, 0.18 mmol), ethyl carbamate **31** (36 mg, 0.18 mmol), and Et_3N (26 μL, 0.19 mmol) in 1,4-dioxane (0.5 mL) was heated at 100 °C for 3 h. The suspension was cooled and filtered, and the collected solid was washed with 1,4-dioxane (2 × 2.5 mL). The filtrates were combined, HCl 2 M (5.6 mL) was added, and the solution was heated to 90 °C overnight. The cool solution was extracted with CH_2Cl_2 (3 × 5 mL), and the combined extracts were dried and evaporated under reduced pressure. The crude was purified by column chromatography (EtOAc/MeOH, 20/1) to afford nucleoside analogue **2d** (12.1 mg, 48 μmol, 27% yield) as a pale yellow syrup: $[\alpha]_D^{20}$ = +44.3 (*c* 0.72, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 7.92 (q, $J_{6,CH3}$ = 1.2 Hz, 1H, H-6), 4.80 (ddddd, $J_{2',3'ax}$ = 4.7 Hz, $J_{2',3'eq}$ = 4.1 Hz, $J_{2',1'}$ = 1.8 Hz, $J_{2',4'}$ = 1.1 Hz, $J_{2',4'}$ = 0.5 Hz, 1H, H-2′), 3.69 (dd, J_{gem} = 10.7 Hz, $J_{1'',5'}$ = 5.3 Hz, 1H, H-1″), 3.61 (dd, J_{gem} = 10.7 Hz, $J_{1'',5'}$ = 5.0 Hz, 1H, H-1″), 1.91 (d, $J_{CH3,6}$ = 1.2 Hz, 3H, $-CH_3$), 1.92−1.82 (m, 1H, H-5′), 1.66 (dq, J_{gem} = 14.5 Hz, $J_{3'eq,2'}$ = $J_{3'eq,4'ax}$ = $J_{3'eq,4'eq}$ = 4.1 Hz, 1H, H-3′eq), 1.49 (ddt, J_{gem} = 14.5 Hz, $J_{3'ax,4'ax}$ = 13.8 Hz, $J_{3'ax,4'eq}$ = $J_{3'ax,2'}$ = 4.7 Hz, 1H, H-3′ax), 1.34−1.23 (m, 2H, H-4′), 1.18 (dddd, $J_{1',7'exo}$ = 9.4 Hz, $J_{1',6'}$ = 7.2 Hz, $J_{1',7'endo}$ = 5.3, $J_{1',2'}$ = 1.8 Hz, 1H, H-1′), 1.09−0.98 (m, 1H, H-6′), 0.89 (td, $J_{7'exo,6'}$ = $J_{7'exo,1'}$ = 9.4 Hz, J_{gem} = 5.3 Hz, 1H, H-7′exo), 0.30 (q, J_{gem} = $J_{7'endo,1'}$ = $J_{7'endo,6'}$ = 5.3 Hz, 1H, H-7′endo); ^{13}C NMR (100 MHz, CD_3OD) δ 166.6 (C-4), 153.0 (C-2), 141.5 (C-6), 110.1 (C-5), 67.3 (C-1″), 52.2 (C-2′), 37.0 (C-5′), 24.5 (C-3′), 19.6 (C-4′), 15.5 (C-1′), 14.0 (C-6′), 12.4 ($-CH_3$), 10.2 (C-7′); IR (ATR) 3398, 3194, 3024, 2928, 2873, 2360, 2341,

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1654, 1467, 1257 cm^{-1}; HRMS (ESI+) calcd for $[C_{13}H_{18}N_2O_3 + Na]^+$ 273.1210, found 273.1193.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01413.

Computational details, ^{1}H and ^{13}C NMR spectra of all new compounds, and 2D NMR spectra for compounds **12–15**, **5**, **18**, **22**, **28**, and **2a–d** (PDF)

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Notes

The authors declare no competing financial interest.

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